# **Original Research Article**

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# Role of gene Xpert test in clinical TB suspect in children

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#### **ABSTRACT**

**Background:** Tuberculosis (TB) is a major global health problem. Childhood tuberculosis (TB) is common in our community but it is relatively neglected, due to greater challenges in diagnosis. Clinical manifestations of childhood TB differ from adults. The diagnosis in most cases is based on clinical evidence but chest X-ray, Mantoux test, history of Kochs contact, malnutrition and sputum/gastric sample microscopy are important supporting investigations. WHO recommended use of newer diagnostic tests like Gene Xpert in pediatric cases where TB is mostly paucibacillary and identification of TB bacilli is difficult for confirmation of diagnosis.

**Methods:** This prospective study was conducted among admitted and OPD patients in the department of Pediatrics over a period of 1 and half year. Clinically suspected cases of TB in the age group 0-12 years who met the diagnostic criteria made the study group. Refusal of consent by parent and children already on TB treatment were excluded from this study. Investigations like chest X-ray, Mantoux test, sputum/gastric aspirate microscopy and Gene Expert were done to confirm the clinical diagnosis.

**Results:** Pulmonary tuberculosis was more common (28%), TB lymphadenitis 22%, TB meningitis 14%, Tubercular Pleural effusion 12 %. and rest were no TB. BCG scar was present in 90%. History of contact was present in 76% and Mantoux test was positive in 76%. Gene Expert was positive only in one case in our study rest 49 cases were negative. The most common symptoms were fever (72%), cough (52%) and weight loss (40%).

**Conclusions:** This study supports that detailed history, clinical evaluation and active investigative workup in addition to newer diagnostic tests like Gene Xpert has a major role in diagnosing childhood tuberculosis.

Keywords: BCG, Childhood tuberculosis, Gene Xpert, Mantoux

# INTRODUCTION

Childhood Tuberculosis is the infection caused by Mycobacterium Tuberculosis (also sometimes known as white plague). In the last decade, tuberculosis has remerged as a major worldwide public health hazard with increasing incidence among pediatric age group despite the availability of effective preventive measures and chemotherapy, the prevalence of TB is increasing in the developing world and in much of industrialized world as well.

Mycobacterium tuberculosis is one of the worlds most successful and sophisticated pathogens as it causes persistent infection in what is estimated to be over 2 billion people, yet largely without causing clinical symptoms. It is estimated that there are more than one half millions cases of TB in children occupy globally each year in setting with a high overall incidence of TB, children account for a large proportion (up to one third).

As consequences, TB is an important cause of morbidity and mortality in children in TB endemic countries like

India. India is a country with the highest burden of TB with WHO statistics for 2013 giving an estimated incidence figure of 2.1 million cases incidence of 9 million.<sup>1</sup>

The estimated TB prevalence figure for 2013 is given as 2.6 million. The burden of TB in children remains high and remerged according to WHO. In 2000, 7 million new cases of TB were diagnosed and 2 million deaths. In 2012 estimated globally 9 million new cases were diagnosed and 1.2 million deaths.<sup>2</sup>

This clearly shows the remerging trend of TB in children. Nevertheless under reporting of child TB cases is very common. The estimated number of children with TB estimates less than 6% in all incident cases and 10-15% in endemic areas like India.<sup>3</sup>

The diagnosis of TB in children relies on through assessment of all the evidence derived from symptoms suggestive of TB and careful history of exposure and clinical examination and relevant investigations. Most children with TB have pulmonary TB although bacteriological confirmation of tuberculosis is always not feasible. Existing diagnostic tests for TB in children have short comings and the full range of tests including bacteriological culture and is often unavailable in setting where majority TB cases occur.

Conventional methods of diagnosis of TB in children like chest x-ray and Mantoux test are very useful in the diagnosis of TB in children but the sensitivity and specificity are not 100%. Chest X-ray has 67% sensitivity and 59% specificity in diagnosis of pulmonary TB in children.

Mantoux test have high percentage of false positive results. Globally under diagnosis of childhood pulmonary tuberculosis remains an obstacle to effective managements therefore children suspected of having pulmonary TB by radiological evidence and skin tuberculin testing i. e. Mantoux should go for single Gene Xpert /RIF. The development of affordable most effective and cost effective novel diagnostic tests for TB in low resource setting has become priority in India. The novel approaches to confirmation of TB have been developed and evaluated. Following successful clinical evaluation WHO endorsed Xpert/MIF assay in 2010 especially in children with unremitting symptoms.

The gold standard method for diagnosis and confirmation of TB is by isolation of M. tuberculosis but the yields of this test is very poor.

Authors are relying on conventional routine methods for diagnosis of Tuberculosis like chest x-ray, ESR Mantoux test which are not very reliable in confirmation of diagnosis of Tuberculosis in children. Hence, we are performing novel strategies for diagnosis after successful clinical evaluation like WHO endorsed Gene Xpert/RIF.

#### **METHODS**

This prospective study was conducted among admitted and OPD patients in the department of Pediatrics over a period of 1 and half year.

### Inclusion criteria

- Fever more than two weeks.
- Cough more than two weeks
- Not eating well/anorexia
- Weight loss/failure to thrive
- Fatigue in the form of reduced playfulness and decreased activity.
- History of contact with tuberculosis.

#### Exclusion criteria

- Children who are already treated with tuberculosis.
- Children who did not follow with the investigations.

All individuals above the age of 18 years were included in to the study. Informed consent was taken prior to conduct of the study.

#### **RESULTS**

As per age groups maximum children were in the older age group (6-12 years) and least in the age group less than 1 year. Results show clinically older age groups are more affected in this study.

Table 1: Distribution of study population according to age groups.

Age group	Frequency	Percent	Mean age	SD
>1 year	1	2.0	0.9	-
1-5 years	14	28.0	3.5	1.4
6-12 years	35	70.0	8.5	1.8
Total	50	100.0	7.00	2.93

Table 2: Distribution of subjects according to history of contact.

Contact	Frequency	Percent
Negative	14	28.0
Positive	36	72.0
Total	50	100.0

There was history of contact present in 36 cases out of total 50 cases and 14 cases were negative. There were higher rates of positive Koch's contact in this study according to the Table 2.

Gene Expert test was positive in only 1 case and 49 cases were negative for the test in this study. The specificity of the test was 100% in this study. PPV (Positive predictive

value) being 100% and NPV (Negative Predictive Value) only 2%.

Table 3: Gene Expert.

Gene expert	Frequency	Percent
Negative	49	98.0
Positive	1	2.0
Total	50	100.0
Sensitivity	50.51	95% CI =40.27%-60.71%
Specificity	100	2.50% - 100%
PPV	100%	-
NPV	2%	1.65% - 2.43%

Mantoux test was positive in maximum cases and negative in 24% cases. AKT (Anti-tubercular treatment) was started in all cases with Mantoux positive.

Table 4: Comparison of Mantaux and AKT.

	AKT						
Mantoux test	Negative		Pos	Positive		Total	
	n	<b>%</b>	n	%			
Negative	12	92.3	0	0	12	24	
Positive	1	7.7	37	100	38	76	
Total	13	100	37	100	50	100	

As per the Figure 1, maximum percentage is seen of pulmonary tuberculosis, and extra pulmonary tuberculosis like TB lymphadenits, TB Meningitis, TB Pleural Effusion. Results show different types of tuberculosis infection was noted in this study.

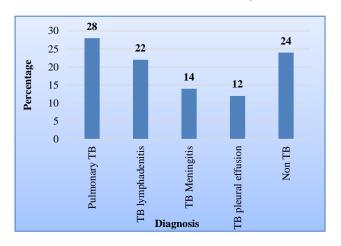


Figure 1: Percent distribution of study population according to diagnosis.

# **DISCUSSION**

The diagnosis of tuberculosis (TB) in children is very difficult in resource-poor regions such as India. The gold standard method for diagnosis and confirmation of TB is by isolation of M tuberculosis but the yield of this test is very poor as most pediatric TB is paucibacillary. We are relying on conventional routine methods for diagnosis of

Tuberculosis like chest x-ray, Mantoux test, clinical symptoms and history of Koch's contact in family. Hence, we are performing novel strategies for diagnosis after successful clinical evaluation like WHO endorsed Gene Xpert/RIF test. Young children rarely expectorate sputum. Other methods of obtaining sputum have various limitations and are either not widely applied in hospitals in the region or are still limited to the research context.

The vast majority of childhood PTB notifications are therefore not confirmed. Because of the problems with diagnosis, algorithms for screening and for diagnosis of childhood TB have been proposed.<sup>3</sup>

Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect).<sup>4</sup> A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment

has started. A clinically diagnosed TB case is one who does not fulfill the criteria for bacteriological confirmation but who has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation.

Present study included 50 children of TB suspect of which 29 were boys and 21 girls. Majority of cases in our study belonged to age group 6-12 years of age around 70%. This age group is most vulnerable for TB exposure and most TB cases are reported in this age group. This is in accordance to study by Kakarani with 68% cases. Sex wise distribution of cases showed a slight male preponderance (58%) in present study which is naturally observed in the Indian scenario. Ratio of male is slightly higher than females according to the demographic data of India. A similar study by Franco Et al in Brazil which showed a male preponderance of 51.6%. Sivanandan S and Xi-Rong Wu et al also observed a male preponderance of 63% and 58% respectively. Sivanance of 63% and 58% respectively.

Analyzing and comparing the above studies with the present study, it may be concluded than in older age groups there is a slight female preponderance. The increased risk may be due to combination of increased biological susceptibility, immunological response in older age group or difference in socialization patterns of male compared to female children.

The frequency of clinical symptoms was observed for TB suspect according to the WHO guidelines such as fever lasting more than 2 weeks, unremitting cough more than 2 weeks, history of weight loss, painless lymphadenopathy, meningitis of insidious onset, spinus gibbus, history of Kochs in family member.

Most common clinical symptoms present were fever in 72%, cough 52% and weight loss in 40%. These are the most common symptoms seen in case of tuberculosis case. Similar observations were reported in a study from north India by Garg P with fever being commonest symptoms followed by weight loss and cough. In a study by Franco et al fever was documented in 73.1% cases and weight loss in 53.1%. Malnutrition is an important factor predisposing to low immunity and TB infection. In 36 cases of presumptive TB, 33 cases had malnutrition and 3 cases were normal with no malnutrition. History of Kochs contact is an important predictor of presumptive TB especially in the children where most cases are paucibacillary and diagnosis becomes difficult.

In 36 cases of presumptive TB, 34 cases had Koch's contact and 2 cases had no TB contact. This was similar to various Indian studies done in children under 15 years of age showing positive history of contact in 33-52% cases (Kakarani VA et al<sup>8</sup> and Bai SS et al)<sup>9</sup>

Classification of tuberculosis was done based on anatomical site of disease.

Pulmonary TB (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.

Extrapulmonary TB (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

In present study pulmonary TB constituted the major group (28%), followed by TB lymphadenitis (22%), tubercular meningitis (14%), tubercular pleural effusion (12%). Present results are consistent with the various studies described in literature Kakarani VA et al and Bai SS et al.<sup>8,9</sup>

In present study CNS tuberculosis accounted for 14% cases, this was comparable with study of Pontual et al where 16.67% cases were had isolated CNS tuberculosis. Tubercular Lymphadenopathy was seen in 22%. <sup>10</sup> This was comparable to study done by Garg P, which showed 16.7% cases of tubercular lymphadenopathy. <sup>11</sup>

Franco et al showed 21.5% cases of tubercular lymphadenopathy.<sup>5</sup> In 36 cases of presumptive TB, 30 cases had chest Xray suggestive of TB and 6 cases had normal chest x-ray. Primary complex was most common finding on X ray accounting for 14 cases (28%) cases and

6 cases (12%) cases showed pleural effusion. Similar to study by Franco et al observed primary complex in majority cases.<sup>5</sup>

BCG vaccination provides substantial protection against the more severe types of disseminated TB, such as miliary TB and tuberculous meningitis, to which infants and young children are particularly susceptible. History of BCG vaccination was positive in 90 % cases and 10 % of those vaccinated did not have a BCG mark on examination. Higher vaccination coverage in our study in comparison to others indicates effective implementation of National Immunization Programme. In 36 cases of presumptive TB, 31 cases had BCG scar and 5 cases had no BCG scar. Maximum positivity was seen in pulmonary TB (28%) Sivanandan et al reported Mantoux positivity in 66% cases which is similar as to our study. In 36 cases of presumptive TB, Mantoux test was positive in all cases.<sup>6</sup> There is statistically significant correlation between AKT and Mantoux test (p<0.001).

Gastric aspirates are used for collection of samples for microscopy and mycobacterial cultures in young children when sputum cannot be either spontaneously expectorated or induced using hypertonic saline. It is most useful for young hospitalized children. However, the diagnostic yield (positive culture) of a set of three gastric aspirates is only about 25-50% of children with TB disease, so a negative smear or culture never excludes TB in a child.<sup>12</sup>

In present study, sputum/gastric aspirate microscopy was negative for AFB in 50 cases (100%) cases. This was in accordance to study done by Franco et al, which showed sputum positivity in fewer cases, and frequency of sputum positivity was lower in pediatric age group.<sup>5</sup> This finding emphasizes that as age increases percentage of sputum positivity increases and hence bacteriological sputum examination is a useful method above 10 years.

GENE Expert also known as automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children was recommended in the Policy Update. Geneva, World Health Organization, 2013.

Gene Xpert test was done in all 50 cases in the present study. One test was positive which was treated as TB case which was bacteriologically positive and ATT was started. The reason low sensitivity of GENE Xpert in children was attributed to following factors- as children less than 8 years could not expectorate so we used gastric lavage, pleural fluid, CSF and these samples have low bacterial counts. Other factors like delay in transportation, storage and neutralization of sample would have inactivated tubercle bacilli. A negative Xpert MTB/ RIF test does not exclude a diagnosis of childhood tuberculosis given the fact that the test was unable to

Identify even the cases of with culture confirmed tuberculosis cases. A clinical decision in the context of the patient is therefore important in initiating antituberculous therapy in a child who has a negative Xpert MTB/RIF test. A simplistic algorithm was used to diagnose cases of childhood negative Xpert MTB/RIF test. A simplistic algorithm was used to diagnose cases of childhood TB in whom ATT was started. 36 cases (72%) as presumptive TB with supportive conventional methods like Chest X-ray, Mantoux Test, History of Contact and one case bacteriologically confirmed and diagnosed by Gene Xpert Test. In total 50 cases with TB suspect, 37 cases were diagnosed TB of which one case was bateriologically confirmed and 36 cases were diagnosed presumptive TB and were started with ATT. Sensitivity of test was 50.51 and specificity was 100. Positive predictive value was 100% and Negative predictive value was 2%.

### **CONCLUSION**

The gold standard test for diagnosis of pediatric aspirate or newer developed Gene Xpert test. In cases of presumptive TB, Gene Xpert was done in all cases and only 2% cases of Gene X pert was Positive. In 72% of cases of TB was diagnosed by TB clinical algorithm. Even though Gene X pert is the best tool for diagnosis of TB as it is difficult to collect adequate sample in pediatrics and secondarily it is paucibacillary disease. Gene Xpert may be negative in children with TB as we saw 72% of cases were started with ATT based on clinical diagnosis, history, chest X-ray, Mantoux test.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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