DOI: https://doi.org/10.53555/nnmhs.v9i9.1838 Publication URL: https://nnpub.org/index.php/MHS/article/view/1838

SCREENING FOR TUBERCULOSIS DISEASE AMONG CHILDREN: A SYSTEMATIC REVIEW

Ratih Pasande*

**Topo Community Health Centre, Nabire, Papua, Indonesia*

Corresponding Author:
ratihpasande2@gmail.com

Abstract

Introduction: *One of the top 10 causes of death worldwide is tuberculosis (TB). An estimated 10 million new cases of TB, including 1.2 million in children, were reported in 2019. Due to the symptoms of pediatric tuberculosis (TB) being similar to those of other juvenile illnesses and the difficulty in obtaining lung samples due to children's propensity to swallow sputum, diagnosing pediatric TB is challenging.*

Methods: *This systematic review's objective was to find reliable screening techniques for paediatric tuberculosis diagnosis. The Cochrane Central Register of Controlled Trials, ScienceDirect, PubMed, and Web of Science databases were all searched in accordance with PRISMA standards.The words "screening" and "(Tuberculosis) OR (TB) OR (TB)" and "(Children")" were used.*

Result: *This investigation covered a total of five studies. TST and IGRA are recommended by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) as techniques for diagnosing M. tuberculosis infection, with certain preferences and considerations. For testing children younger than 5 years old, TST is preferred over IGRA.*

Conclusion: *Testing BCG recipients (either as a therapy or a vaccine) or patients with subpar TST findings is preferred to be done with IGRAs.*

Keywords: *Screening; TB; Child; TST; IGRA*

INTRODUCTION

Tuberculosis (TB) is one of the top 10 causes of death globally. In 2019, there were an estimated 10 million new TB cases including 1.2 million children worldwide. Of the quarter of the world's population who are infected, 5-10% develop active disease (TB disease) during the patient's lifetime. The majority of TB disease in the world is caused by *Mycobacterium tuberculosis* (MTB) bacteria. [1]

Children (<5 years old), people with HIV and those with reduced immunity are at higher risk of developing TB disease. Malnutrition and vitamin D deficiency have been associated with the risk of developing TB disease.[23,4] Children represent approximately 10% of all TB cases. The expected amount of incident cases among children (under the age of 15) is above one million, which reflects ongoing community transmission. In contrast, contacted children who are not appropriately treated can increase the number of childhood TB cases, with only 349,487 children under the age of five beginning TB preventive therapy in 2018 (an increase of 20% from 292,182 in 2017).[5]

According to the World Health Organization (WHO), eradicating tuberculosis (TB) by 2020 and 2025 is only possible if TB diagnostic, treatment, and prevention services are properly provided as part of the goal of universal health coverage (UHC). Children's tuberculosis is a sign of recent MTB transmission and a failure of disease control in the neighborhood.[6] Pulmonary TB is the most typical manifestation in this age range. Due to a lack of an immune response, infants and young children are more likely to get more severe types of TB and may develop meningitis. With atypical signs, the progression may be rapid.[7]

Contact tracing and TB case screening are essential for TB case detection and effective treatment. Therefore, in cases of high TB caseloads, contact screening and preventive treatment of children less than 5 years of age should be prioritised and implemented.[8] MTB exposure risk is determined by a combination of epidemiological, environmental, sociocultural, and behavioral factors that reflect how children, adolescents, and adults interact in community settings.[910]

Pediatric TB is challenging to diagnose partially because its symptoms are similar to those of other pediatric illnesses and it is challenging to obtain lung samples from children since they swallow sputum more frequently. This problem is further complicated by children's decreased susceptibility to microbiological tests.[11] The two TB screening tests that are now available, the tuberculin skin test (TST) and the interferon gamma release assays (IGRA), are designed to detect host immune responses that signify TB exposure or proof of a chronic non-progressive state.[12] Screening uncertainty is frequently present, particularly when there is cross-reaction with TST or unclear IGRA results. The gold standard for TB illness diagnosis is bacterial confirmation (through culture or PCR).[13]

Based on these data, it is important to have further research related to tuberculosis screening in children. Therefore, the researchers were interested in conducting a systematic review of tuberculosis screening in children.

METHODS

A.Eligibility criteria:

The inclusion criteria for this study were as follows:

1. Published in English with *full text* articles accessible.
2. Published between January 2013 and 2023.
3. The studies used are cohort, case control, case series, cross-sectional, randomised control trial (RCT).
4. The study discussed tuberculosis *screening* in paediatric patients

B.Guide:

In this investigation, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. As illustrated in the flow chart in Figure 1, we were able to incorporate five relevant papers in the review.

C.Search strategy:

Following PRISMA criteria, two researchers (XX and XX) separately conducted a literature search on 07 August 2023 for relevant papers available in different databases (PubMed, ScienceDirect, Web of Science, and Cochrane Central Register of Controlled Trials). The following keywords were used: ((Screening) AND ((Tuberculosis) OR (TB) OR (TB)) AND (Children)). A manual search was also carried out in order to find relevant articles that fulfilled the specified criteria. Any inconsistencies were handled through consensus with the third author (XX).

Data were extracted based on the author, year, study design, sample size, results, and discussion. The primary outcome examined was the screening approach employed in paediatric TB cases.

RESULTS

Study characteristics

Overall, we identified five prospective or cohort studies for our systematic review. There were three systematic reviews and five case reports. This study included 14,424 patients in total. These studies all focused on TB screening in pediatric patients, whose ages ranged from 0 to under 18 years old. The studies came from several countries, including Pakistan, India, China, South Korea, and the UK. The study conducted in Pakistan by Brooks, et al.14 had the biggest sample size. This analysis includes articles from 2017 through 2022. One study will be conducted in 2022, two in 2021, one in 2018 and one in 2017. Table 1 provides more information about the research' findings.

Screening of paediatric TB patients

Four studies included in this systematic review indicated that the TST and IGRA tests were utilized as the first screening in paediatric patients with probable tuberculosis. Brooke et al.[14] emphasized a history of symptoms suggestive of

tuberculosis as initial screening, such as contact with a TB patient in the previous two years and symptoms such as swollen glands, cough for more than two weeks, fever for more than two weeks, sweating, and unexplained weight loss. Four more studies compared the TST test and the IGRA test as screening tools and discovered that the TST test was more successful in terms of accuracy and cost effectiveness.

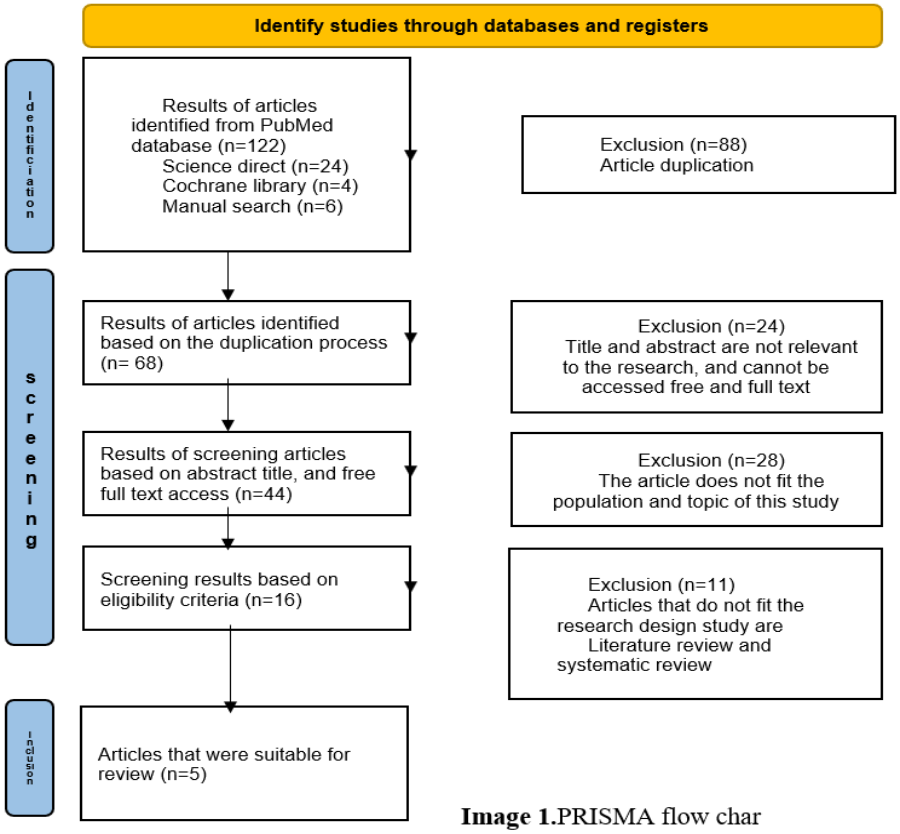

Image 1.PRISMA flow char

Table 1. Study Characteristics

No.	Author	Study design	Sample Quantity	Country	Age	Child TB screening points	Discussion
1	Brooks, et al 2022[14]	Prospective study (2014-2016)	5880	Pakistan	0-14 years	Children were classified as "screened for TB" in this study, if the health worker took a history of: -Children patient -His caregiver The point in question: (a) whether the child has been in contact with someone who has TB in the past two years, (b) whether the child currently has the following symptoms: swollen glands, cough for more than two weeks, fever for more than two weeks, sweating, and unreasonable weight loss, fever that lasts for two weeks or more, night sweats, and unexplained weight loss (or failure to grow)	-Patients undergo history taking, if one of the points is positive then proceed with screening then patient with positive screening result proceed to underwent physical examination, chest X-Ray, complete blood, Gene Xpert test. -In this study, there was a high incidence of TB in children with more than half of the diagnosed cases are below 5 years old. -This intervention provides screening across all ages of children and is implemented in multiple health facilities.
2	Sun, et al, 2021[15]	Prospective study (2013-2015)	6202	China	Average age 4.76 years	Latent tuberculosis infection (LTBI) screening method through examining Tuberculin skin test (TST) and interferon- γ release assay (IGRA) T-SPOT.	-Patients who screened positive for tuberculosis then evaluated and divided into three groups: no contact, risk of contact with caregivers, and no risk of contact from caregivers. -Positive TST screenings were more common in all three groups than IGRAs

No.	Author	Study design	Sample Quantity	Country	Age	Child TB screening points	Discussion
							-IGRA test may be an alternative to TB screening in addition to the use of TST.
3	Shon, et al, 2018[16]	Cohort	1000	South Korea	< 18 years old	This study compared the cost of TB screening in adolescents < 18 years of age, such screening using -Quantiferon-TB Gold In-Tube (QFT-GIT) -Tuberculin Skin Test (TST) -TST/QFT-GIT	-At a cost of $52,566, screening with the TST technique alone might stop 1.6 times as many TB cases. -The QFT-GIT method alone prevented twice as many TB cases, albeit at a greater overall cost of (US$108,435) -The TST/QFT-GIT two-step treatment costs US$75,267 more than TST alone yet prevents 1.3 times as many TB cases. -So, screening using TST is favourable compared to other strategies and is more cost effective.
4	Surve, et al, 2021[17]	Prospective study	950	India	< 5 years	In this study, TB screening in children using TST and QFT-TB gold plus if positive for one of these tests, then a follow-up test using Gene Xpert and a chest photograph.	-This study recommends the use of TST and QFT-TB for screening the diagnosis of latent TB in children less than 5 years of age. -This study highlights the need for screening undernourished children to consider repeating the IGRA test in TST positive cases according to the *window period* and exposure risk.
5	Kampmann, et al 2017[18]	Prospective study (2011-2014)	392	UK	6 years (2.5-11)	This study screened TB patients with : -History of symptoms potentially suggestive of a TB diagnosis -Discovery of TST and or IGRA tests	Based on the initial screening, the patient was further evaluated with : -History -Physical examination -TST and IGRA screening -Chest photo -Microbiology -HIV test Used as the first screening at the first visit are the TST and IGRA tests.

DISCUSSION

The first step in obtaining a diagnosis is TB screening. Brooks et al. discovered that an intense, child-focused TB patient-finding strategy was extremely effective across all ages of children screened in a prospective trial of 3880 children aged 0-14 years in Pakistan. The program depended mainly on clinical TB diagnosis and sputum samples. This emphasizes the relevance of TB history, physical examination, contact and exposure history, and chest X-ray findings in diagnosing children with TB, as well as the need for more accurate clinical prediction techniques.[19]

According to other research, aside from taking a past medical history, further procedures such as TST and IGRA tests are required for TB screening. Sun et al., 2021 conducted a prospective study on 6202 Chinese children with an average age of 4.76 years. The Tuberculin skin test (TST) and T-SPOT interferon-release assay (IGRA) are used to screen for latent tuberculosis infection (LTBI). Positive results are more commonly found in patients who are screened using TST rather than IGRA. In addition to TST, the IGRA test can be used for tuberculosis screening.[20]

In terms of cost effectiveness, Shon et al. did a cohort study on 1000 children aged 18 years in South Korea. In terms of cost, the TST/QFT-GIT testing approach was more expensive than the TST test alone. This is because the TST/QFT-GIT testing method incurs more expenditures and is less effective at preventing TB cases. TST is thus the most cost-effective and successful approach, and our findings are consistent with those of Steffen et al. for Brazilian contact screening.[21]

Tuberculin Skin Testing (TST) is one of the techniques used to determine if a person has Mycobacterium TB infection. TST is a simple and low-cost test that uses tuberculin purified protein derivatives with good sensitivity (about 75%-90%) but limited specificity.[22] A skilled healthcare worker should read the skin test reaction between 48 and 72 hours following the injection. If a patient does not return within 72 hours, testing should be rescheduled. The TST reaction should be

measured in mm of induration. The reader should not quantify erythema (redness) as the positive measurement. The induration area's diameter should be measured on the forearm (perpendicular to the long axis). The interpretation of this skin test is based on two factors: the measurement of induration in millimetres and a person's risk of contracting tuberculosis or developing tuberculosis disease if infected.[23]

TST is the recommended testing procedure for children under the age of five. It should be noted that the American Academy of Pediatrics (AAP) recommends TST or interferon-gamma release assay (IGRA) in children aged 2 years and up. In children who have previously received BCG immunization, IGRA is preferred to avoid false positive TST findings produced by previous BCG vaccination. TST is only contraindicated for those who have had severe reactions to previous TST (e.g., necrosis, blistering, anaphylactic shock, or ulceration). The IGRA test is also the preferred way of testing for patients who have received the BCG TB vaccine.[23]

Interferon-Gamma Release Assays (IGRAs) are blood tests used to detect Mycobacterium tuberculosis infection. In the United States, two IGRAs test kits that have been approved by the Food and Drug Administration (FDA) are commercially available. These are the QuantiFERON® or TB Gold In-Tube test (QFT-GIT) and the SPOT® or TB Test (T-Spot). The sensitivity and specificity of IGRAs generated from pooled data were 74% (95% CI: 0.65-0.82) and 78% (95% CI: 0.68-0.86), respectively.[24] IGRA determines a person's immunological response to M. tuberculosis. The advantages of this test include the fact that it only requires one patient visit, that results can be obtained in less than 24 hours, that it does not affect the results of subsequent tests, and that a prior BCG (bacille Calmette-Guérin) vaccination does not result in falsely positive IGRA results.[25] The test does have certain limitations, such as the requirement that the blood sample be processed within 8 to 30 hours of collection and the possibility that errors in the collection, transportation, or running and interpretation of the level determination could reduce the IGRA's accuracy.[25]

Clinical examination can be used to make a diagnosis of tuberculosis. This includes obtaining a history of TB-related symptoms and signs, getting a chest X-ray, and, if necessary, checking for M. tuberculosis in sputum or other clinical samples. Epidemiological and historical data should be considered while making the diagnosis of M. tuberculosis infection. In all circumstances where the CDC advises TST for the diagnosis of M. tuberculosis infection, IGRAs can be used instead of TST (but not in addition to it), with particular preferences and concerns. Using alternative tests (such as IGRAs or FDA-approved TSTs) is a legitimate medical and public health procedure, regardless of the indications. Due to the lack of information on the usage of IGRAs, caution should be applied when interpreting results when testing particular populations. People who have received BCG (as a vaccination or as a treatment) and those from groups who historically have had poor follow-up visit to have their TST read are best screened using IGRAs. Whereas the TST examination is preferred over IGRAs for testing children under 5 years of age. Similar to TST, IGRAs should not be used to test people at low risk of infection and low risk of disease from M. tuberculosis. Each TB control program and organization should assess the benefits and availability of IGRAs before prioritizing their usage. TST and IGRA testing on a regular basis is not advised. However, the outcomes of both tests might be helpful in certain circumstances.[25,26]

CONCLUSIONS

In screening for TB in children, history taking and TST and IGRA testing modalities can be considered. TST is preferred over IGRA for testing children under 5 years of age. IGRAs are preferred for testing people who have received BCG (either as a vaccine or for therapy) or patients with unclear TST results.

References

[1]. World Health Organisation (WHO). Operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. 2022. 56 p.
[2]. World Health Organisation. Systematic screening for active tuberculosis. Geneva, WHO/HTM/TB/201304. 2015;1-146.
[3]. Minnesota Department of Health. Paediatric Tuberculosis (TB) Risk Assessment. 2019;0127(March):1–3.
[4]. Mandalakas AM, Hesseling AC, Kay A, Preez K Du, Martinez L, Dinardo A, et al. Early View Original article Tuberculosis prevention in children: A prospective community based study in South Africa. 2020;
[5]. Siddhi PS, Raveendranath R, Puligari P, Chinnaswamy A, Song R, Welch SB. A systematic review on correlates of risk of TB disease in children and adults. Indian Journal of Tuberculosis. 2023;70(2):197-213.
[6]. Philip RT, Feucht UD. Challenges in the provision of tuberculosis preventive therapy to children in Gauteng Province, South Africa. SAJCH South African Journal of Child Health. 2022;16(1):18-21.
[7]. UNICEF. Desk Review: Paediatric Tuberculosis with a Focus on Indonesia i Paediatric Tuberculosis with a Focus on Indonesia Desk revIew. 2022;4-30.
[8]. Krause V. Policy recommendation: latent tuberculosis infection screening and treatment in children in immigration detention. Communicable diseases intelligence quarterly report. 2015;39(4):E597-8.
[9]. Triasih R, Rutherford M, Lestari T, Utarini A, Robertson CF, Graham SM. Contact investigation of children exposed to tuberculosis in South East Asia: A systematic review. Journal of Tropical Medicine. 2012;2012.
[10]. Rahmawati A, Utomo B, Makhfudli M. Contact Investigation and Preventive Therapy as Tuberculosis prevention in Children with Tuberculosis Household Contact: A Systematic Review. Ners Journal. 2020;15(1 Special Issue):178-87.

[11]. Rood azad muhammad, Bhawan N. Collaborative Framework to Address the Burden of Tuberculosis among Children and Adolescents. ministry of health and family welfare government of india. 2021;40.
[12]. Togun TO, MacLean E, Kampmann B, Pai M. Biomarkers for diagnosis of childhood tuberculosis: A systematic review. PLoS ONE. 2018;13(9):1-19.
[13]. Lamb GS, Starke JR. Tuberculosis in infants and children. Tuberculosis and Nontuberculous Mycobacterial Infections. 2017;541-69.
[14]. Brooks MB, Dubois MM, Malik AA, Ahmed JF, Siddiqui S, Khan S, et al. Age-specific effectiveness of a tuberculosis screening intervention in children. PLoS One. 2022 Feb 1;17(2 February).
[15]. Sun L, Qi X, Guo Y, Qi H, Li J, Wu X, et al. Tuberculosis infection screening in children with close contact: a hospital-based study. BMC Infect Dis. 2021 Dec 1;21(1).
[16]. Sohn H, Kim HY, Lee SH. Cost-effectiveness of contact screening strategies for tuberculosis among high-school adolescents in South Korea. International Journal of Tuberculosis and Lung Disease. 2018 May 1;22(5):496-503.
[17]. Surve S, Bhor V, Naukariya K, Begum S, Munne K, Tipre P, et al. Discordance between TST and QFT-TBGold Plus for Latent Tuberculosis Screening among Under-Five Children: An Interim Analysis. J Trop Pediatr. 2021 Dec 1;67(6).
[18]. Kampmann B, Seddon JA, Paton J, Nademi Z, Keane D, Williams B, et al. Evaluating UK national guidance for screening of children for tuberculosis a prospective multicentre study. Am J Respir Crit Care Med. 2018 Apr 15;197(8):1058-64.
[19]. Brooks MB, Dubois MM, Malik AA, Ahmed JF, Siddiqui S, Khan S, et al. Age-specific effectiveness of a tuberculosis screening intervention in children. PLoS ONE. 2022;17(2 February):1-12.
[20]. Sun L, Qi X, Guo Y, Qi H, Li J, Wu X, et al. Tuberculosis infection screening in children with close contact: a hospital-based study. BMC Infectious Diseases. 2021;21(1):1-10.
[21]. Sohn H, Kim HY, Lee SH. Cost-effectiveness of contact screening strategies for tuberculosis among high-school adolescents in South Korea. International Journal of Tuberculosis and Lung Disease. 2018;22(5):496-503.
[22]. Xu M, Lu W, Li T, Li J, Du W, Wu Q, et al. Sensitivity, Specificity, and Safety of a Novel ESAT6-CFP10 Skin Test for Tuberculosis Infection in China: 2 Randomised, Self-Controlled, Parallel-Group Phase 2b Trials. Clinical Infectious Diseases. 2022;74(4):668-77.
[23]. CDC. Tuberculin Skin Testing What is it? How is the TST Administered? How Are TST Reactions Interpreted? Classification of the Tuberculin Skin Test Reaction. CDC.gov. 2020; (September).
[24]. Wen A, Leng EL, Liu SM, Zhou YL, Cao WF, Yao DY, et al. Diagnostic Accuracy of Interferon-Gamma Release Assays for Tuberculous Meningitis: A Systematic Review and Meta-Analysis. Frontiers in Cellular and Infection Microbiology. 2022;12(April):1-10.
[25]. Centres for Disease Control and Prevention. TB Elimination Interferon-Gamma Release Assays (IGRAs)-Blood Tests for TB Infection What are they? How do they work? 2016;3-5.
[26]. Lee JE, Kim HJ, Lee SW. The clinical utility of tuberculin skin test and interferon-γ release assay in the diagnosis of active tuberculosis among young adults: A prospective observational study. BMC Infectious Diseases. 2011;11(1):96.