Review of WHO TB diagnostics policy development

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Laboratories, Diagnostics and Drug Resistance Unit

GLI Meeting: Les Pensières, Annecy, France : 17 -19 April 2012
Outline

- WHO TB diagnostics policy formulation process
- Current WHO-endorsed TB diagnostics/approaches
- Policy transfer and uptake
- Policy impact
- Policy innovation
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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
GRADE evaluation

*Grades of Recommendation Assessment, Development and Evaluation*

Clear separation:

- **Recommendation**
  - strong or conditional/optional/weak (for or against an intervention)
  - Benefits and downsides, values and preferences, impact, resource use

  balanced with

- **Quality of evidence**
  - ⊕⊕⊕⊕ (High), ⊕⊕⊕ (Moderate), ⊕⊕○○ (Low), ⊕○○○ (Very low)
  - Methodological quality of evidence
  - Likelihood of bias
  - By outcome and across outcomes

- GRC review cycle 3 to 5 years
Example of GRADE for Xpert MTB/RIF

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

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).
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Acceleration

- **Tools development**: At least 20 new technologies in various stages of development and evaluation in last 10 years

- **WHO policy formulation**
  - 2007: New SS+ case definition, two-specimen approach, liquid culture, rapid speciation
  - 2008: Line probe assay
  - 2009: LED microscopy, ‘same-day diagnosis’, selected non-commercial culture and drug susceptibility testing methods
  - 2010: Xpert MTB-RIF
  - 2011: IGRAs, commercial serodiagnostics

- **Access** to new diagnostics and laboratory strengthening (GLI and EXPAND-TB)

*Available at: [http://www.who.int/tb/dots/laboratory/policy/en](http://www.who.int/tb/dots/laboratory/policy/en)*
Tools/methods not recommended

• Evidence base too weak, to be reassessed
  – 2009: Sputum processing methods
  – 2009: TLA method for rapid DST
  – 2010: LPA for XDR-TB

• ‘Negative’ policy (do-not-use)
  – 2011: Commercial serodiagnostics
  – 2011: IGRAs (high TB or HIV burden settings)
Diagnostics pipeline

Abbreviations: **DST** Drug susceptibility test; **NAAT** Nucleic acid amplification test; **LTBI** Latent TB infection; **POC** Point of care; **MODS** Microscopic observation drug-susceptibility; **NRA** Nitrate reductase assay; **CRI** Colorimetric redox indicator assay; **LED** Light-emitting diode; **LPA** Line probe assay
Policy pipeline 2012

- Laboratory biosafety
  - Procedure (risk)-based, minimum requirements

- Guidance on drug susceptibility testing
  - Update on 2008 guidance

- LPA update
  - New 2nd-line LPA (XDR)

- Evaluation of new technologies
  - LAMP assay
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Surveillance
Reference methods
Network supervision

Case finding
Treatment

Screening
Referral

Tools in tiered health services

Central Reference Level

District & Sub-district Level

Community Level

WHO
THE STOP TB DEPARTMENT
## Tools in combination

**Early diagnosis & care** | **Smear-negative TB** | **Rapid resistance detection**

<table>
<thead>
<tr>
<th>Year</th>
<th>Technology</th>
<th>Turnaround time</th>
<th>Sensitivity gain</th>
</tr>
</thead>
</table>
| Before 2007 | ZN microscopy  
Solid Culture | 2-3 days  
30-60 days | Baseline |
| 2007      | Liquid Culture / DST  
Rapid speciation | 15-30 days | +10% compared to LJ |
| 2008      | Line Probe Assay (1st line, Rif & INH) | 2-4 days | S+ only |
| 2009      | LED-based FM | 1-2 days | +10% compared to ZN |
| 2009      | In house DST (MODS, CRI, NRA) | 15-30 days | 1st line only |
| 2010      | Xpert MTB/RIF (TB, R resistance) | 100 minutes | +40% compared to ZN |
Tools in different algorithms

One size no longer fits all
Policy uptake at country level (1)

• **Rapid uptake**
  – SS+ case definition

• **Limited or no uptake**
  – Two-specimen strategy
  – Same-day-diagnosis
  – Non-commercial culture and DST methods

• **Gradual uptake**
  – LED microscopy
  – Liquid culture and DST
  – Rapid speciation
  – Line probe assay
### Policy uptake at country level (2)

<table>
<thead>
<tr>
<th></th>
<th>Conventional Drug Susceptibility Testing (DST)</th>
<th>Liquid Culture and Rapid Speciation Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incorporated into Policy</strong></td>
<td>91%</td>
<td>64%</td>
</tr>
<tr>
<td><strong>Being Rolled Out</strong></td>
<td>91%</td>
<td>68%</td>
</tr>
<tr>
<td><strong>High TB Burden</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>93%</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td>54%</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>49%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*Source: 2011 WHO TB Control Report*
Policy uptake at country level (3)

<table>
<thead>
<tr>
<th></th>
<th>Line-Probe Assay for Detecting Resistance to Rifampicin</th>
<th>Algorithm for the Diagnosis of TB in HIV-Positive People</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incorporated into Policy</strong></td>
<td><strong>Being Rolled Out</strong></td>
<td><strong>Incorporated into Policy</strong></td>
</tr>
<tr>
<td>High TB Burden</td>
<td>45%</td>
<td>77%</td>
</tr>
<tr>
<td>GH MDR-TB Burden</td>
<td>52%</td>
<td>70%</td>
</tr>
<tr>
<td>Global</td>
<td>27%</td>
<td>44%</td>
</tr>
</tbody>
</table>

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Policy impact (1)

Dec 2010 → Dec 2011

460 GXP machines and 591,450 Xpert MTB/RIF cartridges procured in 47 countries
Policy impact (2)

First ‘negative’ policy guidance by WHO

Unprecedented political commitment by India

Health Ministry set to ban commonly used TB test

Abantika Ghosh : New Delhi, Tue Mar 20 2012, 00:34 hrs

The Health Ministry has decided to ban serological diagnostic test for tuberculosis, in line with a World Health Organisation recommendation. India is going to become the first country to execute the ban on the test, which is highly inaccurate but commonly used.

It is estimated that 1.5 million patients are subjected to the test every year in India for diagnosis of Mycobacterium tuberculosis and many of them are started on anti-TB treatment on the basis of the results. In many cases, all it does is result in antibiotic resistance.
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Guidance documents

- GLI Roadmap, Tools Set, Accreditation Guide
- WHO Policy Framework for Implementing TB Diagnostics
- WHO Fact Sheets
- ‘How to’ documents and online tracking
  - Xpert MTB/RIF Rapid Implementation Document
  - Xpert MTB/RIF Checklist
  - Xpert MTB/RIF Website and Online Data Collection Tool
GRADE evolution for TB Diagnostics

- Refined quality assessment tools (eg. QUADAS-2)
- Refined statistical methodology for meta-analyses
- Standardised proxies for patient- and public health impact
- Cost-effectiveness modeling

**But:** Test-specific recommendations necessary
- Different technologies, targets, performance characteristics

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<table>
<thead>
<tr>
<th>Test</th>
<th>AFB+ Sensitivity</th>
<th>AFB+ Specificity</th>
<th>AFB- Sensitivity</th>
<th>AFB- Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplicor (PCR)</td>
<td>96 (94-97)</td>
<td>83 (80-86)</td>
<td>61 (57-65)</td>
<td>97 (96.8-97.4)</td>
</tr>
<tr>
<td>Cobas Amplicor (PCR)</td>
<td>96 (95-97)</td>
<td>74 (68-8)</td>
<td>64 (59-69)</td>
<td>99 (99.2-99.4)</td>
</tr>
<tr>
<td>BDP (SDA)</td>
<td>98 (96-99)</td>
<td>89 (84-93)</td>
<td>71 (66-76)</td>
<td>97 (96.4-97.4)</td>
</tr>
<tr>
<td>E-MTD (TMA)</td>
<td>97 (95-98)</td>
<td>96 (93-97)</td>
<td>76 (70-80)</td>
<td>97 (96.6-97.4)</td>
</tr>
<tr>
<td>Lcx (LCR)</td>
<td>96 (94-98)</td>
<td>71 (64-78)</td>
<td>57 (50-64)</td>
<td>98 (97.8-98.5)</td>
</tr>
</tbody>
</table>

PCR: polymerase chain reaction; SDA: strand displacement amplification; TM: transcription mediated amplification; LCR: ligase chain reaction.
Dynamic policy refinement

- Feasibility
- Development
- Evaluation
- Demonstration
- Collecting evidence for scale-up
- Scale-up

Research prototype format for new diagnostic product developed and validated

- New in-vitro diagnostic test developed under quality assurance: «product in a box»; design lock

Specifications of new diagnostic product validated in controlled trials at 3-5 trial sites in high-endemic countries

- Registration where needed

Specifications of new diagnostic product validated in uncontrolled trials under field conditions at 5-10 trial sites in high-endemic countries

New product successfully implemented in routine diagnostic services in early implementers' laboratories in high disease endemic countries

New technology rolled out in high disease endemic countries
Acknowledgements

• WHO/STB/TBL staff
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• GRADE Working Group Chair: Holger Schünemann

• Expert Group members

• WHO STAG members

• Funding: USAID, WHO, TDR, TREATTB/The Union

• FIND: Evaluation studies and reports