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Evaluation of Xpert Ultra Assay in Stool for the Diagnosis of Pulmonary Tuberculosis in Under 5 Children

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ABSTRACT

Background: *Diagnosis of paediatric pulmonary tuberculosis (PTB) is a challenge. Symptoms of tuberculosis are nonspecific in children. Young (specially under 5) children are unable to expectorate sputum samples; the procedures for obtaining respiratory samples are invasive. So, stool samples were used as an alternative to respiratory samples for the diagnosis of pediatric PTB using stool Xpert MTB/ RIF Ultra assay. The World Health Organization also recommends the Xpert MTB/RIF Ultra assay for diagnosing pulmonary tuberculosis (PTB) in children. A very few studies were conducted to determine the diagnostic performance of Xpert Ultra on stool specimen. Thus, we assessed the diagnostic performance of Xpert Ultra on stool to diagnose PTB in under 5 children.*

Objectives: *To evaluate Xpert Ultra assay using stool specimen alternative to induced sputum for the diagnosis of pulmonary tuberculosis in under 5 children.*

Methods: *We conducted a cross sectional study among consecutively recruited children (under 5 years of age) with presumnptive PTB admitted in Sir Salimullah Medical College Mitford Hospital Dhaka, Bangladesh, between July 2020 to December 2021. Single induced sputum and stool specimen were subjected to Xpert Ultra. We considered children as bacteriologically confirmed case of PTB either it was Xpert Ultra positive on induced sputum or stool. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24), where required.*

Results: *Out of 83 children, 6 (7.2%) patients were detected as pulmonary tuberculosis in Xpert Ultra on induced sputum and 13 (15.7%) patients were detected in Xpert Ultra on stool. Among 13 patients 9 patient had "trace call". Induced sputum as a reference, Xpert Ultra on stool has sensitivity 83.3% and specificity 89.61%. When we considered trace call" as negative, then sensitivity reduced to 66.7% and specificity increased to 97.4%.*

Conclusion: *Stool sample has the potential of detecting Mycobacterium Tuberculosis using Xpert Ultra assay. So, introduction of stool as a sample for Xpert Ultra assay to diagnose pulmonary tuberculosis in younger children (below 5 years) having PTB could be a solution to overcome challenges of getting respiratory samples.*

Keywords: *Paediatric pulmonary tuberculosis (PTB), Tuberculosis, Xpert Ultra, Stool specimen*

I. INTRODUCTION

Tuberculosis (TB) remains a major public health problem even after more than 20 years of being declared as a global public health emergency. [1] The World Health Organization estimates that tuberculosis remains the second leading cause of death among the infectious diseases after Human immune Deficiency Virus (HIV) worldwide. It is estimated that more than 1.3 million people die each year from TB. [2] Global reports 2020 estimates about 230000 children died from TB in 2019. [3]

Geographically, most people who developed TB in 2019 were in the WHO regions of South East Asia (44%), Africa (25%) and the Western Pacific (18%), with smaller percentages in the Eastern Mediterranean (8.2%), the Americas (2.9%) and Europe (2.5%). Eight countries accounted for two thirds of the global total: India (26%), Indonesia (8.5%), China (8.4%), the Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%). The other 22 countries in WHO‟s list of 30 high TB burden countries accounted for 21% of the global total. [4] It is estimated that with accurate diagnosis and good reporting systems, children less than 15 years are likely to contribute 4-22% of disease burden in 22 high burden countries of the world.

In Bangladesh, according to UN data in 2020 has a population of 164.69 million and estimated children <15 years is 44.14 million (26.8%) (National guidelines for the management of tuberculosis in children, 2021). In 2020 total estimated number of childhood TB cases in Bangladesh were 43320 (12% of estimated cases). [4] The number of missing childhood TB cases in 2019 was 30970, which was 71% of child cases (among of all missing cases 45% were children). In 2013 to 2018 total TB diagnosed cases among children were 50254; among <5 years children it was 11% (5461) and 5-14 years were 89% (44793). Children <5 years of age were grossly underdiagnosed. [4]

TB can progress very rapidly in children because of their immature immune system. [5] So, rapid detection of TB in children should enable more rapid treatment and improved outcomes. [6] But the diagnosis of TB in children is not straight forward as in adult TB patient, hence it requires careful & thorough assessment of all the data derived from a history, clinical examination & relevant investigation, e.g. Mantoux test (MT), Chest X-ray, smear microscopy & other investigations. The MT test is often negative in malnourished children or in other immunocompromised condition and a positive MT only indicates infection with M. Tuberculosis, does not always indicate active disease. [4] Moreover, the reading of the test of tuberculin skin test requires experience and care. Inexperience can lead to error. So, there may be a large chance of misinterpretation of MT test. [7] The diagnosis of childhood pulmonary tuberculosis is also very difficult by Chest X-ray. Because the X-ray are often nonspecific in children and prone to variable interpretation. [4] There are variable nonspecific findings may be found which may suggestive of PTB but does not indicate active disease. Chest X-ray shows very low specificity 52% to confirm the diagnosis of pulmonary tuberculosis. [7]

So, pulmonary tuberculosis in children can't be diagnosed just on the basis of MT and Chest x-ray. For this reason, respiratory specimen or gastric lavage have to collect to diagnose the pulmonary tuberculosis. [6] But sputum from children is often paucibacillary, as children are less likely to form cavitary lesions in lungs to contain the bacilli. [8] Sputum microscopy is not always possible for young children, who can't cough up sputum for microscopic examination. So, sputum sample collection has now been strongly pushed for the older children who are capable of producing sputum. Now a day's sputum induction has been documented to be an effective method for the collection of specimens in younger children. [3] Childhood TB can also be diagnosed by testing early morning gastric aspirates. [9] But the collection procedure of these specimen is invasive and the diagnostic yield ranges from only 20–40%. [6]

Children are therefore often treated empirically for TB, based on clinical features, chest x-ray findings, tuberculin skin tests, and contact with an index patient. This approach may lead to both over and under treatment. [10] Previous studies have shown high sensitivity of PCR (Gene Xpert) when induced sputum [11] and gastric lavage [12] were used. Gene Xpert was therefore endorsed by the World Health Organization as an initial test for diagnosing TB in children. [13] Xpert MTB/RIF Ultra (Ultra; Cepheid), a new diagnostic for TB on the Gene Xpert platform, has a substantially lower limit of detection than Gene Xpert and improved sensitivity. Recently reported that the sensitivity and specificity of Xpert Ultra test done on one induced sputum (IS) in children with suspected PTB was 77% and 97% respectively, compared with liquid culture. [14] WHO recommended, Xpert Ultra as initial diagnostic test for TB in children. Forty-three studies (21 countries) evaluated Xpert Ultra in sputum specimen and sensitivity found on sputum 65%. [15]

Children tend to swallow sputum when they cough and M. tuberculosis remains intact in the gastro-intestinal tract. [16] Therefore, stool specimen can detect M. Tuberculosis for the diagnosis of pulmonary tuberculosis in younger children and sample collection can easily take place in the field or in clinics. [17] Moreover, culture confirmation of disease can take several weeks and disease progresses rapidly in young children. [12] So, rapid diagnostic methods such as PCR (Xpert Ultra) MTB/RIF are an important advance. Previously Gene Xpert on stool had sensitivity and specificity of 37.9% and 100.0%, respectively. However, the limit of detection (LOD) for Gene Xpert is 131 CFU/ml, and specimens with load less than the LOD are missed. Stool specimens have a low load of Mycobacterium tuberculosis (MTB) due to challenges in its processing and lack of standard procedures. Thus, molecular tests with lower LOD could be beneficial. Xpert MTB/RIF Ultra assay (Xpert Ultra, Cepheid) was developed with an LOD of 16 CFU/ml and improved rifampin resistance determination. The sensitivity and specificity of Xpert Ultra on stool are 88.9% and 88.1%, respectively. Compared to Gene Xpert, the Xpert Ultra has an additional semiquantitative category called "trace call"

corresponding to the lowest bacillary burden. The Xpert Ultra has better sensitivity compared to Gene Xpert in detecting paucibacillary TB. [18]

II. METHODOLOGY

This cross-sectional study was carried out in the Department of Paediatrics, Sir Salimullah Medical College Mitford Hospital (SSMCMH), Dhaka during July 2020 to December 2021. A total of 83 patients were participated in the study. Children less than 5 years of age who fulfill the clinical criteria for diagnosis of PTB in children according to NATIONAL GUIDELINES FOR THE MANAGEMENT OF TUBERCULOSIS IN CHILDREN (October, 2021) admitted in department of paediatrics of SSMCMH during the specified period of time. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).

III. RESULTS

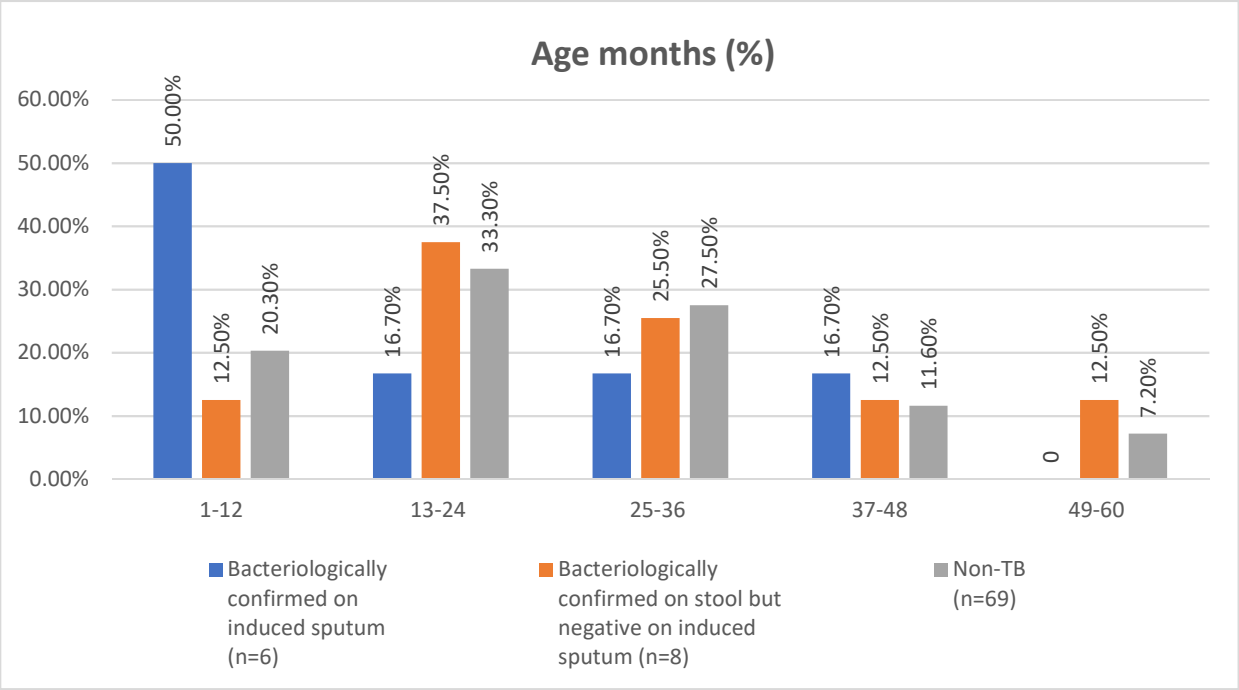

Table-1: Age distribution of the study population

Fig 1 shows the age distribution of the study population, it was observed that patients were belonged to age 1-5 months. According to 1-12 months the bacteriologically confirmed on induced sputum, bacteriologically confirmed on stool but negative on induced sputum and non-TB were 50%, 12.5% and 20.3% respectively.

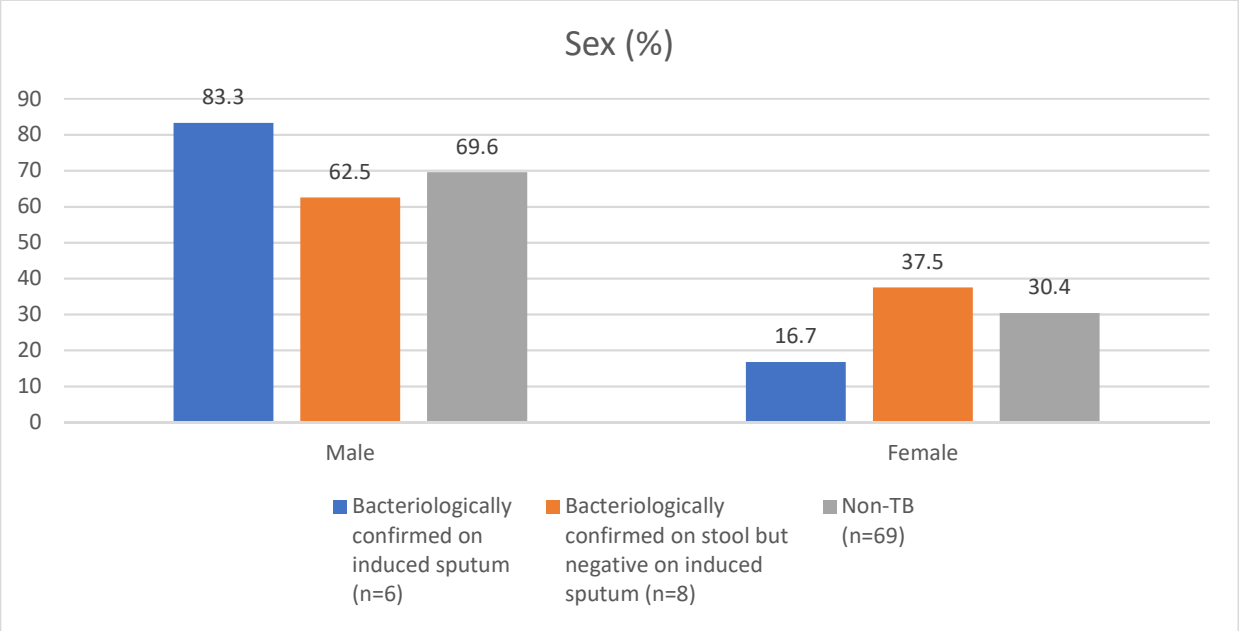

Table -2: Sex distribution of the study population

Fig 2 shows sex distribution of the study population, it was observed that according to bacteriologically confirmed on induced sputum the male and female were 83.3% and 16.7% respectively.

Table-1: Demographic distribution of the patients (n=83)

Characteristics	Total (N=83)	Bacteriologically confirmed on induced sputum (n=6)	Bacteriologically confirmed on stool but negative on induced sputum (n=8)	Non-TB (n=69)
Nutrition status				
malnutrition	17	1 (16.7%)	0 (0.0%)	16 (23.2%)
No malnutrition	66	5 (83.3%)	8 (100.0%)	54 (78.3%)
Cough				
No cough	1	0 (0.0%)	0 (0.0%)	1 (1.4%)
> 2 wks	82	6 (100%)	8 (100.0%)	68 (98.6%)
Fever				
No fever	4	0 (0.0%)	0 (0.0%)	4 (5.8%)
> 2 wks	79	6 (100%)	8 (100.0%)	66 (95.7%)
Weight loss				
Yes	24	2 (33.3%)	6 (75.0%)	16 (23.2%)
No	59	4 (66.7%)	2 (25.5%)	53 (76.8%)
Less activity				
Yes	36	5 (83.3%)	7 (87.5%)	24 (34.8%)
No	47	1 (16.7%)	1 (12.5%)	45 (65.2%)
Chest X-ray				
Suggestive	75	6 (100.0%)	8 (100.0%)	61 (88.4%)
Not suggestive	8	0 (0.0%)	0 (0.0%)	8 (11.6%)

Table-1 shows most of the children were 13 -24 months of age & the study was male dominant.

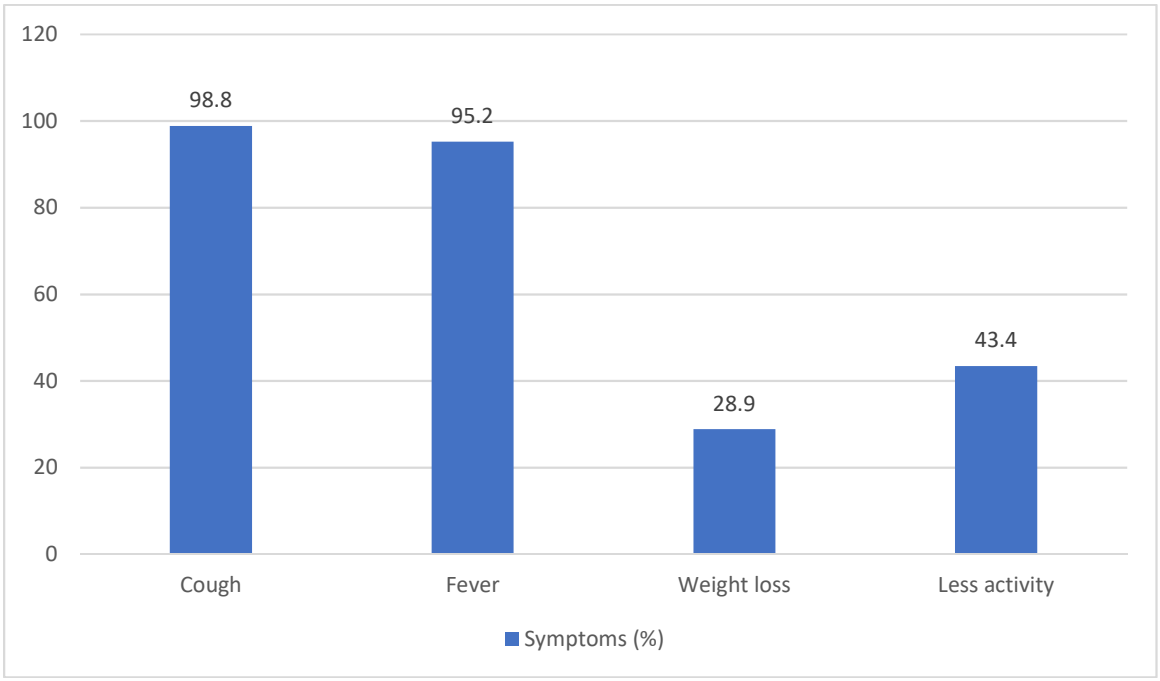

Figure-3: Distribution of Patients according to symptoms criteria (n=83)

Figure-3 shows the distribution of patients according to symptoms, where most of the children 82 (98.8%) presented with cough, then fever 79 (95.2%), weight loss 24 (28.9%) and less activity was present in 36 (43.4%) children.

Table-2: Distribution of the patients according to history of TB contact (n=83)

History of TB contact	History of TB contact	History of TB contact
Yes	Yes	Yes
12	12	12
14.5	14.5	14.5

Table- 2 Shows 12 (14.5%) patients had history of TB contact.

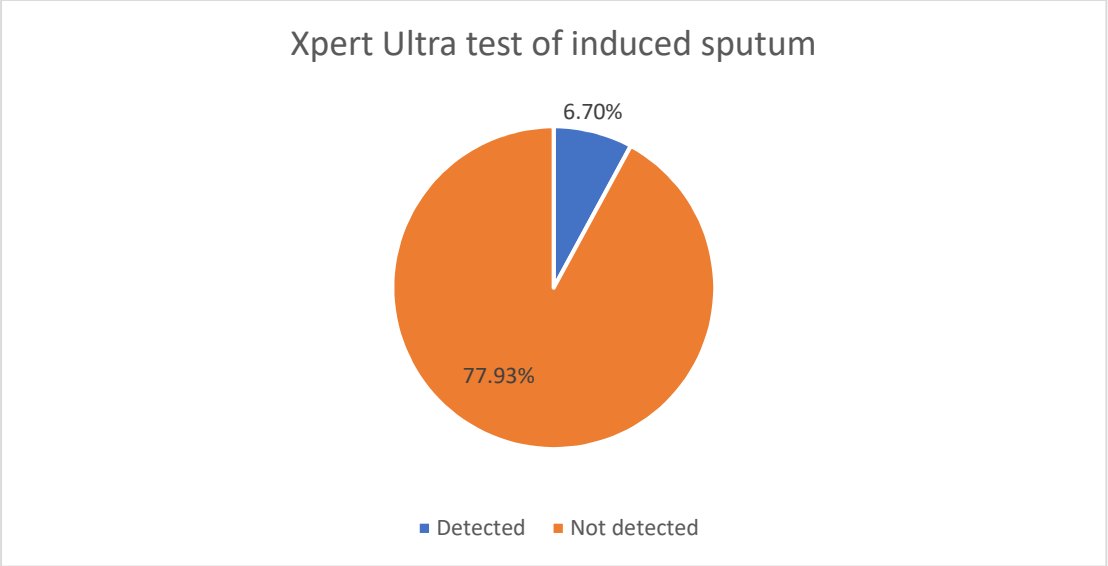

Figure-4: Distribution of Patients according to Xpert Ultra test of induced sputum (n=83)

Figure-4 shows among the studied patient 6 (7%) were detected as PTB by Xpert Ultra test of induced sputum.

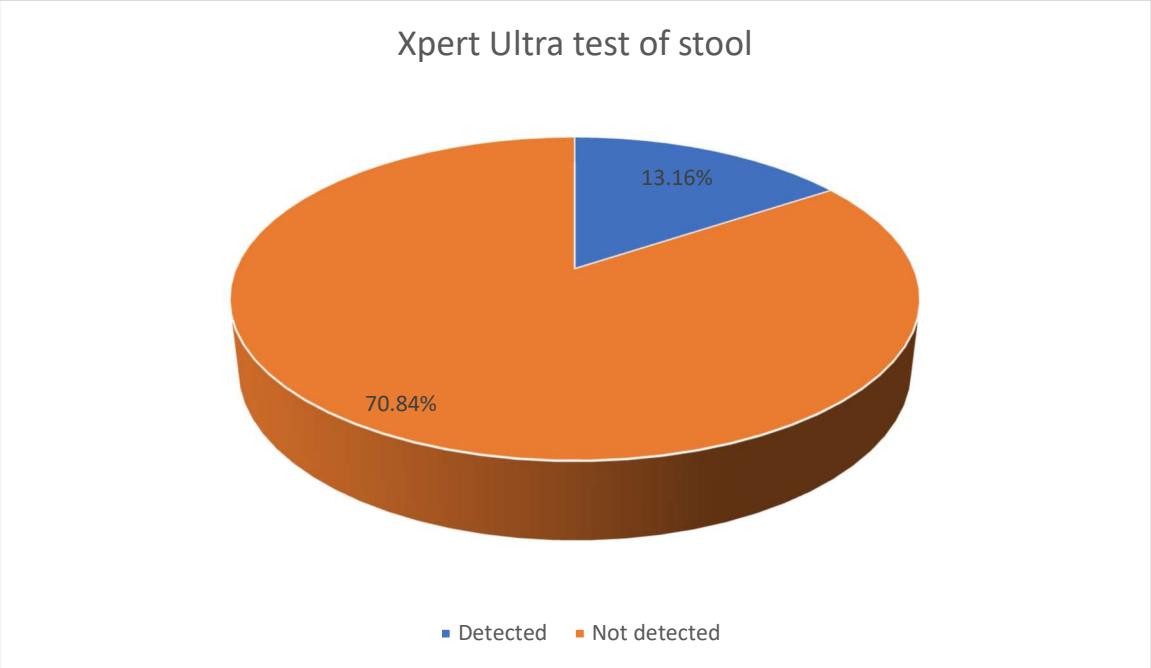

Figure-5: Distribution of Patients according to Xpert Ultra test of stool (n=83)

Figure-5 shows among the studied patient 13 (16%) patients were detected as PTB by Xpert Ultra test of stool.

Table-3: Association between clinical criteria and Xpert Ultra test of induced sputum in study subjects (n=83)

Clinical features	Xpert Ultra test of induced sputum		p-value
	Detected (n=6)	Not detected (n=77)	
Cough	6 (100.0%)	76 (98.7%)	1.000
Fever	6 (100.0%)	73 (94.8%)	1.000

Weight loss	3 (50%)	21 (27.3%)	0.349
Less activity	5 (83.3%)	31 (40.3%)	0.081
History of contact TB	3 (50%)	9 (11.6%)	0.037*

p-value reached from fisher exact test, * significant

Table-3 shows, result of Xpert Ultra test of induced sputum had significant association with history of TB contact (P<0.05). However, no significant association was found with cough, fever, weight loss and less activity.

Table-4: Association between clinical criteria and Xpert Ultra test of stool in study subjects (n=83)

Clinical features	Xpert Ultra test of induced sputum		p-value
	Detected (n=13)	Not detected (n=70)	
Cough	13 (100.0%)	69 (98.6%)	1.000
Fever	13 (100.0%)	66 (94.3%)	1.000
Weight loss	6 (46.2%)	18 (25.7%)	0.183
Less activity	13 (100.0%)	23 (32.9%)	<0.001*
History of contact TB	7 (53.8%)	5 (7.1%)	<0.001*

p-value reached from fisher exact test, *significant.

Table-4 shows, result of Xpert Ultra test of stool had significant association with less activity of children and history of TB contact (P<0.05). However, no significant association was found with cough, fever and weight loss.

Table-5: Association between chest x-ray and Xpert Ultra test of induced sputum in study subject (n=83)

Clinical features	Xpert Ultra test of induced sputum		p-value
	Detected (n=6)	Not detected (n=77)	
Suggestive for TB	6 (100.0%)	69 (98.6%)	1.000^{ns}
Not suggestive for TB	0 (0.0%)	8 (9.8%)	
Total	6 (100.0%)	77 (100.0%)	

p-value reached from fisher exact test, ns= not significant.

Table-5 Shows, no significant association was found for Xpert Ultra of induced sputum with chest X ray findings (P>0.05).

Table-6: Association between chest X-ray and Xpert Ultra test of stool in study subject (n=83)

Chest X ray findings	Xpert Ultra test of induced sputum		p-value
	Detected (n=13)	Not detected (n=70)	
Suggestive for TB	13 (100.0%)	62 (90.2%)	

Not suggestive for TB	0 (0.0%)	8 (9.8%)	1.346[ns]
Total	13 (100.0%)	70 (100.0%)	

p-value reached from fisher exact test, ns= not significant.

Table-6 Shows, no significant association was found for Xpert Ultra test of stool with chest X-ray findings (P>0.05).

Table-7: Comparison between Xpert Ultra test of stool (including trace call) and Xpert Ultra test of induced sputum in study subject (n=83)

Xpert Ultra test of stool (Including trace call)	Xpert Ultra test of induced sputum		p-value
	Detected (n=6)	Not detected (n=77)	
Detected (13)	5 (83.3%)	8 (10.4%)	<0.001*
Not detected (70)	1 (16.7%)	69 (89.6%)	
Total	6 (100.0%)	77(100.0%)	

p-value reached from fisher exact test, *= significant.

Table-7 shows a total of 5 (6%) patients out of 83 were detected having tuberculosis by both induced sputum and stool test (including trace call).

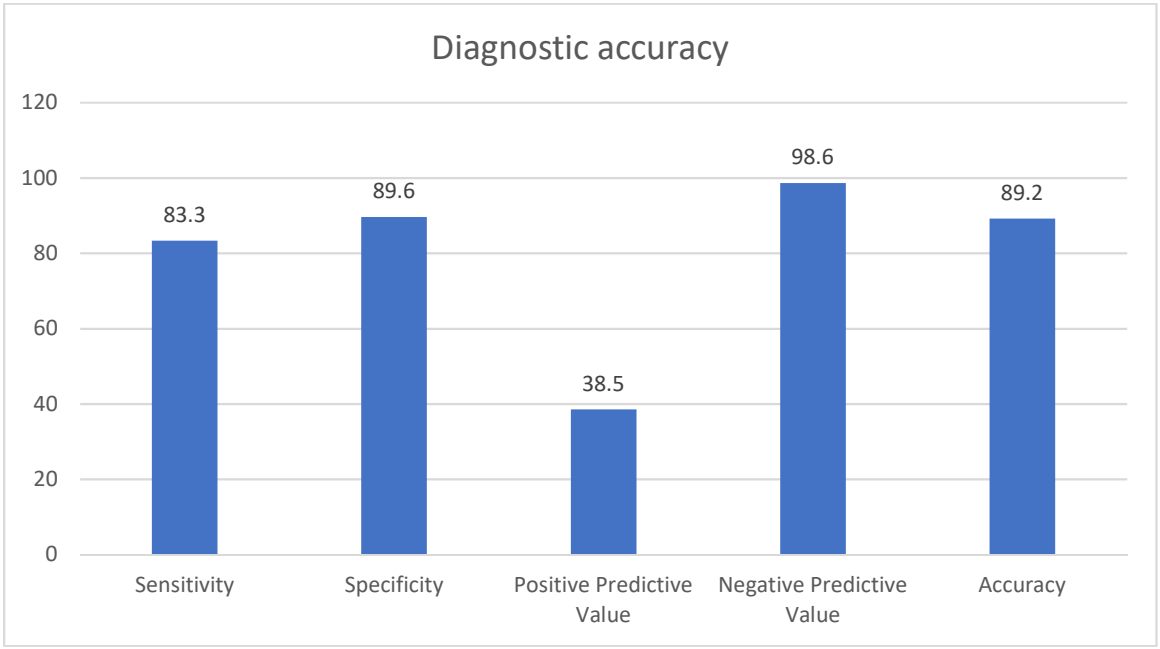

Figure-6: Diagnostic validity of Xpert Ultra test of stool (including trace call) compared to Xpert Ultra test of induced sputum (n=83)

Figure-6 shows considering Xpert Ultra test of Induced sputum as standard, the present study found 83.3% sensitivity, 89.6% specificity, 38.5% PPV and 98.6% NPV respectively with 89.2% accuracy of Xpert Ultra test of stool (including trace call).

Table-8: Comparison between Xpert Ultra test of stool (excluding trace call) and Xpert Ultra test of induced sputum in study subject (n=83)

Xpert Ultra test of stool (excluding trace call)	Xpert Ultra test of induced sputum		p-value
	Detected (n=6)	Not detected (n=77)	
Detected (6)	4 (66.7%)	2 (2.6%)	

Not detected (77)	2 (33.3%)	75 (97.4%)	<0.001*
Total	6 (100.0%)	77(100.0%)	

p-value reached from fisher exact test, *= significant.

Table-8 shows, a total of 4 (4.8%) patients out of 83 were detected having tuberculosis by both induced sputum and stool test (excluding trace call).

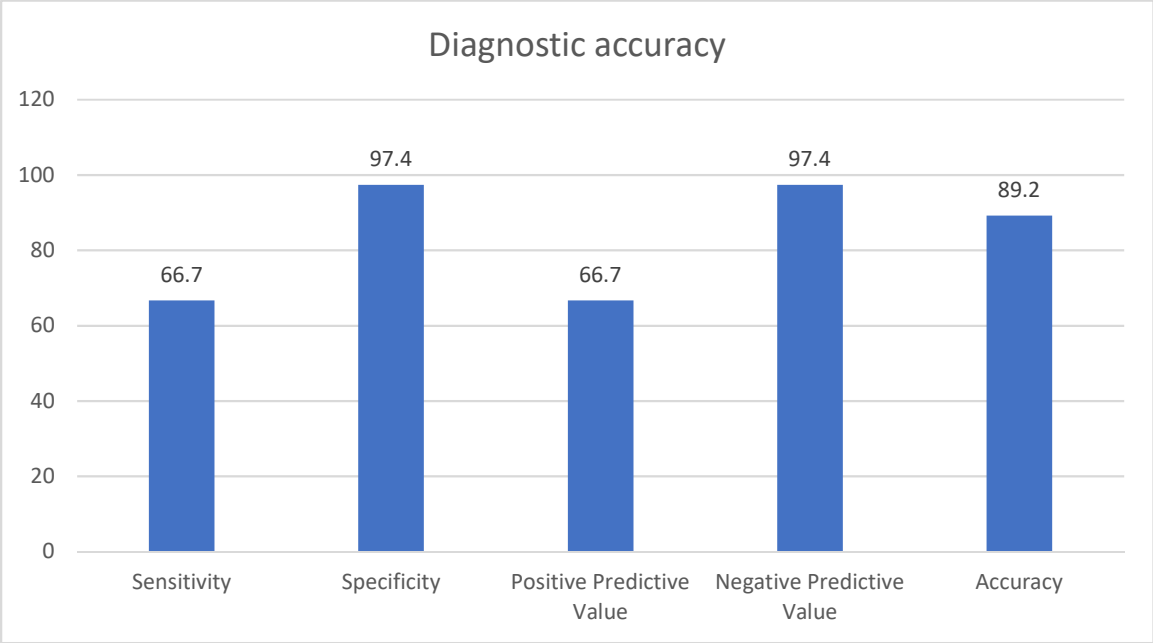

Figure-7: Diagnostic validity of Xpert Ultra test of stool (excluding trace call) compared to Xpert Ultra test of induced sputum (n=83)

Figure-7 shows considering Xpert Ultra test of Induced sputum as standard, the present study found 66.7% sensitivity, 97.4% specificity,66.7% PPV and 97.4% NPV respectively with 95.2% accuracy of Xpert Ultra test of stool (excluding trace call).

IV. DISCUSSION

This cross-sectional analytical study was done in the Department of pediatrics in Sir Salimullah Medical College Mitford Hospital, Dhaka from July 2020 to December 2021. Total 86 presumptive PTB children were included in the study. 3 children were excluded as they were refused to provide induced sputum. So, data of 83 children were analyzed.

In current study 18 (22%) patient were positive and 65 (78%) were negative in Mantoux Test. Chest x-ray shows suggestive PTB was 75 (90.4%). All the positive result of Xpert ultra of induced sputum & stool lies within these 75 children. Current study also shows history of TB contact has significant relation with Xpert Ultra on induced sputum test. This current study compared clinical sign-symptoms of the patient with Xpert Ultra on stool. Here we found less activity and history of TB contact have significant relation with Xpert Ultra on stool test (p value <0.001).

In our current study 6 (7.2%) patients were detected as pulmonary tuberculosis in Xpert Ultra on induced sputum and 13 (15.7%) patients were detected in Xpert Ultra on stool. Among these 13 (15.7%) patients 5 patients was also detected in induced sputum. So, another 8 patients were only detected in stool test. Generally, MTB detection on Induced sputum is higher than MTB detection on stool but here it shows MTB detection in induced sputum is less than stool. It may be due to the collection technique. Induced 54 sputum collection process was invasive & the children did not allow collecting the induced sputum, it had to collect forcefully. So, there may be inadequate amount of induced sputum to detect Mycobacterium Tuberculosis as MTB is paucibacillary in children. But in case of collection of stools, there is no such problem as it is a natural process.

Sensitivity, specificity, positive predictive value and negative predictive value of stool (Xpert Ultra) were compared with that of Xpert Ultra on induced sputum. Xpert Ultra on stool has sensitivity 83.3% (95% CI 35.88% to 99.58%), Specificity 89.61% (95% CI 80.55% to 95.41%). Kabir et al. 2020 study showed sensitivity

& specificity of stool Xpert Ultra was, 88.9% (95% CI 56.5% to 98.0%) and 88.1% (95% CI 84.7% to 90.8%) respectively. When we considered trace call as negative, sensitivity reduced to 66.7% & specificity increased to 97.4%. kabir et al. 2020 also showed the sensitivity reduced & specificity increased when trace call considered as negative.

This study shows that Xpert Ultra on stool is highly sensitive (83.3%), highly specific (89.6%) with high negative predictive value (98.6%) and high accuracy (89.2%) when compared with that of induced sputum. That means there is less chance of false negative result. So, it can aid in the diagnosis of pulmonary tuberculosis who are highly suggestive of PTB.

In this study when the trace call found in stool specimen but not detected in induced sputum, we didn't repeat the test to confirm positivity. Thus, we might have overestimated the sensitivity & underestimated the specificity. Xpert Ultra is a very sensitive test to diagnose PTB, but the obtaining sample is the main obstacle. This study shown that easily collectable stool sample is very useful to diagnose PTB. Further large scale and multicenter study is needed to draw a more significant inference.

Limitations of the study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

V. CONCLUSION

Stool sample has the potential of detecting Mycobacterium tuberculosis using Xpert Ultra assay. So, introduction of stool as a sample for Xpert Ultra assay to diagnose pulmonary tuberculosis in younger children (below 5 years) having PTB could be a solution to overcome challenges of getting respiratory samples.

VI. RECOMMENDATION

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

ACKNOWLEDGEMENTS

The wide range of disciplines involved in Xpert Ultra assay using stool specimen alternative to induced sputum for the diagnosis of pulmonary tuberculosis in under 5 children research means that editors need much assistance from referees in the evaluation of papers submitted for publication. I would also like to be grateful to my colleagues and family who supported me and offered deep insight into the study.

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