Xpert MTB/RIF: Evidence and operational considerations

WHO Global Consultation
30 Nov – 2 Dec 2010
Catharina Boehme
Review of

1. Evaluation studies
2. Demonstration studies
3. Patient important outcomes
4. Operational performance & implementation issues
Multi-center evaluation study

- 5 reference laboratories with high quality gold standard
- Geographically diverse populations
- 1730 patients suspected of pulmonary TB or MDR-TB (4386 samples)
Single, direct Xpert:
Performance similar to solid culture for MTB

<table>
<thead>
<tr>
<th>Site</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity in C+ (95 CI)</th>
<th>Specificity in C- (95 CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lima, Peru</td>
<td>201</td>
<td>0</td>
<td>8</td>
<td>101</td>
<td>96 (93-98)</td>
<td>100 (96-100)</td>
</tr>
<tr>
<td>Baku, Azerbaijan</td>
<td>123</td>
<td>1</td>
<td>24</td>
<td>68</td>
<td>84 (77-89)</td>
<td>99 (92-100)</td>
</tr>
<tr>
<td>Cape Town, SA</td>
<td>136</td>
<td>1</td>
<td>10</td>
<td>185</td>
<td>93 (88-96)</td>
<td>99 (97-100)</td>
</tr>
<tr>
<td>Durban, SA</td>
<td>36</td>
<td>3</td>
<td>7</td>
<td>215</td>
<td>84 (70-92)</td>
<td>99 (96-99)</td>
</tr>
<tr>
<td>Mumbai, India</td>
<td>179</td>
<td>0</td>
<td>8</td>
<td>35</td>
<td>96 (92-98)</td>
<td>100 (90-100)</td>
</tr>
<tr>
<td>Total</td>
<td>675</td>
<td>5</td>
<td>57</td>
<td>604</td>
<td>92 (90-94)</td>
<td>99 (98-100)</td>
</tr>
</tbody>
</table>

Patient group
- Smear-positive, Culture-positive
  - Single LJ: 93.0% (1016/1092)
  - Single MGIT: 97.7% (1104/1130)
- Smear-negative, Culture-positive
  - Single LJ: 69.3% (205/296)
  - Single MGIT: 84.4% (276/327)
- All Culture-positive
  - Single LJ: 88.0% (1221/1388)
  - Single MGIT: 94.7% (1380/1457)

Single, direct Xpert: 98.2% (551/561)
72.5% (124/171)
92.2% (675/732)
Rifampicin resistance detection by Xpert: Performance similar to phenotypic standard

<table>
<thead>
<tr>
<th>Site</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity (95 CI)</th>
<th>Specificity (95 CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lima, Peru</td>
<td>16</td>
<td>3</td>
<td>0</td>
<td>190</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Baku, Azerbaijan</td>
<td>47</td>
<td>4</td>
<td>2</td>
<td>90</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>Cape Town, SA</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>126</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>Durban, SA</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>38</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mumbai, India</td>
<td>119</td>
<td>3</td>
<td>2</td>
<td>61</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>10</td>
<td>5</td>
<td>505</td>
<td>98 (94-99)</td>
<td>98 (96-99)</td>
</tr>
</tbody>
</table>

- Compared to sequencing: 99% sensitivity, 100% specificity.
- 98% of RIF resistant cases were confirmed MDR-TB.
Other take-away messages from evaluation study

- Performance from NaOH-treated pellet – equivalent to raw sputum
- Moderate sensitivity gain in S-C+ with 2\textsuperscript{nd} (+13\%) & 3\textsuperscript{rd} test (+5\%)
- Low indeterminate rate
Multi-center implementation studies

- 9 settings of intended use in 6 countries
- District/sub-district (3), microscopy centers (3), MDR screening / ER (3)
- Diverse laboratory conditions (temp up to 42C, space, staff background)
- 7000 TB or MDR-TB suspected patients screened from diverse populations
Partners and study design

**Lima, Peru**
- INS
- NTP / DISA IV Lima Este
- Instituto A. v. Humboldt
- UPCH

**Manila, Philippines**
- Lung Institute
- TDF
- CDC

**Cape Town, South Africa**
- MOH / NTP
- NHLS
- MSF
- UCT

**Vellore, India**
- Central TB Division
- Community Health Dep.
- Christian Medical College

**Kampala, Uganda**
- NRL
- Makerere University
- Mulago Hospital
- University of California

**Baku, Azerbaijan**
- MOH
- MOJ
- STI/Main Medical Dep.

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**Validation Phase**
- 1 Xpert added to routine examinations;
- Culture / DST added as reference standard;
- Patient management on smear/culture;

**Implementation Phase**
- Patient management on Xpert

**Continuation Phase**
- Culture dropped
Xpert case detection estimates during implementation in line with published evaluation results

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity in culture +</th>
<th>Sensitivity in smear-,culture +</th>
<th>Specificity in smear-,culture -</th>
</tr>
</thead>
<tbody>
<tr>
<td>92.2% (675/732)</td>
<td>90.0 – 93.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90.7% (641/707)</td>
<td>88.3 – 92.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100.0% (29/29)</td>
<td>85.4 – 100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99.9% (4675/4682)</td>
<td>99.7 – 99.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72.5% (124/171)</td>
<td>65.4 – 78.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81.2% (263/324)</td>
<td>76.6 – 85.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>71.5% (38/53)</td>
<td>57.4 – 82.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99.7% (2540/2547)</td>
<td>99.4 – 99.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99.2% (604/609)</td>
<td>98.1 – 99.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>98.5% (1938/1968)</td>
<td>97.8 – 98.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100.0% (25/25)</td>
<td>83.4 – 100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99.9% (7567/7568)</td>
<td>99.9 – 100.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Boehme et al. 2010 (Evaluation)
- Demonstration studies
- Helb et al. 2010
- Naidoo 2010
Summary: Rifampicin Resistance

- **ADF 1**
  - Evaluation studies (99% RIF sensitivity & 100% specificity)
  - Manufacturing scale up (drop to 96% RIF specificity)

- **ADF 2**
  - May 2010
  - Demonstration studies (95% RIF sensitivity & 98% specificity)

- **ADF 3**
  - Oct 2010
  - RIF specificity increase

- **ADF 4**
  - Cartridge
    - Q2 2011
    - RIF specificity & sensitivity increase

- **ND**
  - Further refinements as part of post-marketing surveillance

EGM / STAG
Xpert implementation translates into shortened time to treatment

- Validation $\rightarrow$ Tx based on routine tests.
- Implementation $\rightarrow$ Tx based on Xpert.
- MDR $\rightarrow$ conventional DST (or LPA).
## Operational performance and robustness

<table>
<thead>
<tr>
<th>Variable</th>
<th>Performance / outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indeterminate rate</td>
<td>2.5% and 0.3% after repetition. Culture indeterminate rate 4.7%.</td>
</tr>
<tr>
<td>DNA contamination events</td>
<td>None observed (swabs, neg controls)</td>
</tr>
<tr>
<td>Batching / Pellet / Smear</td>
<td>OK / OK / NO</td>
</tr>
<tr>
<td>Operating and short term storage</td>
<td>High lab temperature = no effect on performance.</td>
</tr>
<tr>
<td>temperature</td>
<td></td>
</tr>
<tr>
<td>Training needs</td>
<td>2 days for non-experienced lab techs.</td>
</tr>
<tr>
<td>User appraisal</td>
<td>Less difficult than microscopy; user friendly; user-independent read-out.</td>
</tr>
</tbody>
</table>
Considerations for implementation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Performance / outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive maintenance</td>
<td>Annual calibration (logistics and costs)</td>
</tr>
<tr>
<td>Storage</td>
<td>2-28°C; cartridges require substantial storage space</td>
</tr>
<tr>
<td>Electrical supply and back-up power</td>
<td>power outage reported; uninterruptable power supply with UPS (400 VA) for 20 min.</td>
</tr>
<tr>
<td></td>
<td>Serial car batteries tested.</td>
</tr>
<tr>
<td>Biosafety requirements</td>
<td>Same as smear microscopy*.*</td>
</tr>
<tr>
<td>Waste management</td>
<td>As for sputum containers; additional waste volume compared to smear microscopy.</td>
</tr>
</tbody>
</table>

Conclusions

- Consistently high sensitivity and specificity for TB detection
- Good performance for RIF resistance, confirmatory testing to be considered in low MDR-TB prevalence areas
- Study data likely to be globally applicable
- Implementation successful after minimal training
- Impact for patients shown to be significant
Future R&D needs

1. Assessing feasibility of further decentralization (rural areas)
2. Further evaluation in pediatric and extra-pulmonary TB
3. Study optimal positioning in existing diagnostic algorithms
4. Accelerate development of a 2\textsuperscript{nd} generation RIF/INH assay
5. Accelerate development of a 1\textsuperscript{st} generation FG/AG assay
Thank you to all partners who generated and shared this evidence for WHO review.