CONCORDANCE OF THE SCORING SYSTEM AND *GENE-XPERT* MTB/RIF TO DIAGNOSE CHILDHOOD TUBERCULOSIS IN PRIMARY HEALTH CARE

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ARTICLE INFO	ABSTRACT
Keywords: Pediatric Pulmonary Tuberculosis;Scoring System;Gene-Xpert MTB/RIF	The Scoring system developed by the Indonesian childhood tuberculosis working group is an alternative way to clinically diagnose TB in children especially in primary health care, however, bacteriological confirmation using gene-Xpert MTB/RIF is still highly recommended. To compare childhood TB scoring system performance and gene-Xpert MTB/RIF results among children suspected of tuberculosis in primary health care. This study was conducted on 47 children who went to the primary health care facility. The design of this study was a cross-sectional study with a conformity test (kappa). Samples that meet the inclusion criteria are recorded in the form of age, gender, weight, height, nutritional status, previous history of BCG vaccination, and physical examination, then the data is entered into the scoring system. Sputum is obtained by induction and then examined using gene-Xpert. The number of boys and girls suspected of having pulmonary TB is almost the same. About 72% of children experience malnutrition and a positive BCG score is found in more than half of the samples. There were 51.1% of children in contact with positive smear adult TB patients. Based on the scoring system obtained a TB diagnosis of 74.5% whereas based on gene-Xpert MTB/RIF examination only 4.3% of children confirm TB. There is no match between the two (conformity test with the kappa values of -0.01 and suitability 0.397). There is no compatibility in making a diagnosis of pediatric tuberculosis between the scoring system and gene-Xpert MTB/RIF at the primary health care facility.
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1. INTRODUCTION

In this day the diagnosis of pulmonary tuberculosis (TB) in children is still a serious problem. This problem due to the difficulties in diagnosing pediatric pulmonary TB compared to adult pulmonary TB.1 Early diagnose of TB is very important to control the incidence of TB disease. Cases that are late to detected and treated can develop into severe TB such as TB meningitis, TB spondylitis, or miliary it can causing morbidity and mortality in children.2 The data of TB in Indonesia shows the proportion of TB cases in children in 2010 was 9.4%, then to 8.5% in 2011 and 8.2% in 2012. The proportion of TB cases in West Sumatra has 7.9% of all TB cases in 2012.3 TB Child cases are grouped in the age group 0-4 years and 5-14 years, with the number of cases in the age group 5-14 years higher than the age group 0-4 years. Positive

cases by smear in children in 2010 were 5.4% of all cases of child TB, while in 2011 it rose to 6.3% and in 2012 it was 6%.3 .

The current diagnosis approach is still not sensitive, especially in daily practice in primary health care facilities. A Scoring system is an alternative to diagnose pediatric pulmonary TB, both in primary and secondary services. This system is very useful especially in developing countries with high endemicity so that cases of pulmonary TB can be immediately found and treated. Indonesia has a scoring system that has been validated by IDAI, the Ministry of Health, and WHO.3 Currently, a new diagnostic method is being used using the PCR principle with minimal cost. This technique uses the gene-Xpert (Xpert) MTB/RIF engine. This method only requires a minimum inspection action in the sample and can provide two results at once, namely detection of MTB germs and detection of rifampicin resistance using the real-time PCR (rt-PCR) method in a short time, ± 2 hours.4-6 Based on ISTC 2014, Xpert MTB/RIF has been included in the standard diagnosis of childhood TB.7

The scoring system is still difficult to do because of limited facilities in primary health services and a lack of experts in conducting assessments in the field, while government policies require that pulmonary TB cases can be enforced and handled in primary care facilities. On the other hand, the gene-Xpert system cannot be applied to diagnose child TB because of the difficulty in obtaining certain amounts of sputum in children and the cost is quite expensive. But compared to culture checks, the number of sputum needed for this examination is relatively small, which ranges from 0.5-1 cc and the examination time needed is very short so that it can be an option as a comparison in assessing the suitability of TB scoring in primary care facilities in diagnosing TB in a child suspected of pulmonary TB. This research aiming to know of diagnosing pulmonary TB and the suitability of TB scoring with Xpert MTB/RIF on amenities service primary health care.

2.   METHOD

The design of this study was a cross-sectional study with a conformity test (kappa). The population was all children suspected of TB who were treated to primary health facilities in the city of Padang during the visit of the researcher, which amounted to a minimum of 27 people. We collected data with the approval of and willingness of parents to follow research. Samples that include the inclusion criteria are carried out data recording in the form of age, gender, weight, height, nutritional status, previous history of BCG vaccination, and physical examination. Then the data obtained is entered into the scoring system.

While children are given sputum containers, we give education to children and parents on how to take sputum. Sputum was taken in the morning before the child eats and after the child gargles. For children who have not been able to remove sputum, sputum induction is carried out after the child has been fasted at least 3 hours before sampling. The child's mouth needs to clean with a toothbrush without toothpaste or with clean gauze before induction to reduce contamination. We give the children inhalation with 1 ampule salbutamol solution, 0.9% NaCl added to the total volume of 5 mL for 15 minutes, and continue with 3% 5 mL NaCl for the other 15 minutes. After that, children were asked to rinse their mouths while holding a sputum pot. We guide the children to take a deep breath two times, hold it for a few seconds then exhale slowly. We asked again the children inhaled for the third time, then exhale vigorously, then the children breathed once again, cough up to release sputum that is deep in the lungs. Cough can be repeated if the amount of sputum was not enough.

The obtained sputum is collected in the transport box and then taken to the microbiology laboratory and stored in a temperature refrigerator 2-8°C. And then the sample was put into a 2 ml Xpert MTB/RIF cartridge and homogenized with buffer. After 15 minutes have been left, the cartridge is put into the Xpert

MTB/RIF machine and awaits reading of the results within ±2 hours. The results will be read and recorded in the research book. Scoring results and Xpert MTB/RIF obtained will be processed using a statistical application with conformity test (kappa).

3.   RESULT AND DISCUSSION

This research was conducted from May 2015 to June 2016 at 7 primary health centres in Padang City, Private Clinic in Padang City, and Microbiology Laboratory, M Djamil Hospital, Padang. Of the 58 children who met the inclusion criteria, 11 samples were excluded because they could not remove sputum according to the amount specified in the study so that only 47 children could be analyzed. In 13 patients, sputum induction was performed to obtain sputum according to the research needs.

Subject Characteristic

From 47 children suspected of TB, their characteristics were based on age, sex, nutritional status, BCG status, TB contact, tuberculin test and clinical symptoms of TB in table 1. In table 1, it appears that the most age range is 5-9 years (61.7%), where boys are slightly more than girls (27 (57.4%) vs 20 (42.6%)). The majority of the samples had poor nutritional status (72.3%), positive BCG scores (70.2), close contact with adult with positive smear TB (51.1%), and negative tuberculin results (46.8%). From the examination, it was found that the majority were symptomatic, namely fever (70.2%) and cough (63.8%). KGB enlargement was found in 24 children (51.1%), while the majority of samples did not have chest radiology examination results (78.7%).

Tabel 1 Distribution characteristic of the subject suspected tuberculosis at primary health care (n=47)

Characteristics	f (%)
Ages	
• 5-9 th	29(61.7)
• 10-14 th	18 (38.3)
Gender	
• Boy	27 (57.4)
• Girl	20 (42.6)
Nutrisional Status	
• Well	7 (14.9)
• Less	34 (72.3)
• Bad	6 (12.8)
BCG Scar	
• Positive	33 (70.2)
• Negative	14 (29.8)
TB Contact	
• BTA +	24 (51.1)
• BTA -/laporan keluarga	20 (42.5)
• Unidentified	3 (6.4)
Tuberculin Test	
• Negatif	22 (46.8)
• Positif	20 (42.6)
• Are not done	5 (10.6)
Clinical Simptoms	
Fever	
• Yes	33 (70.2)
• No	14 (29.8)
Cough	
• Yes	30 (63.8)
• No	17 (37.2)

|	
Pembesaran KGB	
• Yes	24 (51.1)
• No	23 (48.9)
Chest X-Ray	
• Suggestive TB	10 (21.3)
• Normal	0 (0)
• Are not done	37 (78.7)

Prevalence Of TB Based On Scoring System

In Figure 1, it appears that there are more children diagnosed with TB based on the scoring system than children who are not.
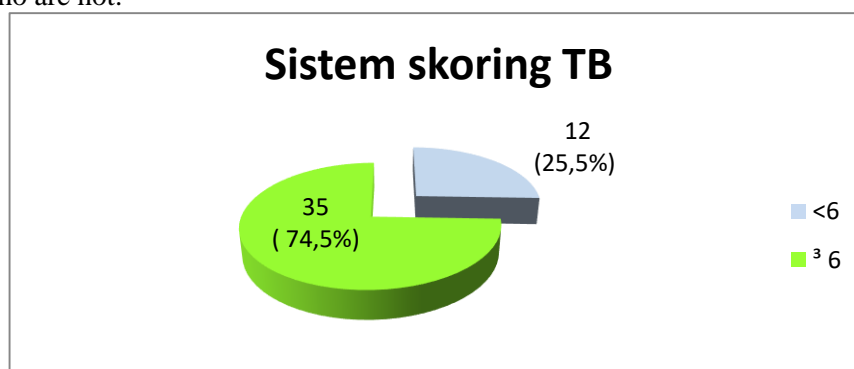
Figure 1 Prevalence Of TB and Not TB Based On Scoring System

In figure 2, it appears that children diagnosed with TB based on Xpert MTB / RIF examination are fewer than children not diagnosed with TB.
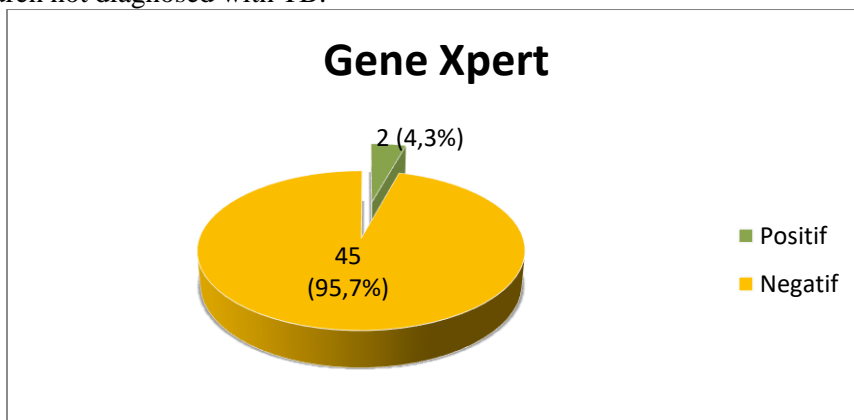
Figure 2. Prevalence Of TB and Not TB Based On *gene-Xpert* MTB/RIF

Concordance between TB Scoring With Gene Xpert MTB/RIF

In table 2 above, it can be seen that cohen's kappa coefficient value is -0.01, which means that there is a bad agreement between the two examination systems used to diagnose pulmonary tuberculosis in children with a significance of p 0.397 (> 0.05).

Table 2 Concordance of TB scoring with Gene-Xpert MTB/RIF

TB Scoring	Xpert MTB / RIF Gene Results		Total	Suitability	Kappa	Information
	Positive (%)	Negative (%)				
< 6	0 (0)	11 (100)	11 (100)	0.397	-0.01	Poor compatibility
≥ 6	2 (5,6)	34 (94.4)	36 (100)			
Total	2 (4,3)	45 (95.4)	47 (100)			

Discussion

In this study, it can be seen that the number of boys and girls suspected of having pulmonary TB is almost the same. This is consistent with several studies which state that there is no difference in the incidence of suspected tuberculosis children in both gender. [8,9] About 72% of children experience malnutrition and a positive BCG scar is found in more than half of the study samples. Nutritional status is very important in the transmission of tuberculosis, children with nutritional status are less easily infected with tuberculosis bacteria compared to children with good nutritional status.[10] Of the 93.7% of patients with positive TB contact, there were 51.1% of children in contact with positive smear adult TB patients. Salazar et al. in Peru showed that the characteristics of suspected tuberculosis children with contact with adult tuberculosis patients were 70%.[9] This is assumed because Indonesia is a developing country with a high incidence of adult TB which is a source of contact for the surrounding environment.

In this study, there were 42.6% of children had positive tuberculin test results, three of which were in contact with adult TB patients and has malnutrition. Research conducted by Nursyamsi in Manado also showed that most children with malnutrition had negative tuberculin test results even though there were 3 malnourished children with positive tuberculin test results.[11] Another factor that might affect this condition is the virulence of acquired M. tuberculosis and the dose of infection, but clinically it is difficult to prove. Sawhney in his research also obtained positive tuberculin test results in immunocompromised children, such as HIV. This problem can be found in countries with TB endemic because it is estimated that the child has been infected since the body still has good immunity so that it can provide a strong positive reaction in the tuberculin test.[12,13] Clinical symptoms of long fever were found in more than half of the children studied (70.2%), followed by coughing and enlarged lymph nodes, namely 63.8% and 51.1%. The history of BCG immunization with positive scoring was found in 70.2% of the study subjects. This is similar to research in India and Uganda which reported 86% and 67.6% of suspected TB children with positive BCG scar.[8,14]

In this study, the scoring system used had a low level of suitability when compared to the *Xpert* MTB/RIF examination. Only 2 of 35 children with a score of ≥ 6 were found to be found on MTB germs based on *positive Xpert* MTB/RIF examination and still sensitive to rifampicin. Both patients who received positive results had a TB score of > 6 with a positive tuberculin test results and there were clinical symptoms of old fever, persistent cough, and chest X-ray of pulmonary TB, while the contact history with adult TB patients was only found in one of the patients. A cross-sectional study in Yogyakarta compared the scoring system with strict clinical assessment in which the child was said to have tuberculosis if there was at least one tuberculosis symptom and followed by at least one of the following: bacteriological confirmation, radiological confirmation, or proven extrapulmonary TB in contact children at home, showing the results of a mismatch between the results of the two examinations. Based on the scoring system, 47% of children were diagnosed with tuberculosis whereas based on rigorous clinical assessment, only 10% of children were

diagnosed with tuberculosis, while 40% had latent tuberculosis infection. These results conclude that the use of a scoring system in children with home TB contacts can lead to *overdiagnosis* in the diagnosis of pediatric tuberculosis.[15] Other studies in India comparing the use of scoring systems that have contact history parameters with TB patients, tuberculin test, persistent cough, old fever and weight loss with bacteriological or radiological examination showed that scoring yielded more results in diagnosing tuberculosis children compared to bacteriological and radiological examination, ie n 15.5%, 0.3%, and 0.8%, so it was concluded that the use of scoring with these variables when used in areas with high prevalence would result in *overdiagnosis*.[16]

The use of *Xpert* MTB/RIF as a diagnostic tool for tuberculosis in children has been recommended by WHO since 2013.[2,6] Study by Sekkade et al. reported the sensitivity and specificity of *Xpert* MTB / RIF examinations to be 79.4% (95% IK: 63,2-89 , 7) and 96.5% (95% CI: 93-98.3) in children with suspected tuberculosis compared with *M*. tuberculosis culture.[8] However, when the clinical diagnosis was made as to the standard, we obtained results of specificity sensitivity, positive predictive value, and negative predictive value of Xpert MTB/RIF examination to be 20.6%, 94.7%, 96.4%, and 14.8 %.[17] The least positive Xpert results compared to clinical-based examinations are estimated in this study because sputum preparations in children have a small number of germs (paucibacillary) and the spread of common germs in lymphogens which undergoes expansion to the lung parenchymal tissue making it difficult to carry when coughing through sputum. This condition is different from adult TB which has a higher number of germs in sputum and the location of primary complexes in endobronchial areas so that the germs can be carried when the sputum is coughed.[18] Sputum collection in children is also quite difficult so that in 13 samples sputum induction was carried out to get sputum according to the amount needed. In this study, one child with an *Xpert* MTB / RIF positive was> 10 years old so it was estimated that she had adult type TB.

4. CONCLUSION

Based on this study, differences in the results obtained between clinical and bacteriological diagnoses increasingly prove the difficulty of diagnosing TB in children, because there is no gold standard that has high sensitivity and specificity. The limitation of this study is that it does not do *M. tuberculosis* culture as a control. This is because of the difficulty in collecting sufficient amounts of sputum for culture. Research with a larger number of samples is expected to strengthen the results of this study so that a more valid conclusion can be taken.

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