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ORIGINAL ARTICLE

Diagnostic Accuracy of XPERT MTB/RIF Sputum Test among Children with Suspected Pulmonary Tuberculosis (TB) by taking Löwenstein–Jensen base as Gold Standard

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ABSTRACT

Objective: To determine the diagnostic accuracy of Xpert MTB/RIF sputum test among children with suspected pulmonary tuberculosis (TB) by taking Löwenstein -Jensen (M) base as a gold standard.

Study Design: This was a cross sectional observational study

Place and Duration of Study: The study was conducted in the outpatient department of national institute of child health. The period of study was from 10th March 2020 to 10th August 2020.

Material and Methods: Data of the 254 patients of either gender with age between 4-16 years and suspected as having TB were included according to inclusion criteria. The data was obtained from data bank of the hospital. The medical records of the children tested with Xpert MTB/RIF and Löwenstein - Jensen media were included for the study. The data was analyzed using SPSS 23 version.

Result: The mean age of the patients was 8.26 ± 3.06 years. There were 159 (62.6%) males and 95 (37.4%) females. Xpert MTB/RIF sputum test showed positive pulmonary tuberculosis in 63 (24.8%) patients while Löwenstein-Jensen showed positive cases in 73 (28.7%) patients.

Conclusion: The study concluded that the diagnostic accuracy of the Xpert MTB/RIF sputum test was very much acceptable in the case of pulmonary tuberculosis among children with suspected TB by taking the Löwenstein-Jensen base gold standard.

Key Words: X pert MTB/RIF sputum test, Löwenstein-Jensen, Pulmonary tuberculosis, Children, Diagnostic accuracy

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INTRODUCTION

Tuberculosis (TB) is the world's 8th leading cause of death in low income countries, ranking higher than HIV/AIDS and globally around 10 million new cases of TB were detected during

2016, of which 90% were adults.¹ Children under 15 years of age accounted for up to 6.9% of the incidence rate of TB reported during the same year. A continuous rise in the case identification rate of childhood TB worldwide has been seen, along with an increased mortality rate. It was

calculated in a statistical modeling report that approximately 240,000 kids died of TB in 2015² and approximate two million deaths occur annually worldwide and the condition has intensified with a growing prevalence of multi-drug resistant TB.³

Tuberculosis is a very contagious disease and it is estimated that one untreated patient with contagious tuberculosis will infect 10 to 15 individuals annually.⁴ The risk of progression to active illness is significantly greater for children than for adults. Tuberculosis in children is relatively overlooked, primarily due to its greater diagnostic difficulties and low preference.

As per reported data, the prevalence of TB in children is 15%.⁵ The disease burden is very high in Pakistan like any other developing country. According to World Health Organization (WHO), every year there are 510,000 new TB cases with 15,000 drug resistant cases. Among the high burden countries of the world Pakistan is ranked fifth and among Eastern Mediterranean countries 61% of all TB cases are reported in Pakistan.⁶ Pakistan has also been ranked high among the world's 30 high burden countries and the trend has increased from 2000 to 2020.⁷

There are many diagnostic methods for TB including AFB smear, chest x-ray, TB-Loop-mediated isothermal amplification, Zeil Neelsen stain etc. All these methods have some limitations. Zeil Nelsen stain is economical to test that requires roughly one to two hours to report. However, it's sensitivity is low and requires a larger amount of sample content (up to 10,000 bacilli/ml).³ In addition to that Mycobacterium tuberculosis cannot be isolated from Mycobacterium subtypes using this method. Therefore this method is primarily used for screening purposes only. Lowenstein-Jensen (LJ) medium culture is the gold standard for TB diagnosis, but the facility is not fully available in underdeveloped countries like Pakistan, Bangladesh, etc to its maximum extent and it requires special procedures, time, and skilled workers.⁸ While Lowenstein—Jensen is more receptive than AFB microscopy, it requires between 2-3 weeks and several months to develop mycobacterium tuberculosis colonies.

In recent years, WHO has made a provisional

endorsement to use Xpert MTB/RIF as the first-line diagnostic test for all individuals needing evaluation for TB, and more recently it has been proposed that diagnosis should move away from smear microscopy and emphasize the initial use of Xpert MTB/RIF.⁹ At the same time, the test can detect species within the Mycobacterium tuberculosis complex (MTBC) and rifampin resistance (RIF) in less than a couple of hours whereas Lowenstein—Jensen requires between 2-3 weeks and several months to develop M. Tuberculosis colonies, and there could be a high probability of contamination. Keeping this in view the aim of this study is “to determine the diagnostic accuracy of Xpert MTB/RIF sputum test among children with suspected pulmonary tuberculosis (TB) by taking Lowenstein-Jensen (M) base as the gold standard” as Xpert MTB/RIF is easily accessible and affordable as compared to other diagnostic test and less work has been done in this part of the world on its validity and reliability.

MATERIAL AND METHODS

This was a retrospective observational study. The study was approved from IRB of National Institute of Child Health. A total of 254 out-patients children (age between 4 to 16 years) of suspected TB found from the records of patients at National institute of child health from 10th March 2020 to 10th August 2020 were included. As per the selection criteria, children with persistent cough of more than 3 per minutes for two weeks and having any of the following conditions were considered as suspected case of TB: contact with TB patients (parents or siblings) during the last two years, history of weight loss, unexplained fever (the axillary temperature more than 100.4 °F) for more than 3 weeks, x-ray chest with either unilateral lymphadenopathy (enlarged hila) or predominance of upper lobe infiltrates (opacities/consolidation) or cavitation (of any size) in either hemithorax. Patients' demographic information, duration of suffering and exposure history were also noted. For collection of gastric aspirate from 4 to 8 years, patients were kept NPO after passing nasogastric tube and gastric aspirate was taken in the morning. Sputum sample of the patients

from 8 to 16 years. Patients were advised to take a deep breath, hold the air for few seconds and the slowly exhale out. This breathing was repeated and then the patient was advised to cough and spit the sputum into a plastic cup sterilized earlier. The sample was then sent for Xpert MTB/RIF and Lowenstein-Jensen media (LJ) which is the selective medium that is used for the cultivation and isolation of *Mycobacterium* species.

The data was recorded for analysis in SPSS version 22.0. The age, weight, height, and duration of symptoms are presented in mean \pm SD whereas categorical values such as gender, residence, socio-economic status, diagnosis on Xpert MTB/RIF sputum test, and M base are presented in frequencies and percentages. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of Xpert MTB/RIF sputum test-taking LJ base as the gold standard were determined.

RESULTS

Out of all 254 enrolled children, 159 (62.6%) were male and 95 (37.4%) were female with a median age of 8.26 ± 3.06 years. Mean weight was calculated as 22.65 ± 9.54 kg for both genders. Majority of the suspected children {150 (59.1%)} presented with <4 weeks of duration of symptoms. Out of all, 125 (49.2%) cases belonged to a family of lower socio-economic status, followed by middle 68 (26.8%) and high 61 (24%) socioeconomic status. However, majority 175 (68.9%) of these were living in rural areas (table 1).

TABLE 1: Baseline characteristics of study population (n=254)

Variable	Frequency (%)
Gender	
Male	159 (62.6°/e)
Female	95 (37.4°/c)
Age (years), mean USD (range)	5.26 z3.06 (4-16)
Age <S, n (%)	152 (71.7°/c)
Age >S, n (°/e)	72 (25.3°/e)
Weight (kg), mean -£SD (range)	22.65 a9.54 (5-37)
Weight <25, n (%)	124 (45.5°/e)
Weight >25, n (*Zo)	130 (51.2°/e)
Duration of symptoms (weeks), range	4.07 +l .17 (2-6)
Duration of symptoms <4, n (%)	150 (59.1°/e)

Duration of symptoms >4, n (°Zc)	104 (40.9°/e)
Socioeconomic status, n (°/e)	
Lower	125 (49.2°/e)
Middle	65 (26.8°/c)
High	61 (24°/c)
Residence	
Urban	79 (31.1°/e)
Rural	175 (65.9°/e)

Microbiological Findings: As presented in fig 1 out of all sputum specimen, 25.7% were positive and 71.3% were negative by conventional standard method using Lowenstein-Jensen Base taken as gold standard. In comparison, sample processed through Xpert MTB/RIF detect *Mycobacterium* Tuberculosis in 24.8% sputum specimens, declared positive with 75.2% negative cases.

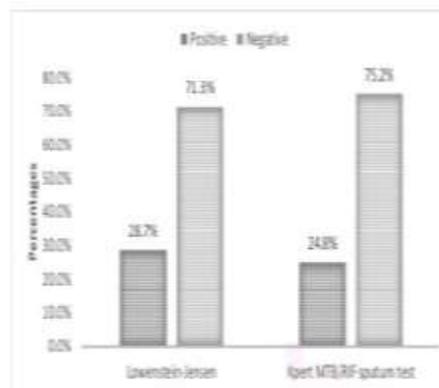


Figure 1: Performance of Xpert MTB/RIF against Lowenstein-Jensen (LJ) Base

Sensitivity, Specificity, PPV and NPV: The overall sensitivity of Xpert MTB/RIF to screen out positive cases of pulmonary tuberculosis was 82.8% and the specificity for excluding disease was 98.3%. The diagnostic performance and accuracy of the assay varied with different baseline characteristics such as age, gender, weight, residence, socio-economic status and duration of symptoms. The sensitivity of the Xpert MTB/RIF test for sputum in age (8 years above), males, weight (25 kg or less), middle socio-economic status and residence were 85%, 92.9%, 97.2%, 90.5% and

100% respectively. High specificity (100%) was observed in female children of age (8 years above) with weight (25 kg or less), living in urban areas and belonging to families with high socioeconomic status. Probability of having disease in a test positive cases was calculated

100% PPV in female of 8 years and above with 25 kg or less in weight and of high socio-economic back-ground living in urban areas. 100% NPV was found in participants residing in rural area. Diagnostic accuracy of the test was found 93.7% overall (table 2).

TABLE 2: Diagnostic performance of Xpert MTB/RIF sputum test

	Over-all	Age		Gender		Weight		Duration of symptoms		Residence		Social-economic status		
		Years	Years	Male	Female	<25 Kg	>25 Kg	<4 weeks	>4 weeks	Rural	Urban	Low	Middle	High
Sensitivity	52.2	81.3	55	92.9	67.7	97.2	67.6	55.4	75.1	100.0	80.0	79.5	90.5	76.9
Specificity	95.3	97.7	100	97.4	100.0	100.0	96.5	95.7	95.8	95.5	100.0	97.7	97.9	100.0
PPV	95.2	93.5	100	92.9	100.0	100.0	59.3	94.6	96.2	72.7	100.0	93.9	95.0	100.0
NPV	93.2	92.7	94.6	97.4	56.5	95.9	55.2	94.7	91.0	100.0	59.4	91.3	95.5	94.1
DA	93.7	92.9	95.5	96.2	59.5	99.2	55.5	94.7	92.3	96.2	92.6	92.0	95.6	95.1

DISCUSSION

In Pakistan, tuberculosis is a main concern to health. Due to the limitation of diagnostic tests of tuberculosis such as Tuberculin skin test, radiological imaging, and sputum smear microscopy, the incidence of pulmonary in addition to extra-pulmonary tuberculosis is relatively high. Therefore, Xpert MTB/RIF was recently recognized diagnostic assay for the prompt diagnosis of pulmonary tuberculosis and has presented encouraging outcomes.¹⁰ This study demonstrated the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of Xpert MTB/RIF against Löwenstein-Jensen culture that were performed in a tuberculosis high burden population.

One cross-sectional study conducted in Pakistan included 225 patients having pulmonary tuberculosis. Mean age of the patients in this study was 37.48 ± 17.49 years. There were 84 (37.3%) females and 141 (62.7%) males. Mean weight, height, and BMI of the patients were 44.22 ± 7.90 kg, 156.26 ± 10.62 cm, and 18.09 ± 2.61 kg/m². Mean duration of symptoms was 10.40 ± 6.69 days. Majority of the patients {114 (50.7%)} presented with ≤ 10 days of duration of symptoms.¹¹ The present study was partially consistent with the above reported research wherein out of 254 patients, 159 (62.6%) were male and 95 (37.4%) were female showing male predilection with a median age of 8.26 ± 3.06 years. Mean weight was reported as 22.65 ± 9.54 kg for both genders. On the contrary, the present study reflected inconsistency in a manner that

majority of the suspected children 150 (59.1%) presented symptoms with less than 4 weeks of duration.

Similarly, one research assessed that even though the Xpert MTB/RIF test was incapable to detect roughly 21% of the culture positive cases, the median time to TB identification was significantly not longer than that for LJ and MGIT culture techniques.¹² As far as the present study is concerned, 28.7% cases were positive on LJ culture whereas 24.8% cases were positive on Xpert MTB/RIF assay proving additional positive cases were detected by Xpert assay on the other hand, the present study did not reveal the median time of TB detection by using culture and both MTB/RIF assay.

Likewise, a cross-sectional design was conducted to detect Mycobacterium tuberculosis complex (MTBC) and RIF resistance using the Xpert MTB/RIF assay. Out of 116 sputum samples inspected, 28 (24.1%) were MTBC positive by culture, whereas 34 (29.3%) were positive by Xpert assay. It was concluded that about 11.7% and 50% more positive cases detected by GeneXpert than Löwenstein-Jensen culture and smear microscopy, correspondingly. Therefore, GeneXpert MTB/RIF assay is a supportive and valuable tool for prompt diagnosis and treatment of TB.¹³ Likewise, the present study corroborated the above mentioned research and indicated that detection of mycobacterium tuberculosis by Löwenstein-Jensen culture showed positive results in 28.7% cases while it was precisely detected by Xpert MTB/RIF in 24.8% cases reflecting the accurateness of this diagnostic tool.

Similarly, another research demonstrated the diagnostic accuracy of Xpert Ultra to identify MTBC. In their study specificity, sensitivity, NPV, and PPV of Xpert Ultra to identify MTBC in pediatric population were 77.14%, 50%, 96.43%, and 11.11% respectively.¹⁰ The present study endorsed the above reported research and revealed that overall sensitivity, specificity, NPV, and PPV of Xpert Ultra to detect MTBC in studied individuals were 52.2%, 95.3%, 93.2% and 95.2% respectively, reflecting the accurateness of Xpert MTB/RIF sputum test.

A Chinese study revealed a marginally greater sensitivity of Xpert MTB/RIF for identification of tuberculosis.¹⁴ Conversely, an Ethiopian research has described a lower sensitivity of Xpert MTB/RIF for identification of tuberculosis.¹⁵ These findings were supported by the present study that revealed a lower sensitivity with greater specificity of Xpert MTB/RIF for identification of tuberculosis.

Prompt diagnosis along with detection of drug resistance is the imperative entity for timely and successful treatment of multidrug-resistant TB. One of the studies reported the specificity and sensitivity of the Xpert MTB/RIF assay for recognition of TB was 88.4% and 86.0%, respectively. Additionally, PPV was reported 71.5% whereas NPV was 95.1%.¹⁶ The present study endorsed the above reported research and revealed that overall sensitivity, specificity, NPV, and PPV of Xpert Ultra to detect MTBC in studied individuals were 52.2%, 95.3%, 93.2% and 95.2% reflecting the accurateness of Xpert MTB/RIF sputum test.

Another study conducted in Thailand reported a marginally lower specificity among suspected cases of TB with smear-negative sputum.¹⁷ Another large prospective analysis showed 95.7% specificity. Moreover, sensitivity and positive predictive value of Xpert MTB/RIF in culture-negative but clinically diagnosed TB was 37.8% and 83.8%, correspondingly.¹⁸ The present study endorsed the above reported research and revealed that overall sensitivity, specificity, NPV, and PPV of Xpert Ultra to detect MTBC were 52.2%, 95.3%, 93.2% and 95.2% respectively.

Moreover, an international study reported a low sensitivity with high specificity, positive and negative predictive value for tuberculosis

diagnosis by Xpert MTB/RIF.¹⁹ Overall, according to the present study, the validity of Xpert MTB/RIF assay was exquisitely sensitive and extremely specific with a high diagnostic accuracy that could help in prompt diagnosis and treatment.

It evidently supported the fact that Xpert MTB/RIF is an extremely specific test for the identification of pulmonary tuberculosis.¹⁵ These findings were consistent with an International study that reported a high positive and negative predictive value for the recognition of mycobacterium tuberculosis.¹¹ The present study was consistent with the above reported researches and revealed a high positive and negative predictive value for the detection of mycobacterium tuberculosis.

There are certain limitations of this study that should be considered. The results of this research cannot be generalized as the enrolled cases were from a single center and the adult population was not included. Moreover, this study did not evaluate drug resistant mycobacterium. Therefore, it is suggested that more studies using Xpert MTB/RIF should be done concentrating on multiple drug resistant mycobacterium. Moreover, a study on adult population should be carried out to further elucidate this assay.

CONCLUSION

Since the management of TB among children is always a challenge, thus a better and more rapid diagnosis could help in a better prognosis. The study concluded that the diagnostic accuracy of the Xpert MTB/RIF sputum test is very much acceptable in the case of pulmonary tuberculosis among children with suspected TB by taking the Lowenstein-Jensen base gold standard.

Conflict of interest: None

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