Implementation and roll-out of the Xpert MTB/RIF system for rapid diagnosis of tuberculosis and drug-resistance. Risk Assessment, introduction

Workshop for Early Implementers
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Summary of Recommendations

1. **Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB.** (Strong recommendation)

2. **Xpert MTB/RIF may be considered as a follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens.** (Conditional recommendation acknowledging major resource implications)

Remarks:
- These recommendations apply to the use of Xpert MTB/RIF in sputum specimens (including pellets from decontaminated specimens). Data on the utility of Xpert MTB/RIF in extra-pulmonary specimens are still limited;
- These recommendations support the use of one sputum specimen for diagnostic testing, acknowledging that multiple specimens increase the sensitivity of Xpert MTB/RIF but have major resource implications;
- These recommendations also apply to children, based on the generalisation of data from adults and acknowledging the limitations of microbiological diagnosis of TB (including MDR-TB) in children;
- Access to conventional microscopy, culture and DST is still needed for monitoring of therapy, for prevalence surveys and/or surveillance, and for recovering isolates for drug susceptibility testing other than rifampicin (including second-line anti-TB drugs).
### Standard evaluation of diagnostic tests

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
<th>No Disease</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test pos</strong></td>
<td>TP</td>
<td>FP</td>
<td><strong>TP/(TP+FP)</strong></td>
<td><strong>PPV</strong></td>
</tr>
<tr>
<td><strong>Test neg</strong></td>
<td>FN</td>
<td>TN</td>
<td><strong>TN/(TN+FN)</strong></td>
<td><strong>NPV</strong></td>
</tr>
<tr>
<td><strong>TP/(TP+FN)</strong></td>
<td>TN/(TN+FP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- PPV is a function of the TP and FP values and is influenced by the prevalence of the disease.
- There is always some degree of overlap between results from normal and diseased subjects.
- Laboratory results which are reported as "positive" or "negative" by analytical instruments are generated from continuous scales by using a cut-off point.
**False positive, false negative and predictive values for TB detection using Xpert MTB/RIF*.**

<table>
<thead>
<tr>
<th>TB prevalence</th>
<th>PPV</th>
<th>NPV</th>
<th>True positive</th>
<th>False negative</th>
<th>False positive</th>
<th>True negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>48%</td>
<td>100%</td>
<td>9.1</td>
<td>0.9</td>
<td>9.9</td>
<td>980.1</td>
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<tr>
<td>2%</td>
<td>65%</td>
<td>100%</td>
<td>18.2</td>
<td>1.8</td>
<td>9.8</td>
<td>970.2</td>
</tr>
<tr>
<td>3%</td>
<td>74%</td>
<td>100%</td>
<td>27.3</td>
<td>2.7</td>
<td>9.7</td>
<td>960.3</td>
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<tr>
<td>4%</td>
<td>79%</td>
<td>100%</td>
<td>36.4</td>
<td>3.6</td>
<td>9.6</td>
<td>950.4</td>
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<tr>
<td>5%</td>
<td>83%</td>
<td>100%</td>
<td>45.5</td>
<td>4.5</td>
<td>9.5</td>
<td>940.5</td>
</tr>
<tr>
<td>6%</td>
<td>85%</td>
<td>99%</td>
<td>54.6</td>
<td>5.4</td>
<td>9.4</td>
<td>930.6</td>
</tr>
<tr>
<td>7%</td>
<td>87%</td>
<td>99%</td>
<td>63.7</td>
<td>6.3</td>
<td>9.3</td>
<td>920.7</td>
</tr>
<tr>
<td>8%</td>
<td>89%</td>
<td>99%</td>
<td>72.8</td>
<td>7.2</td>
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<td>910.8</td>
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<tr>
<td>9%</td>
<td>90%</td>
<td>99%</td>
<td>81.9</td>
<td>8.1</td>
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<td>900.9</td>
</tr>
<tr>
<td>10%</td>
<td>91%</td>
<td>99%</td>
<td>91</td>
<td>9</td>
<td>9</td>
<td>891</td>
</tr>
<tr>
<td>11%</td>
<td>92%</td>
<td>99%</td>
<td>100.1</td>
<td>9.9</td>
<td>8.9</td>
<td>881.1</td>
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<td>12%</td>
<td>93%</td>
<td>99%</td>
<td>109.2</td>
<td>10.8</td>
<td>8.8</td>
<td>871.2</td>
</tr>
<tr>
<td>13%</td>
<td>93%</td>
<td>99%</td>
<td>118.3</td>
<td>11.7</td>
<td>8.7</td>
<td>861.3</td>
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<tr>
<td>14%</td>
<td>94%</td>
<td>99%</td>
<td>127.4</td>
<td>12.6</td>
<td>8.6</td>
<td>851.4</td>
</tr>
<tr>
<td>15%</td>
<td>94%</td>
<td>98%</td>
<td>136.5</td>
<td>13.5</td>
<td>8.5</td>
<td>841.5</td>
</tr>
<tr>
<td>20%</td>
<td>96%</td>
<td>98%</td>
<td>182</td>
<td>18</td>
<td>8</td>
<td>792</td>
</tr>
<tr>
<td>25%</td>
<td>97%</td>
<td>97%</td>
<td>227.5</td>
<td>22.5</td>
<td>7.5</td>
<td>742.5</td>
</tr>
</tbody>
</table>

* in a sample population of 1000, sens 91%, spec 99%
Main considerations during risk assessment

- Individual’s history including treatment history for retreatment cases
- TB contact information
- HIV status
- MDR-TB and HIV prevalence in the setting patient is originating from
- All previous results of TB testing if available

Assists health worker to decide prioritization of Xpert MTB/RIF testing over other available conventional tests.

Planners and decision makers need to consider:
- Available resources
- Need to provide sufficient capacity for treatment of patients
Selection of individuals to test based on risk assessment: summary

A. Individuals at risk of MDR-TB
   - Diagnosed with TB or
   - Suspected of having TB

B. HIV (+) individuals
   (or HIV unknown in high HIV settings)
   suspected of having TB

Primary considerations

HIV (-) individuals
not at risk of MDR-TB with either:
   - Abnormal CXR
   - Sputum smear (-) but still suspected of having TB

Secondary considerations

Indivduals accessing health centre

Xpert MTB/RIF

TB, Rif resistance
Enrol on MDR-TB regimen
DST FLD and SLD
ART if HIV +

TB, no Rif resistance
Treatment regimen based on patient history
ART if HIV +

No TB detected
Appropriate further clinical management
IPT if HIV +
Selection of individuals to test based on risk assessment: primary considerations (1)

A. Individuals known or suspected of having TB and at high risk of MDR-TB. This will include two categories:

✓ Persons who have been treated with anti-TB drugs and in whom pulmonary TB has again been diagnosed, i.e., all retreatment categories (failure, default, relapse);

✓ Persons suspected of having pulmonary TB and considered at risk of harbouring MDR-TB bacilli (risk groups as per national policies or as defined in WHO Guidelines for the Programmatic Management of DR-TB);

These individuals should receive an Xpert MTB/RIF as primary diagnostic test.
Selection of individuals to test based on risk assessment: primary considerations (2)

B. People living with HIV:

All persons living with HIV who:

- have any one of: current cough, fever, weight loss or night sweats,
- those seriously ill and suspected of having TB regardless of HIV status, and
- those with unknown HIV status presenting with strong clinical evidence of HIV infection in HIV prevalent settings,

should receive an Xpert MTB/RIF test as primary diagnostic test.
Where MDR-TB or HIV associated TB is of lesser concern

Prioritization due to resource implications with **pre-test screening strategies** (including CXR where available) depending on **available resources** and the screening and diagnostic algorithms at country level.

✓ Facilities with quality chest X-ray (accessible, free of charge)
  - Chest X-ray use as a screening tool
  - Xpert MTB/RIF in those with abnormal chest X-ray

✓ Facilities with smear microscopy only
  - Sputum smear microscopy – initial diagnostic test
  - Smear negatives tested with Xpert MTB/RIF if clinical suspicion of TB remains (should be referred or their sputum sent for further testing, preferably in a facility with Xpert MTB/RIF).