Implementation and scale-up of the Xpert MTB/RIF system for rapid diagnosis of TB and MDR-TB

Global Consultation
Geneva, 30 November 2010

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WHO, Geneva, Switzerland
Global Tuberculosis Control Report 2010

Launched in Berlin
11 November 2010
Estimated number of cases

- All forms of TB: 9.4 million (range: 8.9–9.9 million)
- HIV-associated TB: 1.1 million (12%) (range: 1.0–1.2 million)
- Multidrug-resistant TB (MDR-TB): 440,000 (range: 390,000–510,000)

Estimated number of deaths

- All forms of TB: 1.3 million* (range: 1.2–1.5 million)
- HIV-associated TB: 380,000 (range: 320,000–450,000)
- Multidrug-resistant TB (MDR-TB): about 150,000

*excluding deaths among PLHIV
• Highest burden in Asia (55% of 9.4 million cases)

• Highest rates in Africa, due to high HIV infection rate
  ~80% of HIV+ TB cases in Africa
~ 45% of cases in China + India
~ 55% in China + India + Russian Federation
Global Plan to Stop TB 2011-2015

Launched in Johannesburg
13 October 2010
### 10 major targets for 2015

#### DOTS/lab strengthening

<table>
<thead>
<tr>
<th>INDICATOR</th>
<th>TARGET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of countries with ≥1 smear microscopy lab per 100 000 population</td>
<td>149 (All countries in plan)</td>
</tr>
<tr>
<td>Patients notified + treated</td>
<td>6.9 million</td>
</tr>
<tr>
<td>Treatment success rate</td>
<td>90%</td>
</tr>
</tbody>
</table>

#### MDR-TB/lab strengthening

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Number of 22 HBCs and 27 MDR-TB HBCs with ≥1 Cx &amp; DST lab to cover 5M population</td>
<td>36/36</td>
</tr>
<tr>
<td>Previously treated cases tested for MDR</td>
<td>100%</td>
</tr>
<tr>
<td>New cases tested for MDR</td>
<td>20%, all at high-risk</td>
</tr>
<tr>
<td>MDR-TB patients treated following WHO guidelines</td>
<td>100%, or ~ 270k</td>
</tr>
</tbody>
</table>

#### TB/HIV

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<tr>
<td>TB patients tested for HIV</td>
<td>100%</td>
</tr>
<tr>
<td>HIV+ TB patients on CPT</td>
<td>100%</td>
</tr>
<tr>
<td>HIV+ TB patients enrolled on ART</td>
<td>100%</td>
</tr>
</tbody>
</table>

*CPT, cotrimoxazole preventive therapy

*ART, antiretroviral therapy*
Urgent need for new rapid diagnostics

- To face the burden of TB, TB/HIV and especially MDR-TB, we need a rapid test for TB and drug susceptibility.

- To achieve the Global Plan targets new diagnostics rapidly implemented in the field are a "must".

- In the past 4 years, WHO has worked intensively with FIND, UNITAID, USAID and other partners to pursue new TB diagnostics and rapid uptake at country level.
WHO TB diagnostics policy formulation process

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

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

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

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

5. Formulating and disseminating policy
   - Guidelines Review Committee
   - Dissemination to Member States
   - Promotion with stakeholders & funders
   - Phased implementation & scale-up plan
## Expert Committee: GRADE summary

### Table: Xpert MTB/RIF

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Absolute difference per 1000 persons</th>
<th>Quality of evidence</th>
</tr>
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<tbody>
<tr>
<td><strong>Pre-test prevalence 10%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB detection</td>
<td>TP: 92, TN: 891, FP: 9, FN: 8</td>
<td>Moderate</td>
</tr>
<tr>
<td>R detection</td>
<td>TP: 95, TN: 891, FP: 9, FN: 5</td>
<td></td>
</tr>
<tr>
<td>Overall quality of evidence</td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Desirable vs undesirable effects</td>
<td></td>
<td>Highly favourable</td>
</tr>
<tr>
<td>Patient values and preferences</td>
<td></td>
<td>No data</td>
</tr>
<tr>
<td>Cost and requirements</td>
<td></td>
<td>Moderate cost</td>
</tr>
<tr>
<td>Added value to conventional methods</td>
<td></td>
<td>Significant</td>
</tr>
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</table>

**Note:** TP = True Positive, TN = True Negative, FP = False Positive, FN = False Negative.
Expert Committee 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 used as a follow-on test to microscopy where MDR and/or HIV is of lesser concern, especially in smear-negative specimens (conditional recommendation, recognising major resource implications)
Expert Committee Remarks

• Recommendations also apply to children

• Access to conventional microscopy, culture and DST is still needed

• Recommendations apply to the use of Xpert MTB/RIF in sputum specimens

• Recommendations support the use of one sputum specimen
Strategic and Technical Advisory Group for TB (STAG-TB)

- Meets once a year
- 22 members – on rotation - from various constituencies: epidemiology, control, research, public health, surveillance, laboratory, community etc
- Reviews policies and strategies prepared by WHO or expert groups
- Provides recommendations for WHO to make policies, strategies and standards
- Preparatory for WHA resolutions
- Today, also a global endorsement mechanism for new tools
Changing TB control dynamics

- Changes in diagnostic and screening algorithms
- Increased capacity needed to treat TB and MDR-TB
- Need to re-define case and outcome definitions
- Monitoring of impact on case detection and cure
- Resource awareness by donors/funders
- Use in non-traditional TB settings (HIV, private sector)
- Innovative new partnerships needed

Global Consultation: 30 Nov - 2 Dec 2010
Moving forward quickly...

WHO endorsement 2010
- Global Consultation
- WHO Policy Guidance
- Roadmap for implementation

Phased implementation 2011
- Through EXPAND-TB, TBREACH, TBCARE, PEPFAR, GF R10, UNITAID
- Selected countries, different health service levels

Scale up 2012
- EXPAND-TB, Global Fund R11, TBREACH, TBCARE, PEPFAR, country budgets, etc
Expectations from the Global Consultation

1. Diagnostic algorithms for risk groups
2. Programmatic implementation: tiered lab services
3. Pricing considerations and market dynamics
4. Cost-effectiveness and cost-benefit considerations
5. Global framework for rapid uptake in countries
Many thanks to all
Responding to change:
rapid policy development by WHO

K Weyer
Stop TB Department

Global Consultation: Geneva, 30 November 2010
Implementation and scale-up of Xpert MTB/RIF
for rapid diagnosis of TB and MDR-TB
Process

• Expert Group assessment: 1 Sep 2010
• STAG-TB evaluation: 27 Sep 2010
• Global Consultation: 30 Nov-2 Dec 2010
• WHO Policy announcement: 7 Dec 2010
Expert Group: Findings

- **Test accuracy high**, single test detecting 91% of culture-confirmed TB patients (99% smear-pos and 80% smear-neg), unaffected by HIV. R resistance detected with 95% sensitivity and 98% specificity;

- **Time to detection <1day**, compared to 17 days (liquid culture); >30 days (solid culture); >75 days (phenotypic DST). Smear-negative TB patients started Rx after 4 days vs 58 days when Xpert not used;

- **TB and MDR-TB case detection significantly increased**, cost-comparison favourable to phenotypic culture and DST; cost-effectiveness highest when used as add-on to microscopy, but impact highest when used as initial diagnostic test in high-risk groups;

- **Operational findings confirmed robustness, safety, minimal training needs, high user satisfaction.** Uninterrupted and stable power supply, security against theft, annual validation, adequate storage capacity and waste disposal management required.
# Expert Group: GRADE summary

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Expert Group Remarks

- **Recommendations also apply to children**, based on 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 recovering isolates for drug susceptibility testing other than rifampicin (including second-line anti-TB drugs); and for prevalence surveys and/or surveillance;

- **Recommendations apply to the use of Xpert MTB/RIF in sputum specimens** (including pellets from decontaminated specimens), as data on the utility of Xpert MTB/RIF in extra-pulmonary specimens are still limited;

- **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.
While not preventing or delaying implementation, operational research should include:

- Evaluation of different diagnostic algorithms
- Cost-effectiveness and impact in different settings
- Feasibility of decentralised use (rural, point-of-care)
- Cartridge & device stability in adverse conditions
- Evaluation in extra-pulmonary & paediatric TB
- Assay for fluoroquinolones and aminoglycosides
Endorsed EG findings and recommendations

Recommended phased implementation within national TB and MDR-TB strategic plans

Requested WHO to:
  • Proceed with policy guidance
  • Develop a global strategy for rapid uptake
  • Organise a Global Consultation on implementation
  • Assist countries with uptake
Draft WHO Policy Guidance

- Positioning at district or sub-district level
- Risk analysis (country-specific epidemiology, available resources, cost-effectiveness)
- Stand-alone diagnostic test*
- Rx response monitored by conventional tests
- Operational issues
- Rapid communication of results and access to appropriate treatment imperative

* Supported by conventional DST in low MDR settings to identify possible FPs