

# ASSESSMENT OF GENEXPERT TEST FOR DIAGNOSIS OF PEDIATRIC PULMONARY TUBERCULOSIS

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## ARTICLE INFO

Received : 23 March, 2023

Accepted : 22 July, 2023

Published : 10 November, 2023

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ORA 352

DOI: <https://doi.org/10.3126/bjhs.v8i2.59853>

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## Citation

Assessment of genexpert test for diagnosis of pediatric pulmonary tuberculosis. Km Roma, Suvesh Kumar Shrestha, Nirajan Bhandari, Gaurav Jung Shah, Shivam Khetan. BJHS 2023;8(2)21. 2024 - 2028.

## ABSTRACT

### Introduction

Pediatric tuberculosis is an infectious disease and is a leading cause of death in Nepal. The incidence of pediatric TB is a key tool of ongoing transmission of tuberculosis within the community and vital indicator of disease control. Its diagnosis is very much challenging and delay in diagnosis leads to mortality.

### Objectives

This study was conducted to assess the utility of the gene Xpert test for diagnosis of pediatric pulmonary tuberculosis.

### Methodology

A hospital based prospective study done at Pediatric department of a teaching hospital, Nepalgunj, Banke conducted over a period of 1 year from 1 January 2021 to 31 December 2021 with presumptive diagnosis of pediatric pulmonary tuberculosis. Chi-square test was used to determine the association between categorical variables and a receiver operating curve (ROC) analysis was performed to compare the performance of gene Xpert test with other lab parameters like sputum/gastric lavage sample microscopy for acid fast bacilli, erythrocytic sedimentation rate, Tuberculin test (TT) and chest X-ray.

### Results

We enrolled a total of 294 patients in our study. Out of 294 samples 5.1% samples came out to be positive for gene Xpert for MTB. The sputum/gastric lavage samples for AFB showed both sensitivity and specificity of 100%. The tuberculin test showed a sensitivity of 80% and specificity of 37.3%. Chest X-ray showed a sensitivity of 66.7% and specificity of 43.7%. The area under the curve for acid fast bacilli in microscopy, tuberculin test and ESR was found to be 100% (95% CI: 100%-100%), 58.6% (95% CI: 44.9%-72.4%), and 52.6% (95% CI: 37%-68.3%) respectively.

### Conclusion

This study highlights the utility of gene Xpert as a good diagnostic tool for rapid diagnosis of pulmonary tuberculosis in pediatric population.

## KEYWORDS

Gene Xpert, Pediatric, Pulmonary tuberculosis, Tuberculosis.



## INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) and is one of the top ten cause of death according to the global Tuberculosis Report of World Health Organization (WHO). The disease burden of tuberculosis is 10.6 million and is responsible for 1.6 million mortalities annually. Globally 134 cases per 1,00,000 world's population is infected with this disease. Out of 10.6 million TB cases 11 percent cases are reported in pediatric patients.<sup>1</sup>

According to data provided by Ministry of Health and population Nepal, 28,677 people tested positive for tuberculosis out of an estimated 69,000 new cases in fiscal year 2020-2021 which is around 40 percent of the total estimated new cases. The incidence of pediatric TB is a key tool of ongoing transmission of tuberculosis within the community and vital indicator of disease control. In poorly control areas children contribute 10-20% of disease burden. National TB control center report shows 6.04% of tuberculosis burden in pediatric population in Nepal.<sup>2,3</sup>

Many cases of tuberculosis are missed by the health care workers leading to deaths because of delayed diagnosis. Efforts are being made to diagnose the missing cases to increase TB diagnosis and to provide timely treatment to save lives. Gene Xpert is more accurate than smear microscopy.<sup>4</sup> Clinical picture of tuberculosis in children is very nonspecific and is different from adults with minor changes like weight loss, failure to gain weight, poor appetite, fatigue, disinclination to play etc. which is usually unrecognized by parents.<sup>5</sup> Delay in diagnosis and treatment occurs in children because of various reasons. Complete blood count (CBC) and Erythrocytic sedimentation rate (ESR) do not have any role in the diagnosis of childhood tuberculosis. CBC is performed for the diagnosis of comorbid condition. ESR is a nonspecific test which is affected by many factors so is not advised. Mantoux test is a delayed hypersensitivity response to tuberculin purified protein derivatives (PPD). Positive Mantoux test shows infection with *mycobacterium tuberculosis* only, which may be a past infection. It does not represent the presence of active tubercular disease.<sup>6</sup> The gold standard diagnostic tool is culture of *mycobacterium* which is time consuming, expensive, contamination liable and may not be necessarily positive even in diseased child as it requires a good laboratory setting.<sup>7</sup> Children less than 6 years cannot expectorate out sputum and the nature of disease is paucibacillary.<sup>8</sup> Gastric aspirate, induced sputum, Broncho-alveolar lavage fluid sample should be taken in situations where sputum is not possible to collect.<sup>9,10</sup> Children below 12 years of age have negative smear in 95% of cases.<sup>11</sup> The missed cases are the source of disease transmission to the community.<sup>12</sup> So, there is need of an accurate, rapid and feasible tuberculosis diagnostic test in the resource limited setting like ours for control of TB. Gene Xpert test is a molecular test which detects DNA of the tubercle bacillus, takes about 2 hours to obtain results and is highly specific and sensitive test.<sup>6</sup>

## METHODOLOGY

This was a hospital based prospective study done at pediatric department of a teaching hospital, Nepalgunj, Banke. This study was conducted over a period of 1 year from 1 January 2021 to 31 December 2021. All the patients who presented to outpatient department and those admitted to inpatient department for workup of pediatric pulmonary tuberculosis during the study period below the age of 15 years were included in this study. Inclusion criteria were presumptive TB cases with symptoms or signs suggestive of TB i.e. cough for two or more weeks, loss of appetite, malnutrition, fever, weight loss, fatigue, reduced playfulness, lethargy. History of contact with tuberculosis patient within the last two years and Chest X-ray findings suggestive of tuberculosis were included in our study. The exclusion criteria were participants having comorbidities or who were previously diagnosed with TB, those suspected of extra-pulmonary tuberculosis, unwillingness to participate in the study and children with other causes of fever and cough such as lower respiratory tract infection, asthma etc. A detailed clinical history and examination for pulmonary tuberculosis was done. The gastric lavage samples were collected as per standards. For the collection of sample patients were called early in the morning with at least 4 hours nil per mouth before the procedure. Counselling and consent of parents/child was done before the procedure. then child was positioned on his/her back and immobilized by rapping in the sheet of cloth. Distance between the earlobe –nose and xphi-sternum was measured and marked. Lignocaine jelly was applied in the NG tube and the tube was gently inserted up to the measured length via the nose and advanced into the stomach and position of the tube was confirmed by auscultation by pushing 3-5ml of air via syringe. gastric content 2-5 ml were withdrawn by NG tube and obtained fluid was transferred in a sterile container. Investigations done were: (i) Sputum/gastric lavage sample microscopy for AFB- demonstration of AFB is diagnostic of tuberculosis (ii) Tuberculin test (TT) (Arkray Healthcare Pvt. Ltd, Surat, India)- induration more than 10 mm is positive, induration more than 5mm is considered as positive in children with malnutrition, immunosuppression and HIV (iii) Chest X-ray- findings on chest x-ray like pleural effusion, consolidation, hilar lymphadenopathy, military mottling etc. were considered as positive finding. (iv) Gene Xpert (on sputum/ gastric lavage specimens) using the automated real-time DNA amplification test for rapid detection of TB (XPRT® MTB/RIF assay; Cepheid Invitro Diagnostics). Gene Xpert test is done free of cost at our center and is supported by National tuberculosis center, Kathmandu. The statistical package program SPSS version 20 was used to analyze data. Contingency tables were used to display data of different categorical variables. Chi-square test was used to determine the association between categorical variables and ROC analysis was performed to compare performance of gene Xpert test with other lab parameters. P value less than or equal to 0.05 was regarded as statistically significant. Sensitivity, specificity of AFB microscopy and Xpert MTB/RIF assay were also calculated. The study was approved by the Ethical Committee. The parents/guardians on behalf of the children and

adolescents included in this study had given written informed consent to participate in the study.

## RESULTS

The present study was done to assess the utility of the gene Xpert test for diagnosis of pediatric pulmonary tuberculosis. We enrolled a total of 294 patients in our study meeting the inclusion criteria during the study period presenting to outpatient department or admitted to pediatric inpatient department. The study subjects comprised of 55.4% males and remaining were females. 51% patients belonged to the age group of 6-10 years followed by 38.8% patient belonging to the age group of 11-15 years and minimum number of patients belonged from the age group of less than 1 year which comprised of 0.7% patients. The clinical and laboratory parameters of suspected pediatric pulmonary tuberculosis patients are elaborated in table 1.

**Table 1.** Clinical, laboratory variables of suspected pediatric TB cases.

Variables	Frequency		Gene Xpert MTB detected		Gene Xpert MTB not detected		Chi square/ Fisher exact test	P value
	n	%	n	%	N	%		
<b>Age (years)</b>							10.958	0.01
<1	2	0.7	1	50.0	1	50.0		
2-5	28	9.5	3	10.7	25	89.3		
6-10	150	51	4	2.7	146	97.3		
11-15	114	38.8	7	6.1	107	93.9		
<b>Sex</b>							1.526	0.217
Male	131	44.6	6	4.5	125	95.5		
Female	163	55.4	9	5.5	154	94.5		
<b>Fever (&gt;2 weeks)</b>							0.970	0.325
Present	277	94.3	15	5.4	262	94.6		
Absent	17	5.7	00	00	17	100.0		
<b>Persistent cough (&gt;2 weeks)</b>							0.336	0.562
Present	139	47.2	6	4.3	133	95.7		
Absent	155	52.8	9	5.8	146	94.2		
<b>H/O TB contact</b>							0.236	0.627
Present	53	18	9	17	44	83		
Absent	241	82	6	2.5	235	97.5		
<b>Weight loss</b>							5.536	0.019
Present	65	22.1	7	10.7	58	89.3		
Absent	229	77.9	8	3.4	221	96.6		
<b>Poor appetite</b>							5.471	0.019
Present	112	38.1	10	8.9	102	91.1		
Absent	182	61.9	5	2.7	177	97.3		

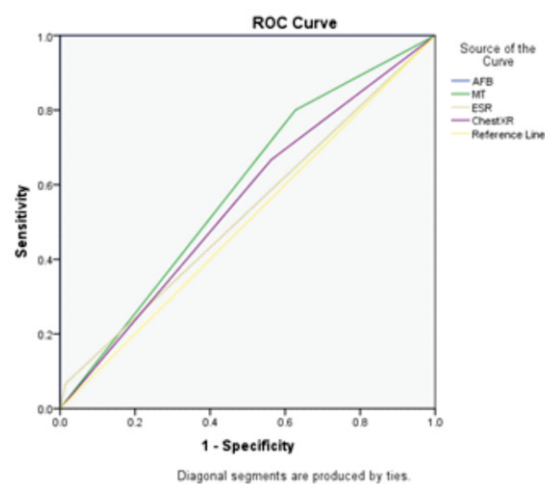
**Table 2:** Diagnostic accuracy of ESR, CXR, TT and sputum/gastric lavage AFB

	Positive	Sensitivity (%)	Specificity (%)
ESR	28 (9.5%)	6.7	98.6
CXR	128 (43.5%)	66.7	43.7
TT	206 (70.5%)	80	62
Sputum/gastric lavage AFB	5(1.7%)	100	100

Out of 294 samples 15(5.1%) samples came out to be positive for gene Xpert for MTB. The sputum/gastric lavage samples for AFB showed both sensitivity and specificity of 100%. The tuberculin test showed a sensitivity of 80% and specificity of 37.3%. The chest X-ray showed a sensitivity of 66.7% and specificity of 43.7%. The ESR showed a low sensitivity of 6.7% and specificity of 98.6% in our study. A receiver operating curve (ROC) analysis was performed. As shown in figure 3, area under curve for AFB was found to be 100%. Area under curve for tuberculin test was found to be 58.6% at 95% CI with lower bound 44.9% and upper bound 72.4%. The area under curve for ESR was found to be 52.6% at 95% CI with lower bound 37% and upper bound 68.3%. The area under curve for Chest X-ray was found to be 55.2% at 95% CI with lower bound to be 40.6% and upper bound 69.8%.

**Table 3:** Area under curve of various lab parameters

Test variable (s)	Area	95 % Confidence Interval	
		Lower bound	Upper bound
ESR	52.6%	37	68.3
CXR	55.2%	40.6	69.8
TT	58.6%	44.9	72.4
Sputum/gastric lavage AFB	100 %	100	100



\*MT (Mantoux test), \*\*AFB (Acid fast bacilli)

**Figure 1:** ROC curve diagnostic accuracy of various lab parameters of tuberculosis.

## DISCUSSION

Worldwide pediatric tuberculosis is associated with high mortality, its clinical features are subtle in children. There is lack of quick and reliable modalities making TB diagnosis further challenging. The gene Xpert test can be a rapid alternative diagnostic modality for diagnosis for pediatric pulmonary TB. The Gene Xpert test is cartridge based real time PCR detection which is very sensitive and result are available in two hours.<sup>13,14</sup> So, we have assessed utility of this

test in diagnosis of pediatric pulmonary tuberculosis. We studied 294 patients which comprised 55.4% males and remaining were females. Highest numbers of patients i.e. 51% belongs to age group of 6-10 years. Similar pattern of age and gender distribution was observed in a study of Venkatesh KS et. al.<sup>15</sup>

In our study, gene Xpert detected 15 cases of tuberculosis which was 3 times of cases found in smear microscopy for AFB of sputum/gastric lavage. Pandey D et al.<sup>16</sup> have also detected extra cases of tuberculosis by gene xpert which were not detected by smear microscopy. Our study showed 100% sensitivity and specificity for gene xpert of sputum/gastric lavage sample for AFB which is similar to the findings of Das A et al.<sup>14</sup> done at Institute of medical sciences, Varanasi, India and study done at in Beijing Children's Hospital.<sup>17</sup> While study done by Zahra Hasan et al.<sup>18</sup> in tertiary care facilities in Karachi Pakistan shows gene Xpert had a sensitivity of 88.9% (95% CI 50.7–99.4) and a specificity of 95% (95% CI 81.8–99.1) which is slightly lower than our findings. Detjen et al.<sup>19</sup> has reported wide variation in the sensitivity of gene xpert in different studies and different specimens where as they found specificity range in between 93-100%. Our study showed sputum/gastric lavage samples for AFB has both sensitivity and specificity of 100% which is in concordance to the study of Bunsow et al.<sup>20</sup> The sensitivity and specificity of tuberculin test was found to be 80% and 37.3% respectively whereas Venkatesh KS et al.<sup>5</sup> found a sensitivity of 73.3% which is similar to our study and specificity of 93.6% which was higher than our study. The reason for low specificity of tuberculin test in our study is poor immune status of children and malnutrition. In our study chest x-ray showed sensitivity of 66.7% and specificity of 43.7% which is slightly different from the study of Venkatesh KS et. al.<sup>15</sup> Positive findings on chest x-ray helps in making the diagnosis of pediatric pulmonary tuberculosis but normal chest x-ray does not rules out the disease. In such cases of normal chest x-ray gene xpert adds to the diagnosis. The ESR showed a low sensitivity of 6.7% in our study which is slightly lower than the study done at Mahatma Gandhi medical college and research institute, Puducherry, India.<sup>14</sup> These studies support no diagnostic role of ESR in diagnosis of TB.

Clinical features of pediatric pulmonary tuberculosis are non-specific and radiological findings also vary widely. Pediatric tuberculosis is pauci-bacillary in nature so; microscopy is usually negative even in positive patients. Although culture being gold standard is time taking and has got its own limitations. In such cases, gene xpert is a diagnostic modality of choice to detect the cases rapidly.

## CONCLUSION

This study highlights the utility of gene Xpert as a good diagnostic tool for rapid diagnosis of tuberculosis in pediatric population in low resource setting like ours.

## RECOMMENDATIONS

As per findings from this study we found gene Xpert test is better for early detection of pediatric pulmonary tuberculosis. So we recommend access of this test as burden of tuberculosis is high.

## LIMITATIONS OF THE STUDY

This study was a single center study on a sample size of 294 only, if we could do such multi-centric study on much larger sample size then we would be able to generalize the findings representing real scenario. Gene Xpert test is an expensive test so multi-centric study would only be possible if this test will be provided free to the patients otherwise cost of the test would be a limitation.

## ACKNOWLEDGEMENTS

Researchers would like to express sincere gratitude to a IRC of Nepalgunj Medical College Teaching Hospital, Nepalgunj, Banke for giving the opportunity to carry out this study. We would like to extend our cardinal thanks to all the respondents and facilitators for their kind co-operation and valuable time.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

## FINANCIAL DISCLOSURE

None

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