

Xpert Ultra assay on stool to diagnose pulmonary tuberculosis in children

Background

An estimated 11% of children under 15 years of age were affected with tuberculosis (TB) globally, and 170,000 children died due to TB in 2018. Though in Bangladesh, around 10,000 (4%) of total reported TB cases are children, childhood TB (ChTB) diagnosis remains challenging. Children's inability to produce good-quality sputum¹ and collection of alternative specimens involve invasive procedures² are some of the reasons. Other reasons are: paucibacillary³ nature of the disease and lack of an improved laboratory diagnostic. Hence, clinical diagnoses lead to over or under-diagnosis of ChTB. Better ChTB detection, therefore, requires an easy-to-collect specimen along with an enhanced laboratory diagnostic. As children swallow sputum, stool can be a potential alternative for bacteriological confirmation of pulmonary TB (PTB). Several studies found stool to be a promising specimen for both adults and children that can be tested with different laboratory tests, including highly sensitive Xpert MTB/RIF assay⁴. Xpert Ultra is the improved version of Xpert, and has better sensitivity in detecting paucibacillary TB using different pulmonary and extrapulmonary (not related to lungs) specimens. However, with stool, it is not yet evaluated.

This study, supported by USAID's Research for Decision Makers (RDM) Activity, assessed the diagnostic validity and yield of Xpert Ultra on stool specimens in detecting confirmed PTB (caused by bacteria) among children.

Methodology

A facility-based cross-sectional study was conducted in selected four hospitals (Sir Salimullah Medical College and Mitford Hospital, Shaheed Suhrawardy Medical College and Hospital, Dhaka Medical College Hospital and icddr,b Dhaka Hospital) located in Dhaka providing tertiary healthcare services. All admitted children between 0 to >15 years age range with presumptive PTB (children having symptoms suggestive of PTB) from selected hospitals were enrolled between January 2018 and April 2019. Parents/guardians of the presumptive enrolled children were interviewed upon taking informed written consent. Induced sputum and stool specimens were collected from children and transported to the icddr,b mycobacteriology laboratory. The specimens were run through tests (smear for AFB microscopy, culture, and Xpert Ultra assays). All the laboratory test reports were provided to the local physicians and the parents/guardians of the child patients upon their availability. Upon confirmation, the physicians initiated anti-TB treatment in the same health facilities where they were admitted.

Results

Of 454 children with presumptive PTB, seven (1.4%) could not provide stool specimens (**Figure 1**). About 254 (56.8%) were males among the 447 included presumptive children. Aged less than five years were 296 (66.2%), 321 (71.8%) had a cough for >2 weeks, 306 (68.5%) had a fever for >2 weeks, 381 (85.2%) had significant weight loss, and 114 (25.3%) had contact with TB patient in the family within last 12 months. With induced sputum, two (0.4%) were positive by microscopy, nine (2%) by culture, and 28 (6.3%) by Xpert Ultra (**Figure 1**). With stool specimens, four were positive by microscopy (0.9%), two (0.4%) by culture, and 60 (13.4%) by Xpert Ultra (**Figure 1**). In total, 72 (16.1%) were bacteriologically confirmed, of which, 43 (59.7%) were exclusively detected by Xpert Ultra on stool specimen (**Table 1**).

¹ a mixture of saliva and mucus coughed up from the respiratory tract

² procedures involving inserting instrument into the body

³ containing few bacilli, a disease-causing bacteria

⁴ Xpert is a TB diagnosis and antibiotic sensitivity test

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Figure 1: Flow chart showing the enrollment, investigation results, and treatment of children aged under 15 years with presumptive PTB admitted in selected four hospitals of Dhaka, Bangladesh during January-2018 to April-2019, N=447

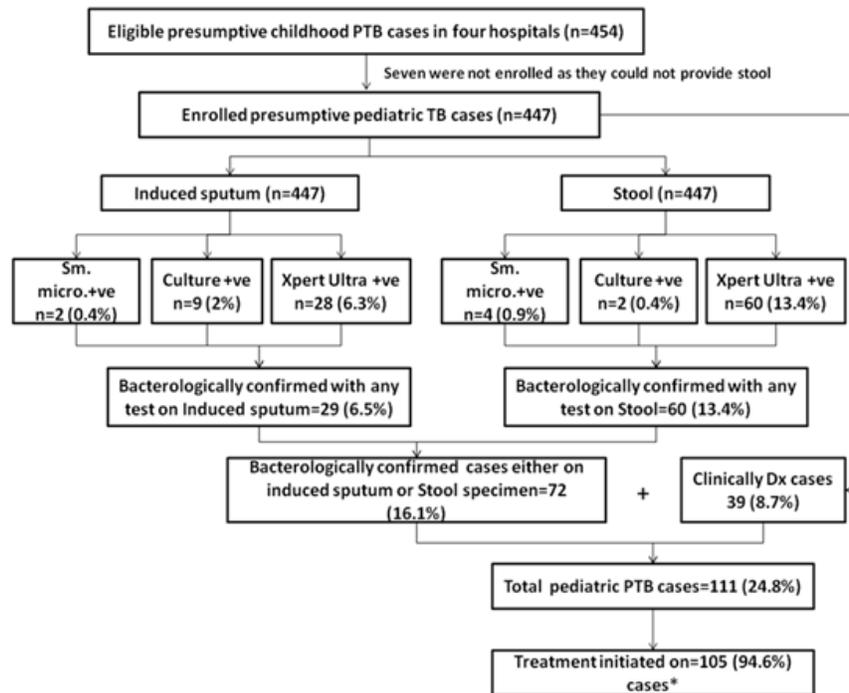


Table 1: Diagnostic validity of Xpert MTB/RIF Ultra assay on stool specimen compared with bacteriological confirmation with induced sputum specimen among children below 15 years with presumptive PTB enrolled from selected four hospitals of Dhaka, Bangladesh during January-2018 to April-2019. N=446#

| Tests on Stool Specimen | | Bacteriological confirmation with induced sputum | | | | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) |
|---|-----|--|---------|-----|---------|--------------------------|--------------------------|
| | | Pos | | Neg | | | |
| | | N | (%)* | n | (%)* | | |
| Total | | 29 | (100.0) | 417 | (100.0) | | |
| Xpert MTB/RIF Ultra | Pos | 17 | (58.6) | 43 | (10.3) | 58.6 (40.7-74.5) | 89.7 (86.4-92.3) |
| | Neg | 12 | (41.4) | 374 | (89.7) | | |
| Xpert MTB/RIF Ultra (trace call as negative) | Pos | 11 | (37.9) | 1 | (0.2) | 37.9 (22.7-56.0) | 99.8 (98.7-100.0) |
| | Neg | 18 | (62.1) | 416 | (99.8) | | |

* Column percentage

One stool specimen showed invalid result on Xpert Ultra

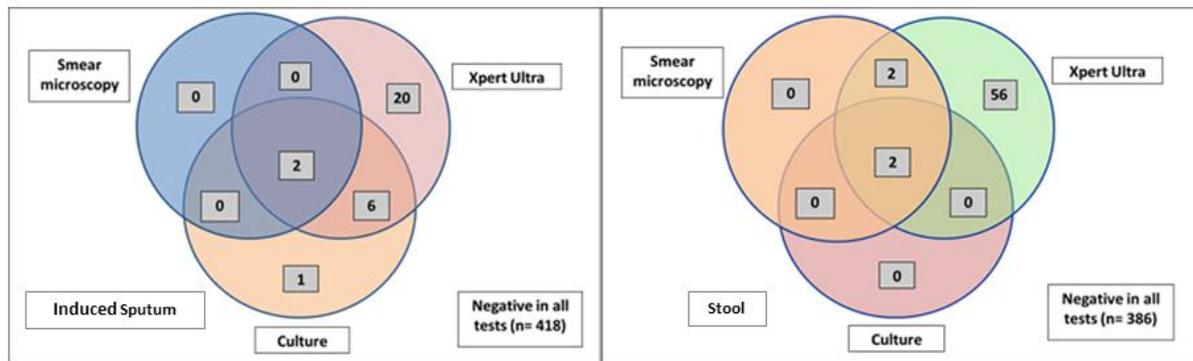
PTB-pulmonary tuberculosis; Pos-positive; Neg-negative

Altogether, 29 (6.5%) were bacteriologically confirmed on induced sputum, of which 20 (68.9%) were exclusively diagnosed with Xpert Ultra (Figure 2). Among the total of 60 (13.4%) that were detected as TB on stool specimens, 56 (93.3%) were exclusively detected with Xpert Ultra (Figure 2).

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Figure 2: Venn-diagram depicting the bacteriological confirmation using culture, Xpert MTB/RIF, and Xpert MTB/RIF Ultra assays on induced sputum and stool specimens from children below 15 years with presumptive PTB enrolled from selected four hospitals of Dhaka, Bangladesh during January-2018 to April-2019, N=447



In this study, the sensitivity of Xpert Ultra on stool specimens was higher compared to the previously conducted studies on Xpert on stool specimens. However, the majority (about eight out of ten patients) of positive patients on Xpert Ultra on stool specimen had very few *M. tuberculosis*, categorized as 'trace call.' In some cases, pediatricians had reservations regarding the management of children with trace calls, as false positivity was not ruled out by performing repeat tests. Considering 'trace call' as negative, the sensitivity of Xpert Ultra reduced, with improved specificity. A high proportion of stool specimens positive by Xpert Ultra were negative on induced sputum in this study. Overall, Xpert Ultra on stool specimen detected 7.2% additional child PTB patients.

Implications

The study found that stool has better sensitivity in children compared to the reference test. Moreover, the stool is a superior specimen to induced sputum in PTB diagnosis by using Xpert Ultra. Therefore, stool can be used for TB detection when respiratory specimen collection is challenging. However, considering the high proportion of 'trace call' results among Xpert Ultra positive stool specimens, the study recommends future longitudinal studies looking at clinical prognosis to suggest the management of children with 'trace call'. At present, icddr,b is implementing a large-scale study, awarded by the Stop TB partnership through TB REACH Wave 7 where Xpert Ultra is being performed in all pulmonary and extrapulmonary specimens including stool for pulmonary TB to increase Child TB diagnosis.

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