Accelerating access to quality TB care for presumptive paediatric TB patients through improved diagnostic strategies
Current progress = Too Slow to reach 2035 target?

WHO Strategy Target For 2035

2013 Global TB incidence

It would take until 2180

target
10 / 100k

global
125 / 100k

Credit: WHO
Background

- Burden of childhood TB is not well understood
  - TB in children not upfront suspected
- Challenges in diagnosis of TB in children
  - Difficulty in obtaining quality specimen
  - Low sensitivity of widely available low costs tools (smear microscopy)
  - Affordability challenges wrt. high sensitivity tools in the private sector
- Diagnosis based on clinical criteria &/or triad of:
  - History of contact with TB case
  - CXR
  - TST
- >80% of Pediatric TB cases- Clinically diagnosed
- No scope of diagnosing Rif resistant TB, which is laboratory diagnosis
Diagnostic algorithm for Pediatric Pulmonary TB

- Persistent Fever ≥2wk, without a known cause and/or
- Unremitting Cough for ≥2w and/or
- Wt loss of 5% in 3m or no wt gain in past 3 months

CBNAAT* (on sputum)

MTB not detected OR Sputum not available

MTB detected

Microbiologically confirmed TB Case

XRC highly suggestive

Gastric Aspirate/Induced Sputum for CBNAAT

+ve

-ve

No other likely alternative diagnosis
Clinically Diagnosed TB case

X.Ray and TST

CXR NS shadows
TST -ve

Give course of Antibiotics

Persistent shadow and symptoms

Gastric Aspirate/Induced Sputum for CBNAAT

+ve

-ve

Refer to expert for work up of persistent pneumonia

CXR Normal
TST +ve

Evaluate for EPTB
Refer to expert

CXR Normal
TST -ve

Look for alternate cause

*If CBNAAT is not readily available, smear microscopy should be performed
Analytical sensitivity of diagnostic tests

MGIT* 10-100/ml

Xpert MTB* 50-150/ml

ILED* fluorescent microscope 10,000/ml

Line-probe* 10,000/ml

Capilia* speciation dipstick (of culture) 1,000,000/ml

*development completed

Log cfu/ml
The Xpert MTB/RIF Assay

1. Sputum liquefaction and inactivation with 2:1 sample reagent

2. Transfer of 2 ml material into test cartridge

3. Cartridge inserted into MTB-RIF test platform

4. Sample automatically filtered and washed

5. Ultrasonic lysis of filter-captured organisms to release DNA

6. DNA molecules mixed with dry PCR reagents

7. Seminested real-time amplification and detection in integrated reaction tube

8. Printable test result

END OF HANDS-ON WORK

Time to result: 1 hour 45 minutes

Test Result: MTB DETECTED LOW, RIF Resistance NOT DETECTED
WHO recommendations - 2013

- 16 studies, 12 published and 4 unpublished, all studies were performed at higher levels of care, and the children included were mainly inpatients.
- Pulmonary TB was evaluated in 13 studies including 2603 participants. The overall pooled sensitivity
  - Xpert MTB/RIF against culture (10 studies) in children presumed to have TB was 66% in 10 studies where expectorated sputum (ES) or induced sputum (IS) was used (pooled 95% CrI 52% - 77%),
  - 66% in seven studies where gastric lavage aspirates (GLA) were used (pooled 95% CrI 51% - 81%).
- Pooled specificity of Xpert MTB/RIF against culture as the reference standard was ≥98% with narrow confidence intervals.
- The sensitivity of Xpert MTB/RIF to detect rifampicin resistance in pediatric specimens was 86% (95%CI 53% - 98%).
## WHO recommendations - 2013

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Comparison (No. of studies, No. of samples)</th>
<th>Median (%) pooled sensitivity (pooled 95% CrI)</th>
<th>Median (%) pooled specificity (pooled 95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node tissue and aspirate</td>
<td>Xpert MTB/RIF compared against culture (14 studies, 849 samples)</td>
<td>84.9 (72–92)</td>
<td>92.5 (80–97)</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>Xpert MTB/RIF compared against a composite reference standard (5 studies, 1 unpublished)</td>
<td>83.7 (74–90)</td>
<td>99.2 (88–100)</td>
</tr>
<tr>
<td></td>
<td>Xpert MTB/RIF compared against culture (16 studies, 709 samples)</td>
<td>79.5 (62–90)</td>
<td>98.6 (96–100)</td>
</tr>
<tr>
<td></td>
<td>Xpert MTB/RIF compared against a composite reference standard (6 studies, 512 samples)</td>
<td>55.5 (51–81)</td>
<td>98.8 (95–100)</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>Xpert MTB/RIF compared against culture (17 studies, 1385 samples)</td>
<td>43.7 (25–65)</td>
<td>98.1 (95–99)</td>
</tr>
<tr>
<td></td>
<td>Xpert MTB/RIF compared against a composite reference standard (7 studies, 698 samples)</td>
<td>17 (8–34)</td>
<td>99.9 (94–100)</td>
</tr>
<tr>
<td>Gastric lavage and aspirate</td>
<td>Xpert MTB/RIF compared against culture (12 studies, 1258 samples)</td>
<td>83.8 (66–93)</td>
<td>98.1 (92–100)</td>
</tr>
<tr>
<td>Other tissue samples</td>
<td>Xpert MTB/RIF compared against culture (12 studies, 699 samples)</td>
<td>81.2 (68–93)</td>
<td>98.1 (87–100)</td>
</tr>
</tbody>
</table>
Recommendations Continue

- For CSF specimens, Xpert MTB/RIF should be preferentially used over culture if the sample volume is low or additional specimens cannot be obtained, in order to reach quick diagnosis.
  - If sufficient volume of material is available, concentration methods should be used to increase yield
- Pleural fluid is a suboptimal sample for the bacterial confirmation of pleural TB, using any method.
  - A pleural biopsy is the preferred sample.
  - Sensitivity of Xpert MTB/RIF in pleural fluid is very low.
  - Nevertheless, any positive Xpert MTB/RIF result on pleural fluid should be treated for pleural TB, while those with a negative Xpert MTB/RIF result should be followed by other tests;
- Children presumed to have pulmonary TB but with a single Xpert MTB/RIF -negative result should undergo further diagnostic testing, and a child with high clinical suspicion for TB should be treated even if an Xpert MTB/RIF result is negative or if the test is not available
- These recommendations do not apply to stool, urine or blood, given the lack of data on the utility of Xpert MTB/RIF on these specimens.
Initially launched in the 4 cities of Delhi, Chennai, Hyderabad and Kolkata

Subsequently, 5 more cities were added – Vizag, Surat, Bangalore, Nagpur and Guwahati

Intervention was added in one more city in 2017 - Indore

The initial 4 sites were transitioned to the RNTCP by 31st March 2017

Currently, the project is operational in six cities covering a total population of >53 million (Census 2011)
Project overview

Additional -
• Rif detection
• Prompt linkage to treatment
• Providing collection tubes to providers
• Culture/DST for Rif cases

01
Intervention

FOC testing through High throughput Xpert lab established within NTP IRLs

02
Intervention

Rapid specimen transportation linkages with public & private health facilities

03
Intervention

Both pulmonary & EPTB samples subjected to Xpert testing

04
Intervention

Rapid reporting (within 24 hours) via SMS and email
How to Engage in the Project?

Specimen of paediatric TB suspect can be sent to the project lab by any provider from public/private sector.

Fill the form-Annex-1 and send the sample for FOC testing.

Samples are tested and results transmitted electronically within 24 working hours.

Specimen transportation costs are covered by the project.

Diagnosed TB cases can opt for free of cost Rx under RNTCP or seek treatment in the private sector.

Simplified Engagement
Provider engagement: Providers/facilities engaged

Overall 94,415 presumptive cases have been tested of which 6270 (6.6%) TB cases detected with 545 (8.7%) Rif resistant.
Positivity trend

Before Transition - Positivity Trend

9 sites data
96.2% of specimens transported on the day of collection

95% of specimens tested on the same day

98.9% of the tested specimens reported the same day

Overall 89.5% of the result reported within 24 hours of collection
**Type Of Specimen Tested**

- **Sputum/IS; 50'057; 50%**
- **Gastric Aspirate/ Gastric Lavage; 34'654; 35%**
- **CSF; 5'589; 6%**
- **Pleural Fluid; 2'770; 3%**
- **BAL; 1'721; 2%**
- **Pus; 1'423; 1%**
- **Lymph Node/ FNAC; 1'709; 2%**
- **Ascitic Fluid; 552; 0%**
- **Others*; 1'118; 1%**

**TOTAL TESTS 99,593**

*Others: Tissue, Pericardial Fluid, Urine, Cervical Aspirate, Peritoneal Fluid, Tracheal aspirate, Abscess, Synovial Fluid, Serum Bone, Chyle fluid, Nasal Aspirate, Pleural Biopsy, Thoracic swab, etc* 

Excludes invalids, errors & no result
## Xpert MTB/RIF & Smear Microscopy Performance

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Specimen Tested</th>
<th>Xpert Positive (%)</th>
<th>Smear Positive (%)</th>
<th>Rif Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum/IS</td>
<td>50,057</td>
<td>3176 (6.3%)</td>
<td>1285 (2.6%)</td>
<td>371 (11.7%)</td>
</tr>
<tr>
<td>Gastric Aspirate/Gastric Lavage</td>
<td>34,654</td>
<td>1767 (5.1%)</td>
<td>355 (1.1%)</td>
<td>167 (9.5%)</td>
</tr>
<tr>
<td>CSF</td>
<td>5,589</td>
<td>353 (6.3%)</td>
<td>7 (0.2%)</td>
<td>34 (9.6%)</td>
</tr>
<tr>
<td>Pleural Fluid</td>
<td>2,770</td>
<td>112 (4.0%)</td>
<td>12 (0.6%)</td>
<td>17 (5.2%)</td>
</tr>
<tr>
<td>BAL</td>
<td>1,721</td>
<td>227 (13.2%)</td>
<td>36 (2.8%)</td>
<td>17 (7.5%)</td>
</tr>
<tr>
<td>Pus</td>
<td>1,423</td>
<td>535 (37.6%)</td>
<td>107 (9.0%)</td>
<td>72 (13.5%)</td>
</tr>
<tr>
<td>Lymph Node/ FNAC</td>
<td>1,709</td>
<td>494 (28.9%)</td>
<td>55 (5.4%)</td>
<td>63 (12.8%)</td>
</tr>
<tr>
<td>Ascitic Fluid</td>
<td>552</td>
<td>24 (4.3%)</td>
<td>1 (0.2%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Others*</td>
<td>1,118</td>
<td>121 (10.7%)</td>
<td>21 (2.9%)</td>
<td>17 (14.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>99,593</td>
<td>6808 (6.8%)</td>
<td>1879 (2.0%)</td>
<td>760 (11.2%)</td>
</tr>
</tbody>
</table>

- **Detection rate >3x higher over Xpert vs smear microscopy**
- **>50% RIF resist. detected from non-sputum samples**
- **High detection rates on Pus, FNAC, Lymph node specimens**

Others* = Tissue, Pericardial Fluid, Cervical Aspirate, Peritoneal Fluid, Tracheal aspirate, Abscess, Synovial Fluid, Serum Bone, Chyle fluid, Nasal Aspirate, Pleural Biopsy, Thoracic swab, etc

Excludes Error, Invalid, No Result
# Treatment Information

<table>
<thead>
<tr>
<th></th>
<th>Total Xpert Positives</th>
<th>Total Rif Resistant</th>
<th>%</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients diagnosed under the project</td>
<td>5725</td>
<td>545</td>
<td></td>
<td>6270</td>
<td></td>
</tr>
<tr>
<td>Number initiated on treatment</td>
<td>5096</td>
<td>467</td>
<td>89.0%</td>
<td>5563</td>
<td>88.7%</td>
</tr>
<tr>
<td>Died before treatment initiation</td>
<td>113</td>
<td>28</td>
<td>2.0%</td>
<td>141</td>
<td>2.2%</td>
</tr>
<tr>
<td>Initial Default/Not traceable/Treatment refusal</td>
<td>492</td>
<td>49</td>
<td>8.6%</td>
<td>541</td>
<td>8.6%</td>
</tr>
<tr>
<td>Referred Out</td>
<td>24</td>
<td>1</td>
<td>0.4%</td>
<td>25</td>
<td>0.4%</td>
</tr>
</tbody>
</table>
Site wise- uptake

[Graph showing site-wise uptake from October 2016 to March 2018 for different locations: Bangalore, Guwahati, STDC Nagpur, Surat, and Vizag.]
Summary

- First routine initiative with upfront access to CBNAAT /GeneXpert for TB detection exclusively for pediatric population;
- For the first time large volumes of non-sputa specimen tested under RNTCP
- 3X increase in detection rates vs. Smear microscopy
- Significant levels of MDR cases in pediatric population documented
- Enhanced involvement of private providers & medical colleges catering to pediatric population
Accelerating access to quality TB diagnosis for pediatric cases

Improving detection and diagnosis

- More sensitive, more specific
- Faster diagnosis
- Dramatically reduces wrong diagnosis and negative treatment
- Clinically validated

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when ‘I’ is replaced by ‘We’... Illness becomes Wellness

- Diagnosis of tuberculosis in children is challenging, with high TB rates among children leading to widespread awareness.
- Designing this challenge, in partnership with USAID, FIND is helping ensure that children receive the diagnosis they need.
- We are working with local governments to address the diagnostic constraints specific to children.
- The challenge is being accelerated to provide critical TB diagnostic capacity and improve child health.
Thank You