



New Approach for Childhood TB Diagnosis: Experiences From A Recent Study

USAID's Research for Decision Maker's (RDM) activity,
Implemented by icddr,b: In collaboration with National TB Control Program

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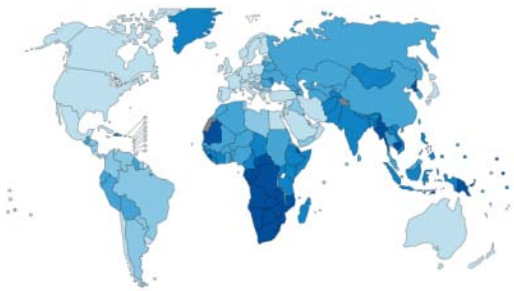
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Disclaimer

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The Global Burden of Tuberculosis (TB): 2019

TB is the leading cause of death from an infectious disease alongside HIV



Estimated number
of cases

Estimated number
of deaths

All forms of TB

10.0 million

1.45 million

HIV-associated TB

0.86 million (8.6%)

251,000

Drug-resistant TB
(MDR+RR)

0.48 million

214,000

TB Burden in Bangladesh

- Population: **161 million**
- Estimated TB cases: **357,000** per year (~**267,000** detected)
- Estimated MDR-TB cases: **5,900** per year (**1228Dx/1147Rx**)
- Estimated number of deaths from TB: **47,200** per year
- MDR-TB rate: **1.5% (New) & 4.9% (Retreatment)**
- NTP introduced DOTS strategy : **1993**
- DOTS geographical coverage : **100% (since 2007)**

Ref: Global TB Report 2019, Annual Report 2018, NTP, Bangladesh & WHO estimates

TB Burden in Children

- Globally, an estimated 11% (~1 million) of the incident TB cases are childhood TB (child TB)
- Annually around 170,000 children died due to TB worldwide
- In **Bangladesh**, around 4% (~10,000) of total reported TB cases are children against an expected 11%
- Immune system is under-developed, younger children are more at risk
- TB infected children develop active TB disease within 2 years of exposure and of them, 90% develop within the 1st year
- Risk of severe forms of TB (TB meningitis, TB with sepsis etc.) and progression to death is higher if primary infection occurs at age <5 years

Ref: Global TB Report 2019

Recommended Approach for Child TB Diagnosis

- Careful history (including contact history and TB suggestive symptoms)
- Clinical assessment
- Investigations-
 - Mantoux test
 - Chest X-ray and other radiological evaluation
 - Bacterial confirmation whenever possible
 - Relevant investigations
 - HIV testing

Ref: National Child TB Guideline 2nd Edition, 2016

Presumptive Child TB Cases

- Persistent, non-remitting cough for >2 weeks not responding to conventional antibiotics, and/or
- Persistent documented fever ($>38^{\circ}$ C/ 100.4° F) for >2weeks, and/or
- Documented weight loss or not gaining weight during the past 3 months, OR severe malnutrition, and/or
- Fatigue, reduced playfulness, decreased activity

NOTE: Child <15 years old with close contact with B+/clinically confirmed TB should be considered as presumptive TB case and referred for further evaluation

Ref: National Child TB Guideline 2nd Edition, 2016

WHO Criteria for Child TB Diagnosis

- Presence of ≥ 3 of the following features suggests TB diagnosis:
 - TB suggestive symptoms (prolonged fever, prolonged cough, weight loss, decreased activity, loss of appetite)
 - Recent close contact (within 12 months)
 - Physical signs highly suggestive of TB
 - Positive Mantoux test
 - TB suggestive chest X-ray
 - Special laboratory test- CSF, Histopathology

NOTE: Child with only 2 features and other criteria from “Recommended approach to Child TB Dx” are not helpful in diagnosis, expert opinion needed to proceed further

Ref: National Child TB Guideline 2nd Edition, 2016

Gaps in Child TB Diagnosis

- **Diagnosis is difficult due to:**
 - **Similarity of clinical features and radiographic impression with other lung diseases**
 - **Inability to expectorate sputum**
 - **Difficulty in collection of alternative respiratory specimens (induced sputum/ gastric lavage)**
 - **Paucibacillary nature of *M. tuberculosis* (MTB) that results in lower diagnostic yield**
 - **Lack of sensitive tool for Child TB diagnosis**
- **Diagnosis mostly clinical: leads to over and under diagnosis**

What is Required?

- An “improved laboratory diagnostic test” for better detection of Child TB
- An alternative and “easy to collect” specimen when respiratory specimen collection is difficult

Improved Diagnostic: Xpert Ultra

- Advanced version of Xpert MTB/Rif Assay
- Detects *Mycobacteria* from specimen with low bacterial load (16 CFU*/ml)
- In March 2017, WHO recommended Xpert Ultra as an
 - initial diagnostic test, specifically for paucibacillary cases (sm-ve** TB, children, EPTB and TB-HIV patients)
- Adult (with paucibacillary disease)***:
 - Sm-ve PTB: Sensitivity 79% and specificity 96% compared to culture
 - EPTB: Sensitivity 95% among B+ve TB meningitis cases
 - TB-HIV: Sensitivity 67% among children;
- Children*: 74% sensitive and 97% specific compared with culture using induced sputum (IS)

* **Atherton RR et al., Review Article on Xpert Ultra for TB in Children, *Frontiers in Pediatrics* Feb 2019

RESEARCH ARTICLE

Evaluation of Xpert MTB/RIF assay for detection of *Mycobacterium tuberculosis* in stool samples of adults with pulmonary tuberculosis

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- Xpert was 90% sensitive for MTB detection in stool of adult PTB patients
- Stool Xpert showed 95% sensitivity in culture positive sputum and was full concordant in Rif susceptibility
- Stool Xpert was suggested to be applied as potential alternative to sputum for detection of MTB and RIF susceptibility in adult PTB patients who cannot expectorate sputum

Study Title

Evaluation of Xpert MTB/RIF Ultra for the diagnosis of childhood pulmonary tuberculosis using stool specimen

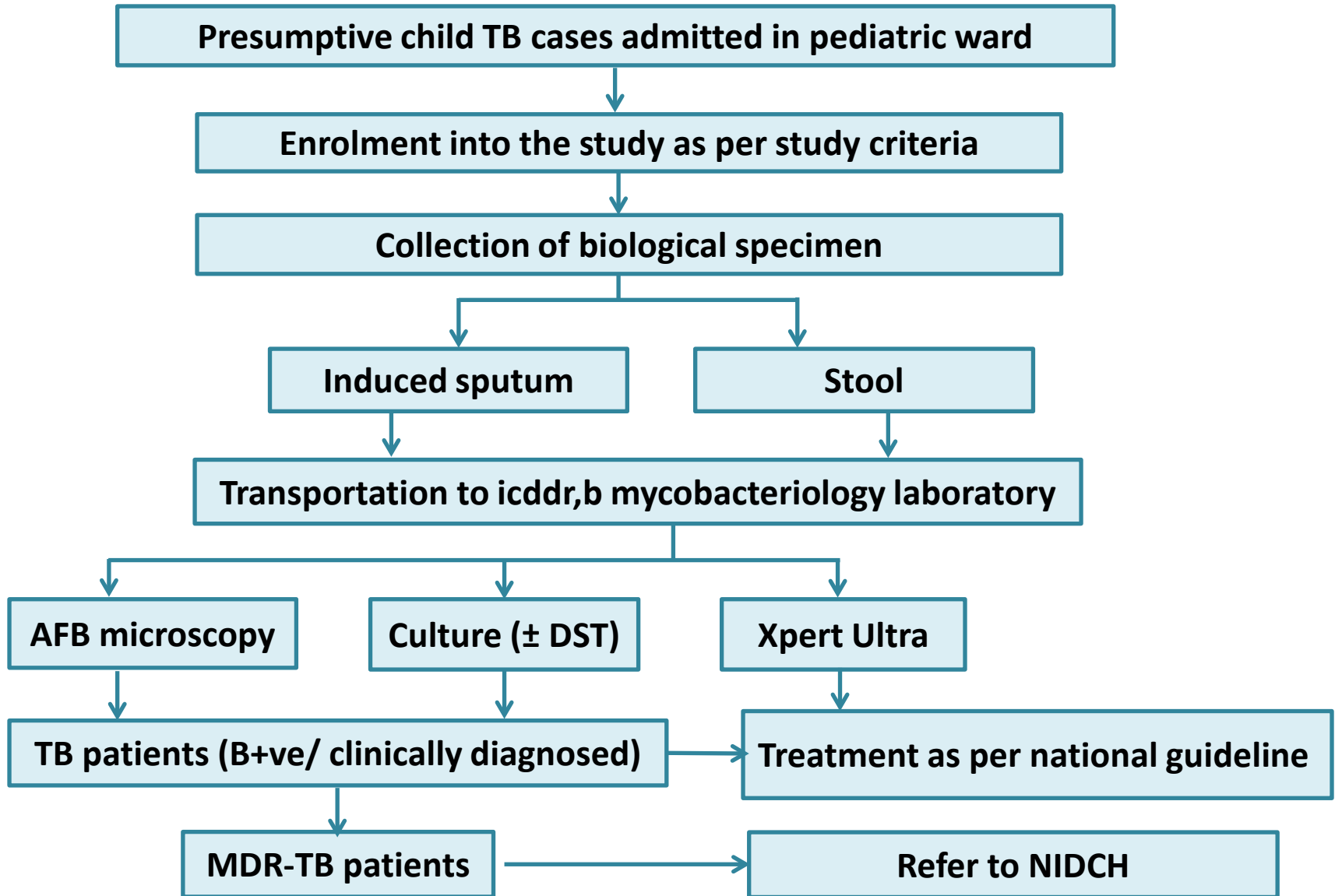
Objectives

To evaluate the diagnostic performance of Xpert Ultra using stool specimen in children with symptoms suggestive of pulmonary TB

Study Settings

- **Study sites:**
 - **Dhaka Medical College and Hospital**
 - **Sir Salimullah Medical College and Mitford Hospital**
 - **Shaheed Suhrawardy Medical College and Hospital**
 - **icddr,b Dhaka Hospital**
- **Data collection period: January 2018 to April 2019**
- **Calculated sample size: *At least 435 (necessary to detect 80% sensitivity and 95% specificity at 10% level of precision with expected 15% TB prevalence among presumptive child TB cases considering 5% loss to follow up/ incomplete data)***

Study Algorithm



Study Criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| Children: | Children: |
| – of ≤ 14 years of age | – with serious co-morbid conditions and specimen collection was contraindicated |
| – with symptoms suggestive of pulmonary TB | – on anti-TB treatment |
| – with any nutritional status | – clinically suspected to have intestinal TB |
| – whose parents/guardians consented to enroll them and children who assented to be enrolled (11-14 years old) | |

Study Activities



Results

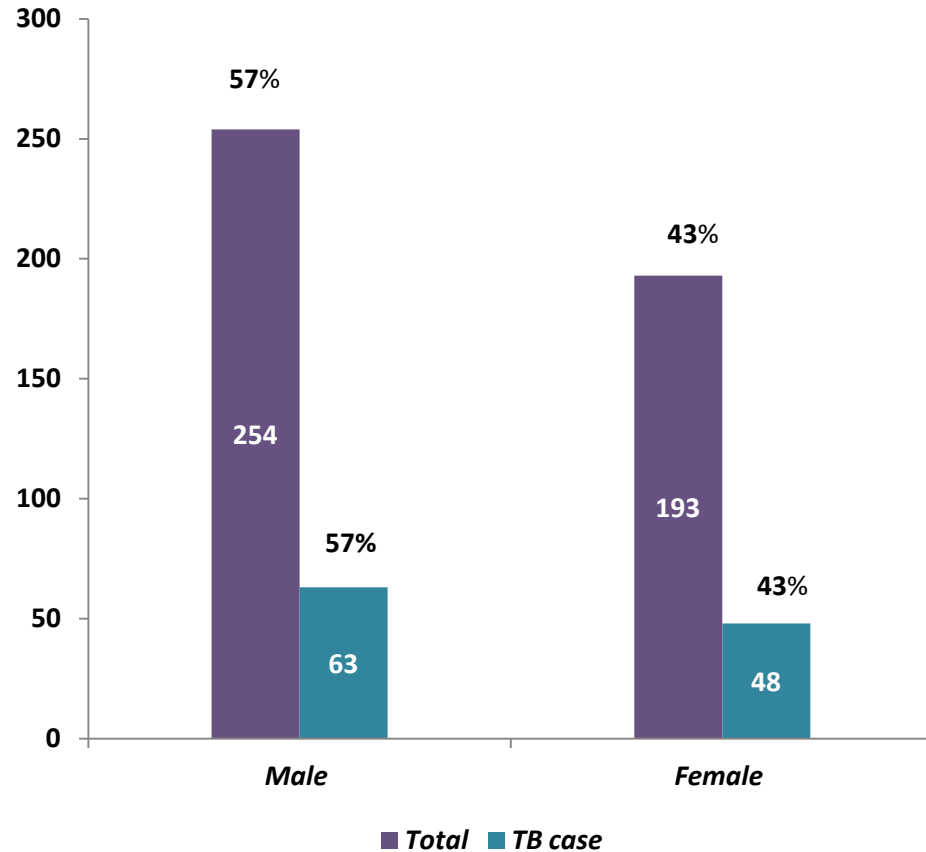
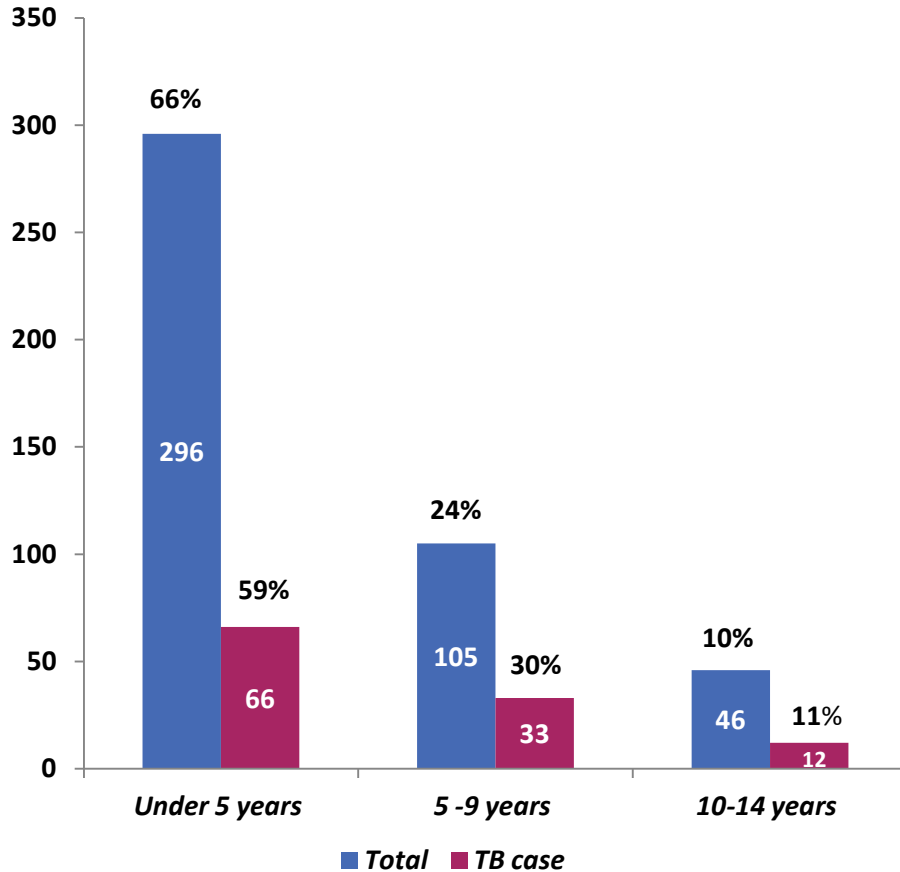
| Category | Number , n (%) |
|---|----------------|
| Total presumptive cases enrolled | 447 |
| Total TB cases identified | 111 (25) |
| B +ve cases* (% of total cases) (AFB/Cul/Xpert Ultra**): | 72 (65) |
| Induced sputum (IS) | 29 (40) |
| Stool*** | 60 (83) |
| Clinically diagnosed (CD) cases | 39 (35) |

**Bacteriologically positive*

***Including Trace detected [IS: 11/28 (39%); Stool: 48/60 (80%)]*

*** *Five "trace detected" cases (10%) by stool Xpert Ultra did not get anti-TB treatment*

Age and Gender Distribution



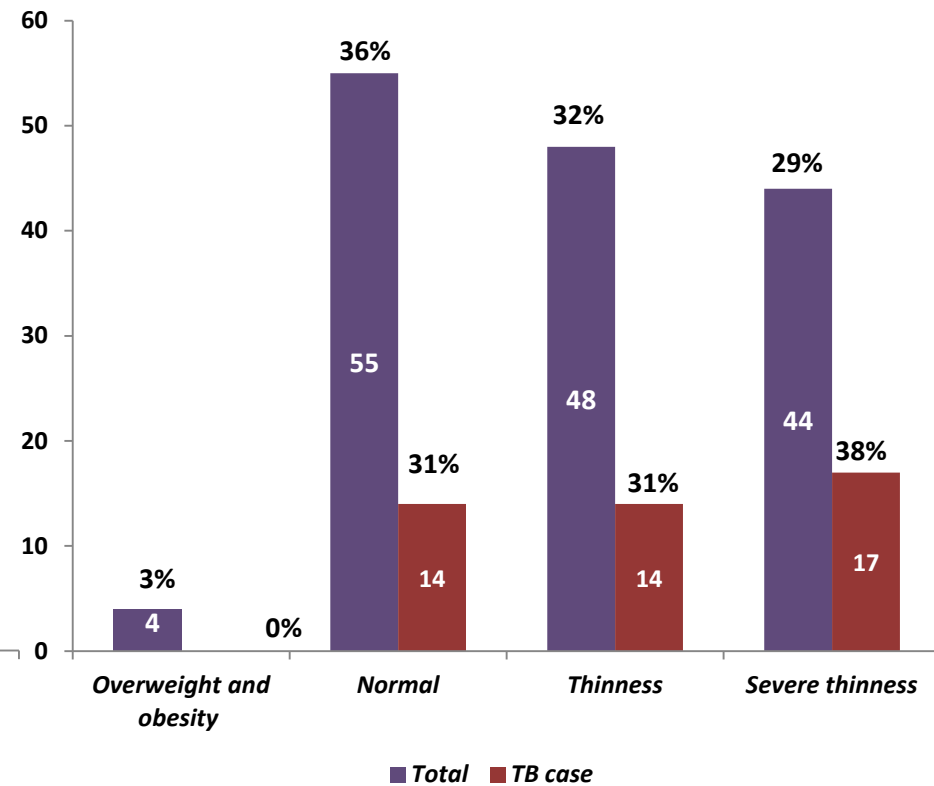
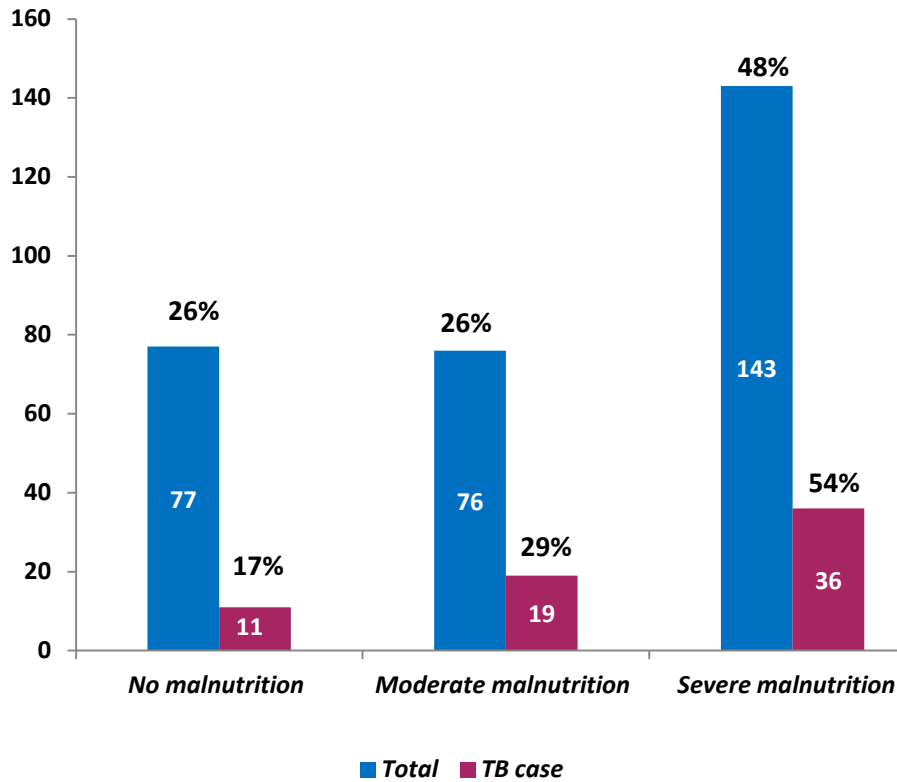
**Age distribution, Total =447
Case= 111 (25%)**

Median age (IQR) : 2.1 (0.74-6.7) years

**Gender distribution, Total =447
Case= 111 (25%)**

Male: Female- 1.3:1

Nutritional Status



**Under 5 years*, Total=296 (66%)
Case=66 (22%)**

**5 to 14 years, Total=151 (34%)
Case=45 (30%)**

**Calculated using WHO Anthro Calculator*

***Calculated using BMI-for-age according to WHO BMI card for children*

Xpert Ultra: Stool vs IS (n=446*)

| Stool ← | IS | | |
|---------|------------|-------------|-------------|
| | +ve (%) | -ve (%) | |
| +ve (%) | 17 (60.7) | 43 (10.3) | 60 (13.5) |
| -ve (%) | 11 (39.3) | 375 (89.7) | 386 (86.5) |
| Total | 28 (100.0) | 418 (100.0) | 446 (100.0) |

Additional detection by stool: 7.2%

**One stool specimen was invalid on Xpert Ultra*

Xpert Ultra on Stool and IS vs B+ve case [both specimens] (n=446*)

| Xpert Ultra (Stool) | B+ve case using both specimens (+ve in any test) | | Total |
|---------------------|--|--------------------|--------------------|
| | +ve (%) | -ve (%) | |
| +ve (%) | 60 (84.5) | 0 (0.0) | 60 (13.5) |
| -ve (%) | 11 (15.5) | 375 (100.0) | 386 (86.5) |
| Total | 71 (100.0) | 375 (100.0) | 446 (100.0) |

*Sensitivity: 84.5%;
Specificity: 100%
Accuracy: 97.5%*

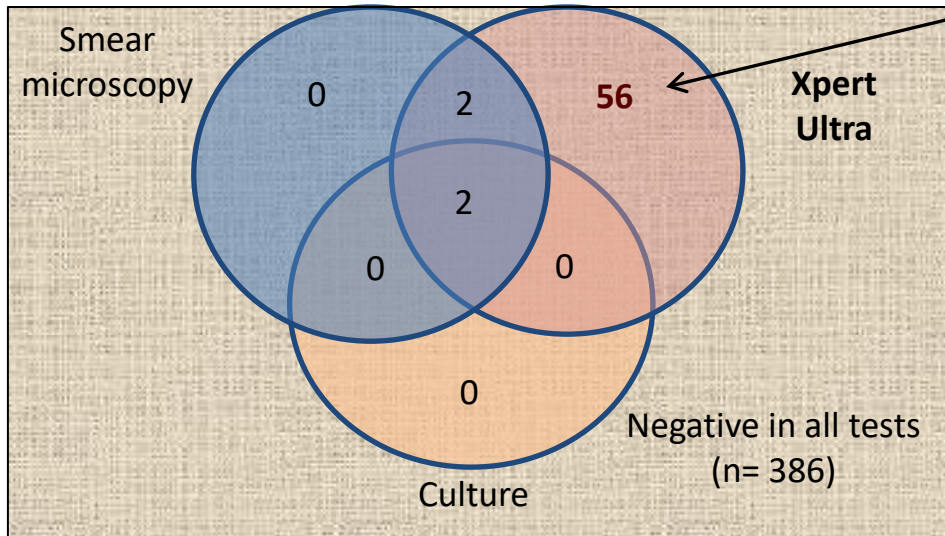
*Sensitivity: 39.4%;
Specificity: 100%
Accuracy: 90.3%*

| Xpert Ultra (IS) | B+ve case using both specimens (+ve in any test) | | Total |
|------------------|--|--------------------|--------------------|
| | +ve (%) | -ve (%) | |
| +ve (%) | 28 (39.4) | 0 (0.0) | 28 (6.3) |
| -ve (%) | 43 (60.6) | 375 (100.0) | 418 (93.7) |
| Total | 71 (100.0) | 375 (100.0) | 446 (100.0) |

**One stool specimen was invalid on Xpert Ultra*

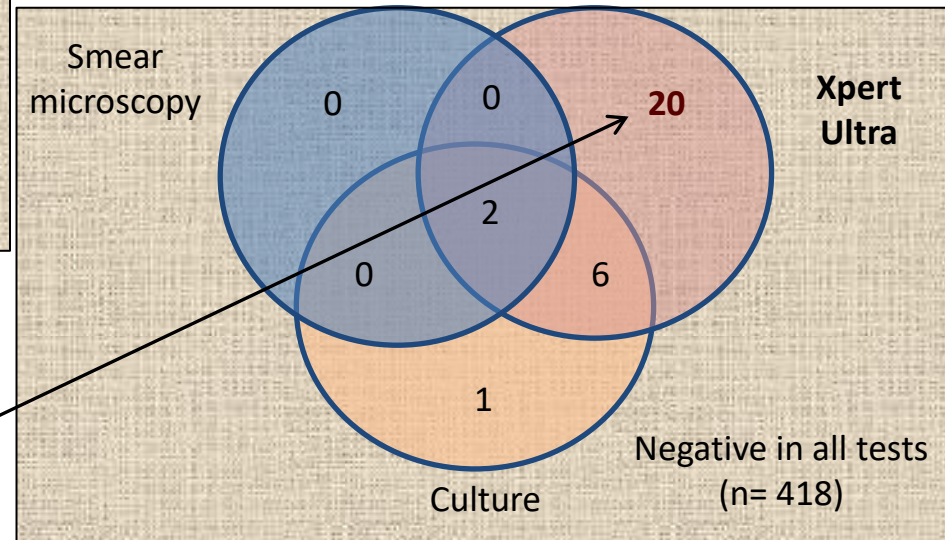
Exclusive Detection of Bact. Confirmed Cases by Diff. Laboratory Tests using Stool and IS

Stool (n=60)



Detection only by Ultra
56/60, 93.3%

Induced sputum (n=29)



Detection only by Ultra
20/29, 71.4%

Summary Findings

- Majority (66%) of children were <5 years old
- Positivity of Xpert Ultra is more in stool than IS (60 vs 28)
- 39% of IS and 80% of stool Xpert Ultra positive specimens were “trace call”
- Additional 7% B+ve PTB cases were detected by Xpert Ultra using stool
- Positivity of Xpert Ultra was significantly higher in stool than IS among B+ve specimens (85% vs 39%; $p<0.001$)
- Exclusively detection by Xpert Ultra:
 - IS: 20 of B+ve specimens on IS (71%)
 - Stool: 56 of B+ve specimens on stool (93%)

Limitations

- **10% (5 out of 48) trace detected cases by stool Xpert Ultra were not considered as TB by clinicians**
- **Repeat test was not done with the “trace call” result of Xpert Ultra using stool**
- **Most of the children positive by stool Xpert Ultra (88%) were treated with anti-TB drugs by physicians, hence, diagnostic validity of stool Xpert Ultra could not be evaluated among clinically diagnosed child TB cases**

Recommendations

- **Stool has been found to be a superior specimen to IS in child TB diagnosis by using Xpert Ultra**
- **Stool presents a great opportunity to improve child TB detection when respiratory specimen collection is difficult**
- **Future studies on clinical evolution are required to suggest on the management of children with ‘trace call’**

Acknowledgement

- **National Tuberculosis Control Program, Bangladesh**
- **USAID**
- **Sir Salimullah Medical College and Mitford Hospital**
- **Shaheed Suhrawardy Medical College and Hospital**
- **Dhaka Medical College and Hospital**
- **icddr,b Dhaka Hospital**

Thank You

