ORIGINAL ARTICLE

Pediatrics Sciences Journal (*PedScij*) 2025, Volume 6, Number 1: 13-17
P-ISSN: 2722-0427, E-ISSN: 2722-1474

Pediatric Sciences Journal

Published by
Pediatrics Sciences Journal

A comparison of test duration for the clinical diagnosis of pediatric tuberculosis using Tuberculin Skin Test (TST) and Interferon Gamma Release Assays (IGRA)

Ery Olivianto[1*], Agustin Iskandar[2], Triyana Dian Dhuha Akmaly[1], Sarah Zoraya Mirza[1], Maxie Felix Jahono[2]

[1]Department of Child Health, Faculty of Medicine, Universitas Brawijaya/ Saiful Anwar General Hospital, Malang, Indonesia;
[2]Department of Clinical Pathology, Faculty of Medicine, Universitas Brawijaya/Saiful Anwar General Hospital, Malang, Indonesia.

*Corresponding to:
Ery Olivianto;
Department of Child Health, Faculty of Medicine, Universitas Brawijaya/ Saiful Anwar General Hospital, Malang, Indonesia;
ery15.fk@ub.ac.id

Received: 2025-01-09
Accepted: 2025-02-16
Published: 2025-03-20

ABSTRACT

Background: Tuberculosis (TB) remains a major global health challenge, particularly among children. Diagnosing pediatric TB is complicated due to nonspecific symptoms and the difficulty of obtaining sputum samples for microbiological confirmation. Immunological tests, such as the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs), are commonly used to support diagnosis. However, TST has several limitations, including the need for multiple patient visits and potential cross-reactivity with Bacillus Calmette-Guérin (BCG) vaccination. This study aimed to compare the efficiency of IGRA and TST in terms of turnaround time and patient compliance.

Methods: A diagnostic time comparison study was conducted in pediatric patients with suspected pulmonary or extrapulmonary TB at Saiful Anwar Hospital, Malang. Patients underwent both TST and IGRA testing. The time required to obtain results and patient compliance was recorded and analyzed. o

Results: A total of 94 pediatric patients were included, with 17 diagnosed with extrapulmonary TB and 77 with pulmonary TB. IGRA demonstrated a significantly shorter turnaround time (25.43 ± 6.31 hours for pulmonary TB, and 25.58 ± 6.37 hours for extrapulmonary TB) compared to TST (50.16 ± 6,93 hours for extrapulmonary TB and 50.34 ± 7.16 hours for pulmonary TB). Additionally, IGRA provided higher positivity rates in both pulmonary and extrapulmonary TB cases.

Conclusion: IGRA offers a faster and more convenient alternative to TST for diagnosing pediatric TB. Despite its higher cost, the efficiency and single-visit requirement of IGRA makes it a preferable diagnostic tool in clinical settings, especially for children suspected of having TB.

Keywords: *Interferon-g, pulmonary TB, tuberculin, test duration*.
Cite This Article: Olivianto, E., Iskandar, A., Akmaly, T.D.D., Mirza, S.Z., Jahono, M.F. 2025. A comparison of test duration for the clinical diagnosis of pediatric tuberculosis using Tuberculin Skin Test (TST) and Interferon Gamma Release Assays (IGRA). *Pediatrics Sciences Journal* 6(1): 13-17. DOI: 10.51559/pedscij.v6i1.118

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacterium *M. tuberculosis*.[1] Tuberculosis is the ninth leading cause of death worldwide and the leading cause of death from a single infectious agent.[2] Globally, an estimated 10 million TB cases were reported, with 1.2 million deaths in 2019.[3] Indonesia is ranked second among countries with a high burden of TB with an incidence of 391/100,000 population.[4] According to the 2017 World Health Organization (WHO) tuberculosis report, children aged below 15 years constituted about 10% of the approximately 10.4 million new TB cases in 2016.[2] *M. tuberculosis* mainly attacks the lungs but can also affect other organs.[5] Extrapulmonary TB is observed more frequently in children especially in young children, although epidemiological data are still limited.[6,7]

Detecting new cases of pediatric TB is challenging. Early symptoms of pulmonary or extrapulmonary TB are often nonspecific. Additionally, chest X-rays of children with TB tend to be less specific compared to those of adult patients. The diagnosis of pulmonary TB is confirmed by identifying the bacterium *M. tuberculosis* in sputum specimens.[4,8] However, this remains challenging, as children often have difficulty expectorating sputum. Moreover, the positivity of microbiological examination is lower compared to that in adults due to its paucibacillary nature in children.[9] This may result in underdiagnosis of TB and delays in initiating anti-TB treatment, which can lead to poor outcomes.[4] Consequently, the diagnosis of TB in children often relies on a combination of clinical symptoms, chest radiography, and immunological tests.[10]

Currently, there are two methods available for diagnosing pediatric pulmonary TB: the tuberculin skin test (TST) and interferon-gamma release assays (IGRA). Both detect the presence of cell-mediated immunity in individuals infected by *M. tuberculosis*.[11] The results of TST and IGRA play a supportive role in establishing the diagnosis of pediatric TB, particularly by providing additional

information when other tests fail to detect the disease.[12] TST typically takes 48 to 72 hours to be read. Ensuring that patients return for timely readings is often challenging, and delayed readings can compromise the reliability of results. IGRA eliminates this issue by offering immediate and dependable results.[12,13] The study aimed to demonstrate that IGRA is more efficient in terms of time and patient compliance, thereby serving as a basis for recommending changes in diagnostic policies at the hospital.

METHODS

Study Design

This study employed a diagnostic time comparison study designed to compare two tests, TST and IGRA, in terms of result turnaround time. Subjects were recruited consecutively from pediatric patients with presumptive pulmonary or extrapulmonary TB.

Research Location and Time

The study was performed at the pediatric respiratory outpatient clinic and the pediatric inpatient ward of Saiful Anwar Hospital, Malang, from November 2021 to January 2022.

Study Population

The population in this study consisted of pediatric patients suspected of having pulmonary tuberculosis (TB) or extrapulmonary TB. The accessible population included pediatric patients with presumptive TB who were treated at the pediatric respiratory outpatient clinic and the pediatric inpatient ward of Saiful Anwar Hospital.

Subjects

The study subjects included pediatric patients under 18 years of age, suspected of having either pulmonary or extrapulmonary TB, who had never previously received TB treatment or TB prophylaxis and were either visited at the pediatric respiratory outpatient clinic or admitted to the inpatient ward. The subjects should have met the inclusion criteria, and the parents or guardians of all patients were informed about the study and provided written informed consent.

Inclusion Criteria

The inclusion criteria for this study were pediatric patients under 18 years of age, with clinically suspected TB, based on one or more of the following: cough lasting ≥3 weeks, fever lasting ≥2 weeks, weight loss or failure to gain weight in the last 2 months, enlarged cervical lymph nodes unresponsive to non-specific treatment for 2 weeks, or chest X-rays suggestive of TB. Patients who had close contact with adult TB patients were also included. Additionally, patients must have never received TB treatment or prophylaxis and must be willing to participate in the study, with informed consent provided by the parents.

Exclusion Criteria

Patients with HIV, pneumonia, or immunocompromising conditions, including those receiving immunosuppressive therapy, were excluded from the study.

TST Protocol

A standardized dose of 0.1 mL (2 TU) of purified protein derivative (PPD) was injected intradermally into the volar surface of the forearm using a 27-gauge needle and a 1 mL tuberculin syringe. The injection was administered at a 15-degree angle, ensuring the formation of a 6-10 mm wheal, confirming proper intradermal placement. The test site was marked and evaluated 48-72 hours after injection by a trained healthcare professional. The induration (not erythema) diameter was measured using a millimeter ruler perpendicular to the long axis of the forearm. A result was considered positive if the wheal measured ≥ 10 mm.

To ensure standardization, all TST procedures are conducted by trained personnel under the same environmental conditions, using the same brand and batch of PPD. Two independent readers interpreted the results to minimize inter-observer variability.

IGRAs Protocol

Blood collection from patients was carried out at room temperature (17–30 °C) from their veins by trained medical personnel, following a standard procedure. To ensure consistency, the collected blood volume was verified using calibrated measuring instrument, and all sample tubes were labeled with unique identifiers to prevent misidentification.

After labeling, a 1 mL blood sample was placed into the QIAreach QFT tube, shaken 10 times with consistent intensity, and incubated at 37 °C for 16-24 hours, ensuring that all samples underwent the same incubation conditions.

After incubation, the blood tube and processing tube were placed into the pre-prepared QIAreach eHub for sample reading. The stick device was inserted into the QIAreach eHub, and 150 µL of diluent buffer was added to the processing tube using a calibrated pipette. To minimize variability in sample preparation, the blood plasma from the blood collection tube was transferred to a processing tube containing diluent buffer and mixed with an up-and-down pipetting motion at least four times, following a standardized protocol. A total of 150 µL of the processed sample was then carefully pipetted into the eStick sample port.

The test was designed to start automatically within 15 seconds after sample application, and results could be read within a maximum period of 20 minutes. By maintaining uniform procedures in blood collection, sample preparation, and eStick reading, potential variability in test processing was minimized, ensuring consistent and reliable results across all samples.

Statistical Analysis

The average duration time for both IGRA and TST were compared to determine which test provides a faster and more efficient diagnosis of pediatric TB.

RESULTS

Ninety-four pediatric patients were included in this study. There were 17 subjects diagnosed with extrapulmonary TB and 77 subjects diagnosed with pulmonary TB. The demographic characteristics of this study are presented in Table 1.

The proportion of positive results is higher in both extrapulmonary and pulmonary TB for the IGRAs test compared to the TST test. These results are shown in Figures 1 and 2.

Table 1. Characteristics of the subjects based on pulmonary-extrapulmonary TB

Characteristics	Pulmonary TB (N=77)	Extrapulmonary TB (N=17)
Male, n (%)	32 (41.6)	11 (64.7)
Age, months, median (min-max)	36 (1-204)	96 (2-180)
TB contact, n (%)	4 (5.2)	1(5.9)
Fever ≥ 2 weeks, n (%)	12 (15.6)	5 (29.4)
Cough ≥ 3 weeks, n (%)	10 (13.0)	5 (29.4)
Joint swelling, n (%)	1 (1.3)	0
Poor weight gain	14 (18.2)	6 (35.3)
Lymphadenopathy, n (%)	0	2 (11.8)
Severe malnutrition, n (%)	11 (14.3)	1 (5.9)
Positive TST results, n (%)	13 (16.9)	4 (23.5)
Positive IGRA results, n (%)	17 (22.1)	10 (58.8)

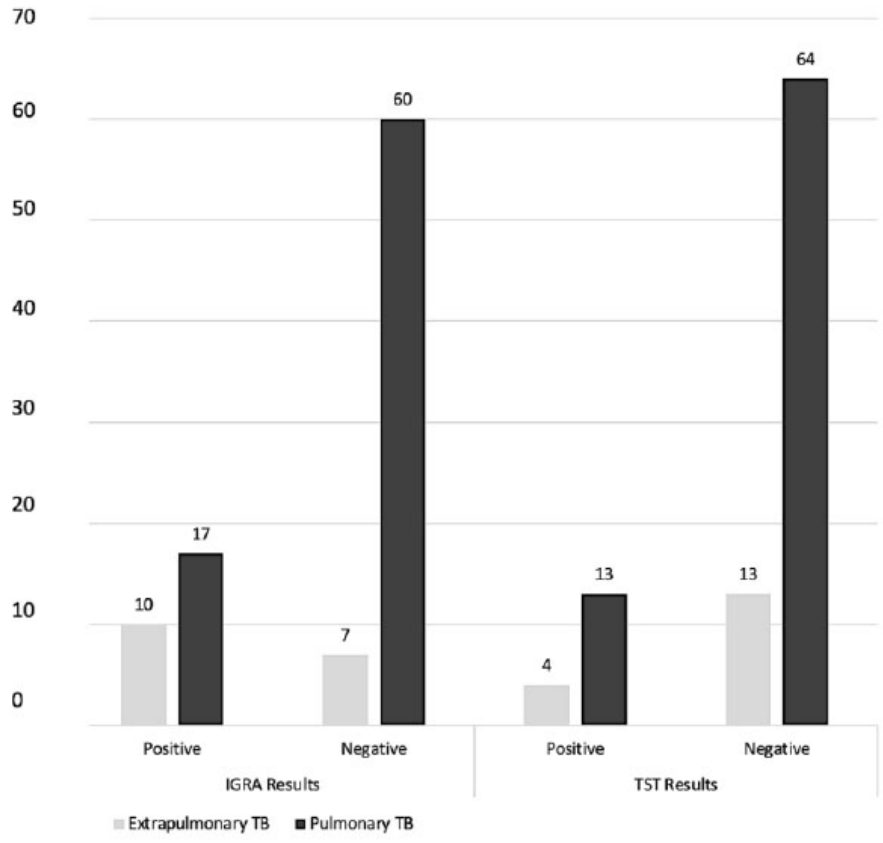

Figure 1. Frequency Distribution of TST and IGRA Results by Type of TB.

IGRA showed a significantly shorter turnaround time (25.43 ± 6.31 hours for pulmonary TB, and 25.58 ± 6.37 hours for extrapulmonary TB) compared to TST (50.16 ± 6,93 hours for extrapulmonary TB and 50.34 ± 7.16 hours for pulmonary TB) (p = 0.000).

The duration of the IGRAs and TST tests, as well as the age linked to the type of TB diagnosed, is shown in Table 2. The IGRA test for pulmonary TB requires an average time of 25.43 ± 6.31 hours, and for extrapulmonary TB, the average time is 25.58 ± 6.37 hours. The TST test requires a longer time, which is 50.16 ± 6,93 hours; extrapulmonary TB and pulmonary TB require 50.34 ± 7.16 hours. The total duration of IGRAs and TST tests are shown in Figure 2. The overall duration of the IGRAs test is shorter than that of the TST.

DISCUSSION

The identification and treatment of TB infection in the pediatric population is an important disease control component as a strategy to prevent future TB transmission and reduce TB-related morbidity and mortality.[14] A study conducted in Zanzibar, one of the developing countries, showed that 43% of adult patients in the study reported reduced working capacity during their illness but an improved condition at the end of their treatment.[14] Establishing a diagnosis of TB disease in pediatric patients can be challenging because of the various presentations of TB symptoms that appear in children, ranging from non-specific symptoms to severe symptoms.[15]

Taking specimens for microbiological examination is difficult because most children are unable to expectorate. There are other simple procedures, such as gastric aspiration and sputum induction, that can serve as alternatives to this problem; however, the lack of ability among health workers who meet the standards is an obstacle.[16] This study compared the duration of the IGRA-based test with the tuberculin skin test (TST) in pediatric patients suspected of tuberculosis. The TST, also known as the Mantoux test, is one of the oldest diagnostic methods still in use and has been routinely used since 1910. This test is based on cellular intradermal immune response against the cellular antigens of mycobacteria, thus making it non-specific for the diagnosis of Mycobacterium tuberculosis. A practical example of the non-specificity is false positive results in cases of vaccination by Bacillus Calmette-Guerin (BCG).[17]

Other significant limitations associated with TST are the need for trained individuals to administer and interpret the test and low specificity, especially in immunocompromised patients.[17]

There are also procedural disadvantages to the TST test, including reduced sensitivity due to excessive depth when taking the sample and inconvenience for patients, as they need to be pricked twice.[18] On the other hand, Interferon-g Release Assays (IGRAs) based test targets almost exclusively specific Mycobacterium tuberculosis proteins that are not found in nontuberculous mycobacteria. The increased use of IGRA tests has also been

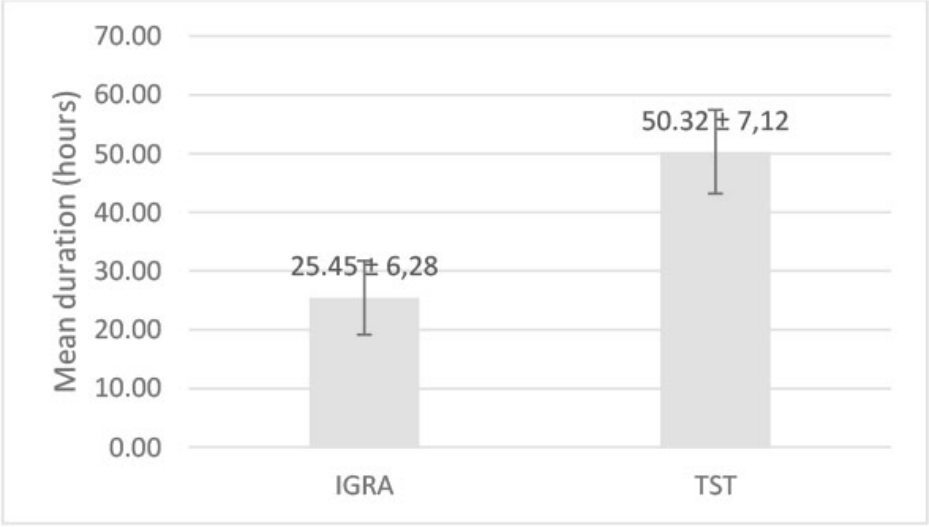

Figure 2. The Total Mean Duration of IGRA Compared to TST.

Table 2. Test Results and Duration Adjusted for Age

	Frequency n (%)	Duration (hours)
< 5 Years (n=55)		
IGRA test result		25.43 ± 6.31
– Negative	43 (78.18)	
– Positive	12 (21.82)	
TST test result		50.34 ± 7.16
– Negative	48 (87.27)	
– Positive	7 (12.73)	
≥ 5 Years (n = 39)		
IGRA test result		25.63 ± 6.58
– Negative	24 (61.54)	
– Positive	15 (38.46)	
TST test result		49.83 ± 6.56
– Negative	29 (74.36)	
– Positive	10 (25.64)	

attributed to their convenience, which is the most advantageous aspect, as they require only a single visit to perform the blood test.[19,20] The blood sampling can also be done for several other tests all at once. One of the disadvantages of the IGRA test is the reagent cost, which is significantly higher than that of the TST.[21] Currently, IGRAs are the preferred diagnostic test for immunocompetent children above 5 years old who have received BCG vaccination, according to the US Centers of Disease Control and Prevention (CDC).[20]

The result of this study shows a significant difference in the duration of the IGRAs compared to the TST test. The shorter duration of the IGRAs test is also described in multiple studies. The IGRAs test results are typically available within a 16- to 24-hour period, compared to a 48- to 72-hour period for the TST test.[19] This was also found in this study. Regardless of the diagnosis, the duration of IGRAs (25.43 ± 6.31 hours for pulmonary TB, and 25.58 ± 6.37 hours for extrapulmonary TB) is significantly shorter than TST (50.16 ± 6,93 hours for extrapulmonary TB and 50.34 ± 7.16 hours for pulmonary TB). An Indian multicentre study of TB diagnosis also mentioned that IGRA test results for the study were obtained within 24 hours.[22] Studies evaluating the duration of IGRA test tools similar to the one used in this study also described the procedure to be shorter in duration, requiring 18–24 hours for supernatant culturing or incubation and a maximum of an additional 20 minutes for IFN-γ measurement on each test.[23,24] These findings, in addition to the simplicity of the procedure for patients, support the IGRAs test as a convenient choice for diagnostic testing of pediatric tuberculosis.

This study also demonstrates the relationship between IGRA results and TB diagnosis, compared to the TST, in both unadjusted and age-adjusted analyses. There is no significant relationship between TST results and whether the TB is pulmonary or extrapulmonary. This may suggest the ability of IGRAs to distinguish between pulmonary and extrapulmonary TB diagnoses. This is also described in several past studies comparing TST and IGRAs tests in detecting active and latent TB infection. The studies showed that T-cell assays are more specific than the TST, although they are currently unable to distinguish between active disease and latent TB infection.[10] The preferable result of the IGRAs test in this study may be due to the nature of TB infection in children. The paucibacillary nature of childhood TB reduces the sensitivity of microbiologically based diagnostic tools, such as acid-fast smears and bacterial cultures.[16] A review states that only 10–15% of children with pulmonary TB are smear-positive, and only 20–40% are culture-positive despite strict specimen collection and laboratory methods. Microbiological confirmation of extrapulmonary TB also remains elusive.[16] Diagnostic tests based on the measurement of immune responses to *M. tuberculosis* may be preferred over direct detection of bacteria in these cases, thus making IGRAs test a reasonable choice.[25]

This study has several limitations. The limited availability of IGRA reagents and the small sample size of patients with suspected pediatric TB restricted the scope of the findings. Future studies should address these limitations by utilizing a broader registry, including multiple research centers, or extending the study period to increase the sample size and enhance the generalizability of the results.

CONCLUSION

In conclusion, this study found that the IGRA test has a shorter duration compared to the TST for diagnosing pediatric TB. Additionally, despite its higher cost, IGRA offers greater convenience than TST. Therefore, based on the aspects evaluated in this study, IGRA is a superior option

for use as a supporting diagnostic test for both pulmonary and extrapulmonary TB in children.

ETHICAL CLEARANCE

This study was conducted after obtaining ethical clearance from Saiful Anwar Ethical Board with approval number 400/126/K3/302/2021

CONFLICT OF INTEREST

None declared.

FUNDING ACKNOWLEDGEMENT

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

AUTHORS CONTRIBUTION

Ery Olivianto: conceptualization and study design, primary data collection, statistical analysis, and drafting and revising the manuscript

Agustin Iskandar: Overall supervision of the study, validation of results, data interpretation, and critical review of the manuscript.

Triyana Dian Dhuha Akmaly: Clinical data collection, coordination of study logistics, and editing the manuscript to meet journal formatting requirements

Sarah Zoraya Mirza: Clinical data collection and editing of the manuscript to meet journal formatting requirements

Maxie Felix Jahono: laboratory analysis (including IGRA and TST), interpretation of technical results.

REFERENCES

1. WHO. Global Tuberculosis Report 2021. Geneva: World Health Organization; 2021.
2. Kaba Ö, Kara M, Odacılar CA, *et al.* Evaluation of cases of pediatric extrapulmonary tuberculosis: a single center experience. *Turk Pediatri Ars*. 2019; 54(2):86-92.
3. Soedarsono S. Tuberculosis: Development of new drugs and treatment regimens. *J Respirasi*. 2021; 7(1):36-45.
4. Triasih R, Helmi R, Laksanawati IS. Clinical profile and outcome of extrapulmonary tuberculosis in children in Indonesia. *Pediatr respir Crit Care Med*. 2(3):51-5.
5. Gopalaswamy R, Dusthackeer VNA, Kannayan S, Subbian S. Extrapulmonary tuberculosis—an update on the diagnosis, treatment and drug resistance. . *J Respir*. 2021; 1(2):141-64.
6. Sharma SK, Mohan A, Kohli M. Extrapulmonary tuberculosis. *Expert Rev Respir Med*. 2021; 15(7):931-48.
7. de Oliveira MCB, Sant'Anna CC, Raggio RL, Kritski AL. Tuberculosis among children and adolescents in Rio de Janeiro, Brazil – Focus on extrapulmonary disease. *Int J Infect Dis*. 2021; 105:105-12.
8. García-Basteiro AL, Schaaf HS, Diel R, Migliori Giovanni B. Adolescents and young adults: a neglected population group for tuberculosis surveillance. *Eur Respir J*. 2018; 51(2):1800176.
9. World Health Organization. Global Tuberculosis Report Supplementary Material. 2022.
10. Mandal N, Anand PK, Gautam S, Das S, Hussain T. Diagnosis and treatment of paediatric tuberculosis: An insight review. *Crit Rev Microbiol*. 2017; 43(4):466-80.
11. Sharma SK, Vashishtha R, Chauhan LS, Sreenivas V, Seth D. Comparison of TST and IGRA in diagnosis of latent tuberculosis infection in a high TB-burden setting. *PLoS One*. 2017; 12(1):e0169539.
12. Kay AW, Islam SM, Wendorf K, Westenhouse J, Barry PM. Interferon-γ release assay performance for tuberculosis in childhood. *Pediatrics*. 2018; 141(6).
13. Pai M, Denkinger CM, Kik SV, *et al.* Gamma interferon release assays for detection of *Mycobacterium tuberculosis* infection. *Clin Microbiol Rev*. 2014; 27(1):3-20.
14. Jørstad MD, Aßmus J, Marijani M, Sviland L, Mustafa T. Diagnostic delay in extrapulmonary tuberculosis and impact on patient morbidity: A study from Zanzibar. *PLoS One*. 2018; 13(9):e0203593.
15. Loh SW, Thoon KC, Tan NWH, Li J, Chong CY. Paediatric tuberculosis in Singapore: a retrospective review. *BMJ Paediatr Open*. 2018; 2(1):e000308.
16. Chiang SS, Swanson DS, Starke JR. New diagnostics for childhood tuberculosis. *Infect Dis Clin North Am*. 2015; 29(3):477-502.
17. Siqueira RC dan Oréfice F. The potential of the IGRA (interferon gamma release assay) test for the diagnosis of ocular tuberculosis . Review and comparative analysis with the tuberculosis skin test. *Rev Bras Oftalmol*. 2019; 78(3):202-9.
18. Maulahela H, Simadibrata M, Nelwan EJ, *et al.* Recent advances in the diagnosis of intestinal tuberculosis. *BMC Gastroenterol*. 2022; 22(1):89.
19. Elliot C, Marais B, Williams P, *et al.* Tuberculin skin test versus interferon-gamma release assay in refugee children: A retrospective cohort study. *J Paediatr Child Health*. 2018; 54(8):834-9.
20. Cruz AT dan Starke JR. Relationship between tuberculin skin test (TST) size and interferon gamma release assay (IGRA) result: when should clinicians obtain IGRAs in children with positive TSTs? *Clin Pediatr (Phila)*. 2014; 53(12):1196-9.
21. Kestler B dan Tyler SK. Latent tuberculosis testing through the ages: the search for a sleeping killer. *Am J Physiol Lung Cell Mol Physiol*. 2022; 322(3):L412-l9.
22. Lagrange PH, Thangaraj SK, Dayal R, *et al.* A toolbox for tuberculosis (TB) diagnosis: an Indian multicentric study (2006-2008). Evaluation of QuantiFERON-TB gold in tube for TB diagnosis. *PLoS One*. 2013; 8(9):e73579.
23. Fukushima K, Akagi K, Kondo A, Kubo T, Sakamoto N, Mukae H. First clinical evaluation of the QIAreach(TM) QuantiFERON-TB for tuberculosis infection and active pulmonary disease. *Pulmonol*. 2022; 28(1):6-12.
24. Hur YG, Hong JY, Choi DH, *et al.* A feasibility study for diagnosis of latent tuberculosis infection using an IGRA point-of-care platform in South Korea. *Yonsei Med J*. 2019; 60(4):375-80.
25. Whitworth HS, Badhan A, Boakye AA, *et al.* Clinical utility of existing and second-generation interferon-γ release assays for diagnostic evaluation of tuberculosis: an observational cohort study. *Lancet Infect Dis*. 2019; 19(2):193-202.