http://ejournal.seaninstitute.or.id/index.php/healt
Jurnal eduhealth, Volume 14, No 02, 2023
E-ISSN. 2808-4608

Diagnosis Of Pulmonary Tuberculosis In Children Systematic Literature Review

Sara Fadila[1], Tri Yunis Miko Wahyono[2]
[1,2] Departemen Epidemiologi, Fakultas Kesehatan Masyarakat, Universitas Indonesia

ARTICLE INFO

Keywords:
Aloe vera gel,
facial wash aloe vera,
Acne vulgaris.

Email :

ABSTRACT

Tuberculosis (TB) is one of the top ten causes of death caused by infectious agents in Indonesia. In children, more than 96% of TB-related deaths are due not receiving anti-TB treatment, this is significant challenges to diagnosing TB in children. This study aims to analyze the methods of diagnosing TB in children. The research design used a systematic literature review which summarized and compared as many as 12 studies published through Pubmed and Sciencedirect in 2010-2022 concerning methods of diagnosing TB in children. Descriptive analysis showed that the subjects were male with an average age of 4.5 years. Diagnostic enforcement of TB in children found that the scoring system was the most widely used method to diagnosing TB in children with a high sensitivity and specificity, sensitivity and specificity using the modified Edwards Score was 93.3% and 95%. Furthermore, the PCR method by detecting the IS6110 gene using gastric lavage specimens showed sensitivity and specificity was 100% and 98.18%. The QFT-GIT diagnostic method showed a sensitivity of 82.6%, and Xpert MTB/RIF of 76%.

1. INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. TB in children is a form of TB that affects children aged 0-14 years. In 2021, Pulmonary Tuberculosis ranked second as the leading cause of death due to a single infectious agent after COVID-19. However, the reported number of people diagnosed with TB in 2020 compared to 2017 and 2019 has decreased by 18% from 7.1 million to 5.8 million, and this reporting also affects children who are diagnosed with TB, where 69% of children under the age of five are not diagnosed with TB [1].

Indonesia is the country with the second highest burden of TB cases in the world. Based on the Indonesian Ministry of Health in 2022, only 443,235 cases of TB were detected, which accounts for only 45.7% of the estimated total of 969,000 TB cases. It is estimated that there are still 525,765 (54.3%) undetected and unreported cases. Meanwhile, the estimated number of TB cases in children in Indonesia is 42,187, and only around 56% of these cases have been found and treated [2]. In the management of TB cases in children, accurate TB diagnosis is a significant point, as there are numerous challenges in sample collection and bacteriological examination methods. Therefore, this research will review studies on diagnosing TB in children.

2. METHOD

This study utilizes a literature review method that summarizes, compares, and analyzes several studies on diagnosing Pulmonary TB and Latent Pulmonary TB in children. The selected articles are open-access articles published through PubMed, Sciencedirect, and international scientific journals in English, which provide information on methods for diagnosing Pulmonary TB and Latent Pulmonary TB in children published from January 1, 2010, to October 31, 2022, using the keywords "diagnostic," "Tuberculosis or Mycobacterium tuberculosis," and "children." Exclusion criteria include systematic literature reviews and meta-analyses, treatment outcome evaluations related to tuberculosis infection, and evaluations related to tuberculosis immunization programs.

The article selection process follows the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) method in each stage. After selecting the articles that meet the inclusion

and exclusion criteria using PRISMA, the articles will undergo summarizing, comparing, analyzing, and synthesizing stages. In the summarizing stage, systematic summaries will be created and presented in a table, including researcher information, study location, journal name, research objectives, study design, data sources, sample size, and research findings. Next is the comparing stage, where the results will include comparisons based on research objectives, methods, results, and conclusions from the reviewed articles. Then, in the analyzing stage, each article will be examined to ensure that the diagnostic methods for Pulmonary TB in children meet the inclusion and exclusion criteria, and a qualitative decision will be made on whether the article is suitable for inclusion in the literature review or not. The final stage is synthesis, where the key findings or general conclusions from the reviewed articles will be extracted to evaluate the methods that can assist in diagnosing Pulmonary TB in children.

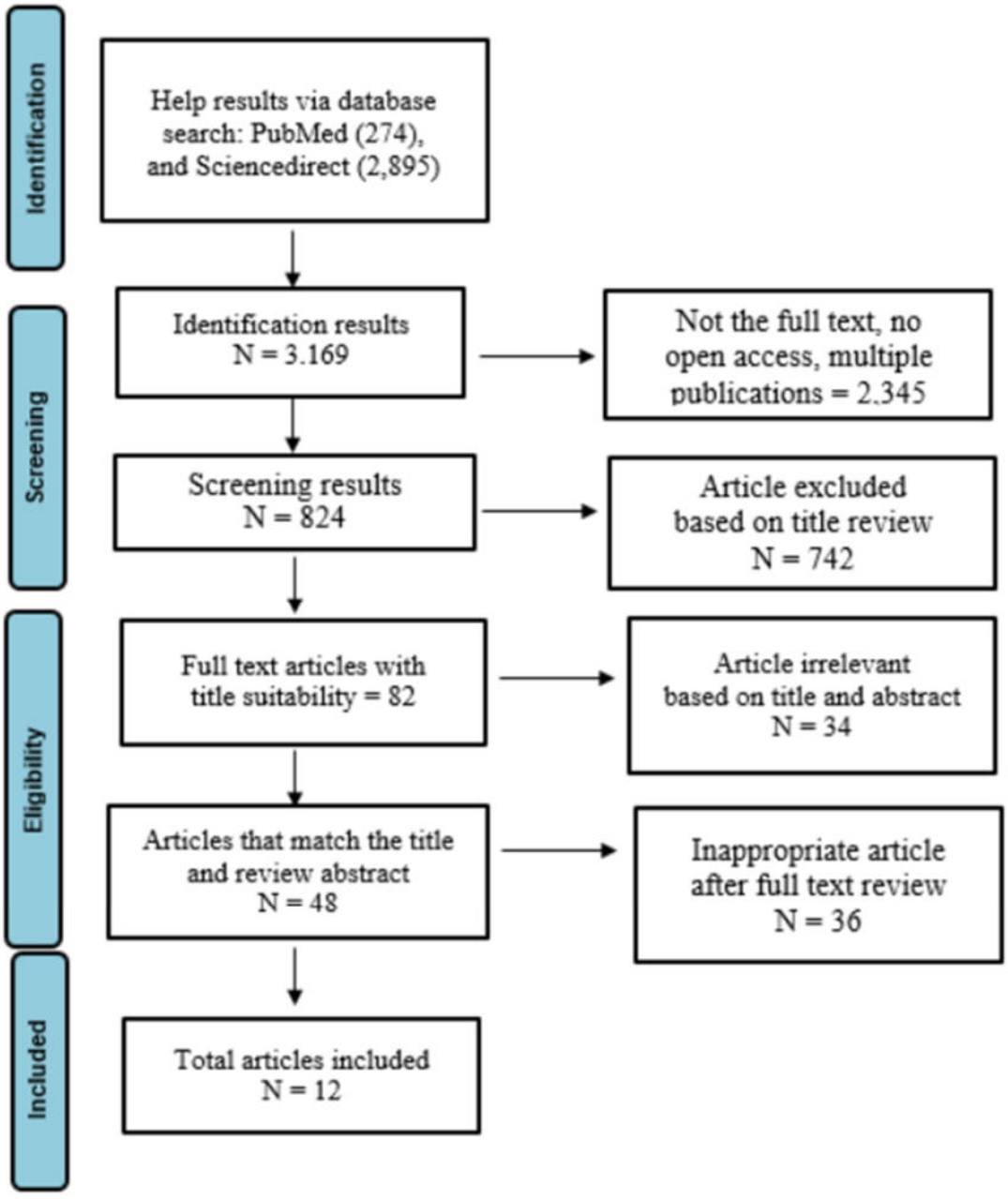

Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) method

3. RESULTS AND DISCUSSION

Based on the search results using the above keywords or terminology, sixteen articles were selected from various countries, with subjects ranging from healthcare facilities to different populations and varying study durations. A systematic summary of the fifteen journals is presented in Table 1.

Table 1. Summary of Reviewed Scientific Journals

No	Writer, Research sites, Journal	Objective, Research design	Data Source and Number of Samples	Results
1	Lodha R, et.al. [3] (India) International Journal of Tuberculosis and Lung Disease. 2013: 17: 1383-1388	Comparing the performance of the Quanti-FERON®-TB Gold In-Tube test (QFT-GIT) with the tuberculin pinch test (TST) in the diagnosis of childhood tuberculosis. Randomized controlled trial	Data source based on 2 tertiary care hospitals in New Delhi, India. Total sample was 362 children aged less than 15 months (median age 115.5 months, IQR 73–144)	TST results were positive in 337 children (93%) and QFT-GIT in 297 children (82%). The sensitivity of the culture-confirmed TST was 90.5% and the culture-confirmed QFT-GIT was 82.6%. QFT-GIT positivity rate correlated with TST induration (P<0.001).
2	Santos S, et al.[4] (Brazil) J Bras Pneumol. 2013: 84-91	To evaluate the diagnosis of pulmonary tuberculosis of indigenous children and adolescents under the age of 15 years with smear-negative using the modified Brazilian National Ministry of Health Scoring System (mBNMH-SS). Retrospective descriptive	Data source from Equipes de Saúde Indígena (ESI, Indigenous Health Care Team) of Distrito Sanitário Especial Indígena de Mato Grosso do Sul (DSEI-MS) J The sample size was 49 children aged less than 15 years who were natives from the state of Mato Grosso do Sul, Brazil who were treated for TB between 2007 and 2010.	In the diagnoses made by ESI, the Brazilian NMH Rating System was used in 45% of cases, but was not used in 45%. and does not apply in 7% of cases (due to extrapulmonary TB). In addition, no diagnostic criteria were recorded in 3% of cases The modified Brazilian NHM Health Assessment System for the diagnosis of pulmonary tuberculosis in smear-negative indigenous children and adolescents can be used by 30 patients (61%), whereas scores cannot be assigned to 14 patients (29%) due to incomplete information, and in 5 patients (10%) was extrapulmonary TB.
3	Nicol M, et.al. (Afrika Selatan) [5]	Assessing the diagnostic accuracy of urinary lateral flow lipoarabinomannan	Data source from Nolungile primary health facility and Red Cross War	The lateral flow urine lipoarabinomannan test showed poor accuracy against reference

		and ELISA tests, with mycobacterial culture as the reference standard	Memorial Children's Hospital.	standards with a sensitivity of 48.3% and a specificity of 60.8% (56·1–65·3). The ELISA test showed poor sensitivity in children without HIV, which was 3.0% and 0% in children with HIV. The overall specificity is 95.7%.
	The Lancet Global Health. 2014: 2: e278-84	Prospective cohort	Total sample was 535 children aged less than 15 years (median age 42.5 months, IQR 19.1–66.3)	
4	Giang D, et.al. (Vietnam) [6]	Comparing Xpert MTB/RIF with sputum smear and culture	Data source from TB referral hospital in Ho Chi Minh City, Vietnam.	Sputum smear sensitivity was 9.2%, Xpert MTB/RIF was 20.6%, and culture with MGIT was 29.0% Sputum specificity was 100%, Xpert MTB/RIF was 94.7%, culture with MGIT was 94.7%. Xpert is more sensitive than smear (P = <0.001) and less sensitive than MGIT (P = 0.002)
	BMC Infectious Diseases. 2015:15:70	Prospective cohort	Total sample was 150 HIV-negative children aged less than 15 years (median age 18 months, IQR 5-170)	
5	Brent A, et.al. (Kenya)[7]	Comparing the Xpert MTB/RIF examination, MGIT culture, and MODS (Microscopic Observation Drug Susceptibility) for the diagnosis of TB in children.	Data source from Coast Provincial General Hospital and Kilifi County Hospital	The specificity of 1164 specimens from 892 children showing Xpert MTB/RIF was 100% (99.7–100%). For MGIT, MODS and Xpert MTB/RIF Culture Sensitivities were 88%, 71% and 76%, respectively, among 104 true positive specimens (culture and/or Xpert MTB/RIF positive).
	Scientific Reports. 2017: 1: 7	Prospective cohort	The number of samples was 1442 children with a median age of children with confirmed TB, namely 53 months, IQR 21-112	
6	Osman A, et.al. (Sudan) [8]	Determining the best method for diagnosing TB in children using gastric lavage specimens using the PCR method by detecting the IS6110 gene, ZN strain, auramine strain, and TST	Data sources were Elbolok Hospital, Jafar Ibn Owf Hospital, Elasha'ab Education Hospital, Soba University Hospital and Amal Academy Hospital.	All tests showed a sensitivity of 100% for TST, 59.38% for Auramine strain, 43.75% for ZN strain and 100% for PCR. While the specificity of TST was 67.27%, Auramine strain was 98.18%, ZN strain was 89.79% and PCR was 98.18%.
	International Journal of Mycobacteriology. 2014: 3: 252-258	Kros-sectional	The number of samples was 197 children aged less than 18 years with a median age of 8 years.	

7	Chisti M, et.al. (Bangladesh) [9] PLoS ONE. 2015: 10.	Evaluating the method of measuring antibodies in lymphocyte supernatants (ALS) for the diagnosis of TB in severely malnourished children suspected of having pneumonia. Prospective cohort	Source of data from RS International Center for Diarrhoeal Disease Research (ICDDRB), Dhaka. The total sample was 224 children aged less than 5 years with severe malnutrition and suspected pneumonia.	Among the 224 children who had ALS analysis, 5.4% had confirmed TB. ALS is positive in 40% of children and negative in 39% of children. The sensitivity of ALS when comparing confirmed TB to non-TB was only 67% (95% CI: 31–91%) with a specificity of 51% (95% CI: 42–60%).
8	Andreas N, et.al. (Gambia) [10] Scientific Reports. 2020: 10.	Identify metabonomic strategies with serum biomarkers to diagnose pediatric TB Prospective cohort	Data source from the TB clinic for children in the Gambia MRC unit. The number of samples is 112 children.	Data obtained using H NMR showed a sensitivity of 69%, with a specificity of 83%. The most discriminatory MS data show a sensitivity of 67%, with a specificity of 86%.
9	David S, et al. (Brazil) [11]	Analyze and compare several scoring systems (using four scoring systems: Kenneth Jones, Tidjani, Ben Marais, Ministry of Health of Brazil) in diagnosing TB in HIV-infected children and adolescents in referral hospitals in Rio de Janeiro Retrospective Cohort	Data source from TB and HIV referral hospital for children, Municipal Jesus Hospital. The number of samples is 121 children aged less than 15 years	The Ben Marais (BM) score had the highest sensitivity (93.8%) when microbiological data was included in the analysis, while the Ministry of Health's score with a cut-off of 30 points had the highest sensitivity (85.0%) when microbiological data was not included. Tidjani's score had the highest specificity (93.0%) and accuracy (86.7% and 67.8%), regardless of whether or not microbiological data was included. While the sensitivity of the BM scoring decreased only slightly in the absence of microbiological data, namely to 84.4%, the sensitivity of the other scores decreased by about half after microbiological data were excluded. On

	International Journal of Infectious Diseases. 2017: 150-155, 59			the other hand, the specificity of all scoring systems has no impact if microbiological data is included or not.
10	Yassin M, et.al. (Etiopia) [12]	Analyzing interferon-gamma (INFγ) and IP10 expression in children with TB infection to assess latent and active TB.	Data source from Awassa Health Center, Major Bushullo Health Center and Hawassa University Referral Hospital	Children with confirmed TB have a risk of INFγ (+) of 59.3% and children with a history of contact with TB have a risk of INFγ (+) of 44.7%. IP10 sensitivity is 81.8% and specificity is 96.5%.
	PLoS ONE. 2011: 6	Kros-sectional.	The number of samples is 295 children aged less than 15 years.	
11	Koura, et al. (Mesir) [13]	To compare the validity of Edwards' score and modified Edwards' score in diagnosing pediatric pulmonary tuberculosis	Source of data from Al-Azhar University Hospital	The sensitivity and specificity for the diagnosis of pulmonary tuberculosis were higher for the modified Edwards score than for the previous Edwards score. Sensitivity and the specificity of the modified Edwards scoring was 93.3% and 95% while the previous Edwards scoring was 86.7% and 88.30%.
	Clinical Medicine and Diagnostics, (2015), 39-44, 5(3)	cross-sectional	The number of samples is 120 children.	
12	Sanogo B, et al. (Burkina Faso) [14]	Evaluating the QFT-GIT in diagnosing active TB in HIV-infected children and suspected TB	Source of data from Souro Sanou University Central Hospital (CHUSS), Bobo-Dioulasso	The sensitivity of the QFT-GIT is 20.69% and the specificity is 96.55%.
	PLoS ONE, (2020), 15(11 November)	Prospective cohort	The number of samples was 63 children aged less than 13 years who were infected with HIV with a median age of 8 years (IQR 6-10)	

Characteristics of the twelve reviewed articles revealed that the research subjects were male with an average age of 4.5 years. Based on the study designs, there were 6 studies with prospective cohort designs, 3 studies with cross-sectional designs, 1 study with a descriptive retrospective design, 1 study with a retrospective cohort design, and 1 study with a randomized controlled trial design.

Regarding the research objectives of the twelve reviewed articles, three articles evaluated and compared the use of scoring systems in diagnosing TB in children, two articles evaluated the use of the

Xpert MTB/RIF method compared to sputum microscopy in diagnosing TB in children. Furthermore, two articles diagnosed TB in children using interferon-gamma release assay (IGRA) with the QuantiFERON®-TB Gold In-Tube test (QFT-GIT) compared to the Mantoux or tuberculin skin test (TST), one article also used IGRA to evaluate the profiles of Interferon-gamma (INFγ) and Interferon-gamma-induced protein 10 (IP10) in active and latent TB in children, two articles performed TB diagnostics with the Mantoux or tuberculin skin test (TST). Additionally, one article compared the method of urine lateral flow lipoarabinomannan (LAM) test with the enzyme-linked immunosorbent assay (ELISA) method in diagnosing TB in children, one article compared Polymerase Chain Reaction (PCR), ZN strain, auramine strain, and TST methods using gastric lavage specimens in diagnosing TB in children, one article used serum biomarker methods to diagnose TB in children, and one article used the measurement of antibodies in lymphocyte supernatant (ALS) method to diagnose TB in children.

Based on the sensitivity and specificity of each method for diagnosing TB in children, PCR detecting the IS6110 gene using gastric lavage specimens showed the highest sensitivity of 100% and specificity of 98.18%. Scoring systems also showed reasonably high sensitivity and specificity, with the modified Edwards Scoring system at 93.3% and 95%, and the Tidjani Scoring system at 82.8% and 93%. The application of other scoring systems also yielded relatively high results, such as the Ben Marais Scoring system with a sensitivity of 93.8% and the Edwards Scoring system with a sensitivity of 86.7% and specificity of 88.30%. Furthermore, the method of diagnosing TB in children using INFγ and IP10 expression analysis showed a relatively high sensitivity and specificity for IP10 at 81.8% and 96.5%, respectively. QFT-GIT examination in diagnosing TB in children demonstrated the highest sensitivity at 82.6% with a specificity of 96.55%. Xpert MTB/RIF in diagnosing TB in children using sputum specimens showed a sensitivity range of 76% to 20.6%, with the highest specificity of 100%. One study measuring ALS in diagnosing TB in children showed a sensitivity of 67% and specificity of 51% when comparing confirmed TB cases to non-TB cases. Another study assessing the accuracy of diagnosing TB in children using urine lateral flow LAM test showed low sensitivity and specificity at 48.3% and 60.8%, respectively. This study also evaluated the accuracy of the ELISA test, which demonstrated low sensitivity in HIV-positive children (0%) and non-HIV children (3%). Another strategy for diagnosing TB in children utilized metabolomic serum analysis with H Nuclear Magnetic Resonance (NMR) spectroscopy and untargeted ultra-performance liquid chromatography-mass spectrometry (UPLC-MS).

H NMR showed a sensitivity of 69% and specificity of 83%, while UPLC MS demonstrated a sensitivity of 67% and specificity of 86%.

Discussion

In this study, the average occurrence of TB in children was found to be 4.5 years. This result is consistent with the studies conducted by Marcy et al. and Nurwanti et al. in Sumedang, which found the highest incidence of TB in children aged 4-9 years [15] [16]. This study also showed that TB occurred more frequently in male children. Studies conducted by Sun et al. and Nicol et al. yielded similar results, indicating a higher incidence of TB in male children [17] [5].

In selecting diagnostic methods for confirming TB in children, the Indonesian Ministry of Health formulated four common criteria for diagnosing TB in children: bacteriological confirmation of TB, typical clinical TB symptoms, evidence of TB infection indicated by a positive tuberculin test or close contact with TB patients, and suggestive chest X-ray findings. The Ministry of Health also established a scoring system that refers to these criteria to facilitate its application in primary healthcare facilities [18]. In this study, four articles were found that used and compared various scoring systems for diagnosing TB in children, such as Edwards and modified Edwards scoring systems, Kenneth Jones, Tidjani, Ben Marais, and the scoring system of the Brazilian Ministry of Health. The study conducted by David et al. showed that the Tidjani scoring system had a high sensitivity of 93% with an accuracy of 86.7% and 67.8%, regardless of the inclusion of microbiological results. The sensitivity of the Ben Marais scoring system decreased from 93.8% to 84.4% when microbiological test results were not included. These findings are consistent with the study conducted by Rejeki et al., where 74% of children diagnosed with TB had scoring results of more than 6 points [19]. A study conducted by Farisatrianto

in the South Tangerang City Primary Health Center showed a significant relationship between the occurrence of overdiagnosis of TB in children and the availability of TB scoring forms [20].

In this study, the PCR method showed the best sensitivity and specificity, namely 100% and 98.18%. PCR is a new method that is more sensitive and specific in diagnosing TB in children based on nucleic acid amplification, specifically the IS6110 target. The study conducted by Tiwari et al. showed high sensitivity and specificity of the PCR method, at 93.55% and 92.75%, respectively [21]. However, a study conducted by Kabir et al. using the PCR method showed lower sensitivity and specificity, at 87.5% and 43%, respectively, in diagnosing TB in children [22]. A study conducted by Kaswandani et al., comparing PCR and tuberculin tests in four hospitals in Jakarta, found sensitivity and specificity of PCR at 69% and 57%, respectively, and concluded that PCR examination was not superior to the tuberculin test [23].

IGRA tests have now become an alternative choice in assisting the diagnosis of TB in children. There are two types of IGRA tests. The first type uses the principle of blood incubation with Early Secretory Target-6 (ESAT-6) under the trade names QFT/QFT-G (Quantiferon TB and Quantiferon TB Gold), and Culture Filtrate Protein-10 (CFP-10) using the Enzyme-Linked Immuno Spot assay under the trade name T-spot TB [24]. In addition to these two types of IGRA tests, there is an IGRA test that analyzes INFγ and IP10. In this study, the sensitivity of IP10 was found to be 81.8% and the specificity was 96.5%. The study conducted by El-Sheikh et al. showed a sensitivity and specificity of IP10 in diagnosing TB in children of 94.2% and 95.2%, respectively [25]. However, a study conducted by Sudbury et al. found low sensitivity and specificity of IP10, which were 80.7% and 86%, respectively [26]. Furthermore, in this study, the use of QFT-GIT in diagnosing TB in children showed the highest sensitivity of 82.6% with a specificity of 96.55%. The study conducted by Dayal et al. showed a lower sensitivity of QFT-GIT at 51.2% with a specificity of 48%.28 However, the diagnosis using IGRA has not been recommended by the Indonesian Ministry of Health (Kemenkes RI) because IGRA cannot differentiate between active TB and latent TB, and its use is not superior to the tuberculin test.

Xpert MTB/RIF is a rapid test that uses molecular nucleic acid amplification tests (NAAT) to diagnose TB and test for drug resistance in TB. The World Health Organization (WHO) has recommended the use of Xpert MTB/RIF (Xpert) as an initial diagnostic test, especially in developing countries and countries with a high TB burden. However, the results of several studies have shown low sensitivity, especially in important populations such as children and HIV-positive patients, due to its paucibacillary nature [27]. In this study, the consecutive sensitivities were found to be 76% and 20.6% with specificities of 100% and 94.7%. Another study conducted by Marcy et al. showed a sensitivity of Xpert MTB/RIF of 79.3% and a specificity of ≥97.5%. Another study found a sensitivity of 57.1% with a specificity of 98.9% [28].

The use of the ALS method is one of the methods based on biomarkers to assess the immune response to TB antigens [29]. In this study, ALS showed a sensitivity of 67% and a specificity of 51% in diagnosing TB in children. A study conducted by Sariko et al. using the ALS method to diagnose TB in adults showed a sensitivity of 92% and a specificity of 96% [29].

The urine LAM method is a WHO-recommended method for diagnosing TB in adults infected with HIV and with low CD4 counts or severe illness, and this recommendation has been extended to children infected with HIV [30].

In this study, the sensitivity and specificity of the urine LAM method were found to be relatively low at 48.3% and 60.8%, respectively, in diagnosing TB in children. These results are not far different from a study conducted by LaCourse et al., which showed a sensitivity of 43% and a higher specificity of 91% [30].

4. CONCLUSION

Based on the systematic literature review conducted by Koura et al. and David et al., it can be concluded that the diagnosis of TB in children using scoring systems has the advantage of being more easily applicable, especially in primary healthcare facilities. In this study, articles on the diagnosis of TB in children using PCR IS1660 and IGRA by analyzing INFγ and IP10 showed high sensitivity and specificity. However, their use is not superior to the tuberculin test, which is included in the scoring system for diagnosing TB in children.

REFERENCES

[1] G. WHO, "Global tuberculosis report 2022," *Glob Tuberc. Rep*, 2022.
[2] J. S. Sipayung, W. Hidayat, and E. M. Silitonga, "Faktor Risiko yang Memengaruhi Kejadian Tuberkulosis (TB) Paru di Wilayah Kerja Puskesmas Perbaungan," *J. Ilm. Kesehat. Masy. Media Komun. Komunitas Kesehat. Masy.*, vol. 15, no. 2, pp. 55–63, 2023.
[3] R. Lodha *et al.*, "Role of the QuantiFERON®-TB Gold In-Tube test in the diagnosis of intrathoracic childhood tuberculosis," *Int. J. Tuberc. lung Dis.*, vol. 17, no. 11, pp. 1383–1388, 2013.
[4] S. C. dos Santos, A. M. C. Marques, R. L. de Oliveira, and R. V. da Cunha, "Scoring system for the diagnosis of tuberculosis in indigenous children and adolescents under 15 years of age in the state of Mato Grosso do Sul, Brazil," *J. Bras. Pneumol. Publicação Of. da Soc. Bras. Pneumol. e Tisilogia*, vol. 39, no. 1, p. 84, 2013.
[5] M. P. Nicol *et al.*, "Urine lipoarabinomannan testing for diagnosis of pulmonary tuberculosis in children: a prospective study," *lancet Glob. Heal.*, vol. 2, no. 5, pp. e278–e284, 2014.
[6] D. C. Giang *et al.*, "Prospective evaluation of GeneXpert for the diagnosis of HIV-negative pediatric TB cases," *BMC Infect. Dis.*, vol. 15, pp. 1–10, 2015.
[7] A. J. Brent *et al.*, "Bacteriological diagnosis of childhood TB: a prospective observational study," *Sci. Rep.*, vol. 7, no. 1, p. 11808, 2017.
[8] A. L. Osman, N. S. Saeed, and M. M. Elhassan, "Polymerase Chain Reaction targeting insertion sequence IS6110 for the diagnosis of pulmonary tuberculosis among Sudanese children and young adults," *Int. J. mycobacteriology*, vol. 3, no. 4, pp. 252–258, 2014.
[9] M. J. Chisti *et al.*, "Validity of antibodies in lymphocyte supernatant in diagnosing tuberculosis in severely malnourished children presenting with pneumonia," *PLoS One*, vol. 10, no. 5, p. e0126863, 2015.
[10] N. J. Andreas *et al.*, "Performance of metabonomic serum analysis for diagnostics in paediatric tuberculosis," *Sci. Rep.*, vol. 10, no. 1, p. 7302, 2020.
[11] S. G. David *et al.*, "A comparison of tuberculosis diagnostic systems in a retrospective cohort of HIV-infected children in Rio de Janeiro, Brazil," *Int. J. Infect. Dis.*, vol. 59, pp. 150–155, 2017.
[12] M. A. Yassin *et al.*, "Can interferon-gamma or interferon-gamma-induced-protein-10 differentiate tuberculosis infection and disease in children of high endemic areas?," *PLoS One*, vol. 6, no. 9, p. e23733, 2011.
[13] H. Koura and A.-H. Mohammed, "Value of new modification of tuberculosis score in diagnosis of childhood pulmonary tuberculosis," *Int. J. Infect. Dis.*, vol. 16, p. e285, 2012.
[14] B. Sanogo *et al.*, "Performance of a lymphocyte t interferon gamma test (Quantiferon-TB gold in tube) in the diagnosis of active tuberculosis in HIV-infected children," *PLoS One*, vol. 15, no. 11, p. e0241789, 2020.
[15] O. Marcy *et al.*, "Performance of Xpert MTB/RIF and alternative specimen collection methods for the diagnosis of tuberculosis in HIV-infected children," *Clin. Infect. Dis.*, vol. 62, no. 9, pp. 1161–1168, 2016.
[16] M. A. Nurwanti, C. Chrysanti, and S. Sudarwati, "Application of Scoring System Components in Children Diagnosed with Tuberculosis in Jatinangor Primary Health Care, Sumedang," *Althea Med. J.*, vol. 4, no. 4, pp. 495–500, 2017.
[17] L. Sun *et al.*, "Use of Xpert MTB/RIF Ultra assay on stool and gastric aspirate samples to diagnose pulmonary tuberculosis in children in a high-tuberculosis-burden but resource-limited area of China," *Int. J. Infect. Dis.*, vol. 114, pp. 236–243, 2022.
[18] R. Kemekes, "Petunjuk Teknis Pelayanan Puskesmas Pada Masa Pandemi Covid-19." Kemenkes RI, 2020.
[19] A. P. Rejeki, U. A. Lantika, and S. Masria, "Gambaran Sistem Skoring Tuberkulosis Anak di Rumah Sakit Bhayangkara Indramayu Tahun 2019," *J. Integr. Kesehat. dan Sains*, vol. 3, no. 2, pp. 154–156, 2021.
[20] N. Farisatrianto, "Prevalensi overdiagnosis TB anak berdasarkan sistem skor TB anak dan faktor yang mempengaruhinya di puskesmas wilayah kota Tangerang Selatan periode Januari 2010-

Agustus 2013".

[21] S. Tiwari, G. Nataraj, S. Kanade, and P. Mehta, "Diagnosis of pediatric pulmonary tuberculosis with special reference to polymerase chain reaction based nucleic acid amplification test," *Int. J. Mycobacteriology*, vol. 4, no. 1, pp. 48–53, 2015.

[22] S. Kabir *et al.*, "Role of PCR method using IS6110 primer in detecting Mycobacterium tuberculosis among the clinically diagnosed childhood tuberculosis patients at an urban hospital in Dhaka, Bangladesh," *Int. J. Infect. Dis.*, vol. 68, pp. 108–114, 2018.

[23] N. Kaswandani, D. B. Setyanto, and N. N. Rahajoe, "Akurasi Polymerase Chain Reaction (PCR) Dibandingkan dengan Uji Tuberkulin untuk Diagnosis Tuberkulosis pada Anak," *Sari Pediatr.*, vol. 12, no. 1, pp. 42–46, 2016.

[24] R. RUSDIANA, "UBUNGAN UJI INTERFERON GAMMA DAN UJI TUBERKULIN PADA ANAK DENGAN KONTAK SERUMAH TUBERKULOSIS CORRELATION INTERFERON GAMMA TEST AND TUBERCULIN TEST IN CHILDREN WITH HOUSEHOLD CONTACT OF TUBERCULOSIS." Universitas Hasanuddin, 2013.

[25] N. El-Sheikh *et al.*, "Assessment of Interferon Gamma-Induced Protein 10 mRNA Release Assay for Detection of Latent Tuberculosis Infection in Egyptian Pediatric Household Contacts," *Int. J. Infect. Dis.*, vol. 109, pp. 223–229, 2021.

[26] E. L. Sudbury *et al.*, "Mycobacterium tuberculosis-specific cytokine biomarkers for the diagnosis of childhood TB in a TB-endemic setting," *J. Clin. Tuberc. other Mycobact. Dis.*, vol. 16, p. 100102, 2019.

[27] R. R. Atherton, F. V Cresswell, J. Ellis, S. B. Kitaka, and D. R. Boulware, "Xpert MTB/RIF Ultra for tuberculosis testing in children: a mini-review and commentary," *Front. Pediatr.*, vol. 7, p. 34, 2019.

[28] H. J. Zar, L. Workman, W. Isaacs, K. Dheda, W. Zemanay, and M. P. Nicol, "Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: a prospective study," *lancet Glob. Heal.*, vol. 1, no. 2, pp. e97–e104, 2013.

[29] M. Sariko *et al.*, "Evaluation of the antibody in lymphocyte supernatant assay to detect active tuberculosis," *PLoS One*, vol. 12, no. 1, p. e0169118, 2017.

[30] S. M. LaCourse *et al.*, "Stool Xpert MTB/RIF and urine lipoarabinomannan (LAM) for diagnosing tuberculosis in hospitalized HIV-infected children," *AIDS*, vol. 32, no. 1, p. 69, 2018.