Update: Xpert MTB/RIF system for rapid diagnosis of TB and MDR-TB

DOTS Expansion Working Group Meeting
Lille, France 25th October 2011

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TB Diagnostics and Laboratory Strengthening Unit, Stop TB Department
Content

✓ WHO diagnostic policies 2007-2011
✓ WHO policy formulation
✓ Positioning technologies
✓ Xpert MTB/RIF Roll-out
Scaling up diagnostics and laboratories

• Accelerating WHO policy development
  2007: Commercial liquid culture and DST
  2008: Molecular line probe assay
  2009: LED microscopy, MODS, NRA and CRI methods
  2010: IGRAs, commercial serodiagnostics,
  2011: Xpert MTB/RIF, Laboratory bio-safety

• Moving new diagnostics into countries
  EXPAND-TB: New technologies in 27 countries with funding from UNITAID and other donors

• Providing laboratory tools & training
  Global Laboratory Initiative: Roadmap and tools set, Laboratory accreditation

• Increasing laboratory support and quality
  WHO Supranational Reference Laboratory Network
Positioning technologies

Integrating new tools in tiered health systems

Reference Level:
- Automated liquid culture & DST
- In-house DST (MODS, NRA, CRI)

Regional Level:
- Solid culture & DST
- Automated NAAT*

District Level:
- ZN microscopy
- LED** microscopy

Sub-district Level:
- ZN microscopy
- LED microscopy

Microscopy Level:
- Manual NAAT*

Community Level:
- RDT Gen1 / Gen 2*

**pending WHO endorsement

- Screening
  - Passive case finding
  - Detect and treat

- Resolution testing (screening-test negative drug resistance)

- Surveillance
  - Reference methods
  - Network supervision

- Clinical screening
  - Primary care
WHO TB diagnostics policy formulation process

Identifying the need for policy change
- WHO strategic monitoring of country needs
- Partners (researchers, industry, etc)
- Body of evidence available

Reviewing the evidence
- Commissioning of systematic reviews
- QUADAS or other diagnostic accuracy tool
- Meta-analyses (where feasible)

Convening an Expert Group
- Experts, methodologists, end-users
- Guidelines Review Committee
- GRADE process for evidence synthesis

Assessing policy proposal and recommendations
- Strategic and Technical Advisory Group
- Endorsement/revision/addition
- Advise to WHO to proceed/not with policy

Formulating and disseminating policy
- Guidelines Review Committee
- Dissemination to Member States
- Promotion with stakeholders & funders
- Phased implementation & scale-up plan
Pour Sample Reagent into sample tube. Incubate for 15 minutes at room temperature. (Acceptable sample types: unprocessed sputum or sediment from concentrated specimen.)

Pipette diluted sample into cartridge.

Insert cartridge and start assay.
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).
Xpert MTB/RIF evaluations

Three groups of studies

1. Multi-centre clinical validation studies (FIND co-ordinated)
   - 1,730 subjects in five evaluation sites (four countries)

2. Demonstration studies (FIND co-ordinated)
   - 6,673 subjects in nine evaluation sites (six countries)

3. Single-centre evaluation studies (investigator-driven)
   - 4,575 subjects in 12 studies (nine countries)
Multi-centre FIND Validation Studies
Four geographically and epidemiologically diverse settings

Overall sensitivity of a single Xpert test 92.2%

Smear-negative/ Culture-positive, single Xpert test - 72.5% sensitivity; Two tests 85.1%; Three tests 90.2%

Rifampicin resistance detection sensitivity 98%; specificity 99%
Multi-centre FIND Demonstration Studies
9 district, sub-district laboratories and microscopy centers in 6 countries

Sensitivity

**PULMONARY TB**
Smear pos. / Culture pos. 99%
Smear neg. / Culture pos. >80%

- **HIV-positive 86% sensitivity**
- **HIV-negative 92% sensitivity**

**RIFAMPICIN RESISTANCE**
Sensitivity 95.1%
Specificity 98.4%

<table>
<thead>
<tr>
<th>Location</th>
<th>Country</th>
<th>HIV</th>
<th>TB (C+)</th>
<th>MDR TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manila</td>
<td>Philippines</td>
<td>&lt;1%</td>
<td>20.3% (12/59)</td>
<td>53.7% (116/216)</td>
</tr>
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<td>Vellore</td>
<td>India</td>
<td>&lt;1%</td>
<td>9.8% (73/744)</td>
<td>6.7% (6/90)</td>
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<tr>
<td>Baku</td>
<td>Azerbaijan</td>
<td>6%</td>
<td>47.5% (179/377)</td>
<td>22.4% (52/232)</td>
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<tr>
<td>Cape Town</td>
<td>South Africa</td>
<td>77% (K), 30% (P)</td>
<td>26.4% (289/1096)</td>
<td>3.9% (17/437)</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Lima</td>
<td>Peru</td>
<td>3%</td>
<td>16.8% (126/752)</td>
<td>8.1% (13/161)</td>
</tr>
<tr>
<td>Manila</td>
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**Sensitivity**

- **PULMONARY TB**
  - Smear pos. / Culture pos. 99%
  - Smear neg. / Culture pos. >80%

- **HIV-positive 86% sensitivity**
- **HIV-negative 92% sensitivity**

**RIFAMPICIN RESISTANCE**
Sensitivity 95.1%
Specificity 98.4%
Varying study designs and study populations, pulmonary and extrapulmonary samples

Detection of TB

- Pooled crude sensitivity 92%
- Pooled crude specificity 98%

Detection of rifampicin resistance

- Pooled crude sensitivity 98%
- Pooled crude specificity 99%
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

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

Individuals 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 +
Positioning and site selection criteria for Xpert MTB/RIF

1. Ideally intermediate level, not central/reference lab level
2. Magnitude of the drug resistance or HIV associated TB problem
3. Current or estimated workload of the facility (taking into consideration 4 module system testing capacity, 15-20/day)
4. Infrastructure – stable electricity supply, secure room for GeneXpert system, computer and cartridges, appropriate ambient temperature
5. Personnel who can be trained, perform testing and keep equipment in good order
6. Facility where transportation of sputum specimens or suspect referral is feasible
7. **Sufficient capacity for appropriate treatment of all identified patients including those with rifampicin resistance**
Adoption of Xpert MTB/RIF to be phased in considering that GeneXpert:

- Is a **technology platform** for other diagnostic services (MRSA, CD, in future HIV viral load)
- Doesn’t eliminate **need for conventional smear, culture, DST**
- Requires **stable electricity supply**
- Has range of ambient **operating temperatures** max. 30°C (under revision)
- Requires **storage space for cartridges** (at 2-28°C), shelf life 18 months
- **Testing capacity** of 4 module system per working day is 15-20 tests (depending on working hours, each test 100 min.)
- Requires **annual calibration**
- Xpert MTB/RIF testing require **bio-safety** conditions similar to the conventional sputum smear microscopy sample processing or testing
# Practical considerations: preferential pricing and eligible countries*

<table>
<thead>
<tr>
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<td>Nicaragua</td>
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<td>Niger</td>
<td>Sri Lanka</td>
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<td>Nigeria</td>
<td>Sudan</td>
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<td></td>
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<td></td>
<td>Zimbabwe</td>
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</tbody>
</table>

*as of 19.02.2011

**GeneXpert System**
- 4 module
  - with desktop – 17'000 $
  - with laptop – 17’500 $
- Cartridge – 16.86 $
### Practical considerations: installation and running costs

**Sample annual itemized budget**

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Equipment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GeneXpert 4 module with laptop (Ex-Works price)</td>
<td>$17,500.00</td>
<td>&gt;60% price reduction compared to EU/US</td>
</tr>
<tr>
<td><strong>B</strong> Shipment</td>
<td>$1,000.00</td>
<td>Depends on destination</td>
</tr>
<tr>
<td><strong>C</strong> Uninterruptible Power Source</td>
<td>$500.00</td>
<td>Local purchase, depends on the market</td>
</tr>
<tr>
<td><strong>D</strong> Printer</td>
<td>$200.00</td>
<td>Local purchase, depends on the market</td>
</tr>
<tr>
<td><strong>E</strong> Maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual calibration costs</td>
<td>$1,800.00</td>
<td>Highest price if done in Cepheid Toulouse</td>
</tr>
<tr>
<td><strong>F</strong> Cost per cartridge</td>
<td>$16.86</td>
<td>75% price reduction compared to EU</td>
</tr>
<tr>
<td><strong>G</strong> Number of working days per year</td>
<td>250</td>
<td>Number can vary depending on local context</td>
</tr>
<tr>
<td><strong>H</strong> Consumables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average number of tests per instrument /day</td>
<td>15</td>
<td>Number can vary depending on working hours</td>
</tr>
<tr>
<td><strong>I</strong> Number of tests/1 year/ full load 1 instrument</td>
<td>3750</td>
<td>G*H</td>
</tr>
<tr>
<td><strong>J</strong> Losses due to damage/incorrect use (high estimate 10%)</td>
<td>375</td>
<td>10% of I</td>
</tr>
<tr>
<td><strong>K</strong> HR costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technician annual salary</td>
<td>$5,000.00</td>
<td>Country-specific</td>
</tr>
<tr>
<td><strong>L</strong> Training and TA</td>
<td>$5,000.00</td>
<td>Depends on the needs</td>
</tr>
<tr>
<td><strong>M</strong> Installation costs</td>
<td>$19,200.00</td>
<td>A+B+C+D</td>
</tr>
<tr>
<td><strong>N</strong> Running costs (annual, 1 instrument)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>$71,347.50</td>
<td>E+F*(I+J)</td>
</tr>
<tr>
<td><strong>O</strong> GRAND TOTAL</td>
<td>$100,547.50</td>
<td>N+M+L+K</td>
</tr>
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</table>
Country orders

145 eligible countries, wide definition of public sector
Xpert MTB/RIF roll-out monitoring website

Country & Partner plans

<table>
<thead>
<tr>
<th>Partner</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of California, San Francisco (USA)</td>
<td>- Procured</td>
</tr>
<tr>
<td>AISPO (Italy)</td>
<td>- Procured</td>
</tr>
<tr>
<td>FIND</td>
<td>- Procured</td>
</tr>
<tr>
<td>Johns Hopkins School of Medicine (USA)</td>
<td>- Procured</td>
</tr>
<tr>
<td>MSF (France)</td>
<td>- Procured</td>
</tr>
<tr>
<td>PEPFAR</td>
<td>- 2 planned in 2011, as part of EMRG project (1 reference lab, 1 clinic)</td>
</tr>
</tbody>
</table>

Reported problems: None

Roll-out of Xpert MTB/RIF

40 countries had ordered a total of 279 GeneXpert instruments (1,441 modules) at concessional prices, as of 30 September 2011.

More info at: www.who.int/tb/laboratory/mtbrifrollout

Source: FIND
Cumulative numbers of GeneXpert modules and Xpert MTB/RIF cartridges ordered

More info at: www.who.int/tb/laboratory/mtbrifrollout

Source: FIND
Roll-out of Xpert MTB/RIF

In order to facilitate coordination, WHO collects information on planned orders, funding sources, placement of machines, and any reported problems with usage reported from the field.

![Map showing countries with information on Xpert MTB/RIF rollout](map.png)

41 countries for which the national TB programme and/or partners have shared information on procurements, plans and any problems

More info at: [www.who.int/tb/laboratory/mtbrifrollout](http://www.who.int/tb/laboratory/mtbrifrollout)
Next steps

1. Coordinating & monitoring roll-out
   - STB systematically coordinating, collecting and sharing information on progress and plans of countries and partners, as well as sales information and reports of problems from the field
   - STB to organise a GLI/ SRLN/ Meeting of Early Implementers in Q2 2012 to share experiences

2. Collecting evidence for scaling-up
   - STB inviting countries and partners to submit core data
   - STB collaborating with the manufacturer to revise the proprietary GeneXpert software to allow for easy collection of the needed laboratory indicators
3. Providing updated guidance
   - Guidance on diagnostic algorithms, site selection and operational considerations to be revised based on lessons learnt and shared with countries and partners to inform scale-up from 2012 onwards

4. Ensuring quality of laboratory performance
   - Laboratory validation system (specimen panels to be distributed to laboratories when purchasing GXP instruments and calibrating modules) to be established and laboratory performance data assessed by STB/TBL

5. Evaluating additional data on Xpert MTB/RIF performance
   - Meeting to be organised in Q4 2012 to assess additional data on Xpert MTB/RIF performance (including extrapulmonary and paediatric TB)
Guidance documents

Automated Real-time Nucleic Acid Amplification Technology for Rapid Simultaneous Detection of Tuberculosis and Rifampicin Resistance in Xpert MTB/RIF System

Policy Statement

Rapid Implementation of the Xpert MTB/RIF diagnostic test

Technical and Operational 'How' Practical considerations

Prerequisites to country implementation of Xpert MTB/RIF and key action points at country level.

Checklist