The changing environment for diagnostics implementation

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Laboratories, Diagnostics and Drug Resistance
Strengthening TB laboratories

‘From unimaginable...to indispensable’

1st GLI Meeting, Annecy
April 2008
Landscape rapidly changing

- Growing diagnostics pipeline
- Accelerated WHO policy formulation
- Policy transfer, uptake and innovation
- Policy impact
- Access to new diagnostics and laboratory services
- Need to align diagnosis, treatment and care delivery
The development pipeline for new TB diagnostics
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
  - 2012: TB laboratory biosafety
  - 2012: Updated guidance on drug susceptibility testing

- **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
  – 2012: TB-LAMP

• ‘Negative’ policy (do-not-use)
  – 2011: Commercial serodiagnostics
  – 2011: IGRAs (high TB or HIV burden settings)
Policy pipeline 2013

- Guidance on drug susceptibility testing
  - Update on 2008 guidance

- LPA update
  - Update on 2008 guidance
  - New 2nd-line LPA (XDR)

- Xpert MTB/RIF update
  - Extra-pulmonary TB
  - Paediatric TB
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
Figure 4. Body of evidence required by WHO for policy development

Phase 1: Research and Development
- Upstream research and development to define and validate a prototype
- Laboratory validation under international standards that culminate in a design-locked product
- WHO may interact with developers to discuss end-user requirements

Phase 2: Evaluation and Demonstration
- Controlled trials at 3-5 trial sites in high-burden TB and HIV countries
- Data often used for product registration with global and/or national regulatory authorities
- Product specifications, performance validated in field trials in 5-10 intended-use sites

Phase 3: WHO evidence assessment using GRADE
- New technologies/new indications for use: Dossier with Phase 1 and 2 data to WHO for assessment
- Fast-follower/generic technologies: ISO 13:485 standards; equivalence shown in 2-3 SRLs
- WHO is not a regulatory authority and does not recommend technologies for individual country use

Phase 4: Phased uptake & evidence for scale-up
- Implementation in routine TB services by early implementers in high-burden TB and HIV countries
- Systematic assessment of algorithms, laboratory workload, operational constraints, cost-effectiveness
- Lessons learnt by early implementers used for country adaptation

Phase 5: Scale-up & policy refinement
- Scale-up, with subsequent data to inform and refine WHO policy guidance
GRADE evolution for TB Diagnostics

- Refined quality assessment tools (e.g., 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

<table>
<thead>
<tr>
<th>Test</th>
<th>AFB+</th>
<th></th>
<th>AFB-</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<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.
Policy uptake at country level (1)

- **Rapid uptake**
  - SS+ case definition
  - Xpert MTB/RIF

- **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
### Incorporation of WHO policy guidance for diagnosis of TB, 2011

<table>
<thead>
<tr>
<th>Test</th>
<th>High-burden countries</th>
<th>High MDR-TB burden countries</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional drug susceptibility testing (DST)</td>
<td>95%</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>Liquid culture and rapid speciation test</td>
<td>73%</td>
<td>75%</td>
<td>67%</td>
</tr>
<tr>
<td>Line probe assay for detecting resistance to rifampicin</td>
<td>64%</td>
<td>74%</td>
<td>44%</td>
</tr>
<tr>
<td>Algorithm for the diagnosis of TB in people living with HIV</td>
<td>86%</td>
<td>87%</td>
<td>74%</td>
</tr>
<tr>
<td>Xpert MTB/RIF assay</td>
<td>64%</td>
<td>50%</td>
<td>33%</td>
</tr>
</tbody>
</table>
Policy impact (1)

99 GeneXperts (524 modules) in the public sector in 23 countries

898 GeneXperts (4,660 modules) in the public sector in 73 countries
Cumulative number of GeneXpert modules and Xpert MTB/RIF cartridges procured under concessional pricing

Data: FIND
Policy impact (2)

First ‘negative’ policy guidance by WHO

Unprecedented political commitment by India

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.
## Laboratory capacity, 2011

<table>
<thead>
<tr>
<th></th>
<th>Smear microscopy: Laboratories per 100,000 population</th>
<th>Culture: Laboratories per 5 million population</th>
<th>DST: Laboratories per 5 million population</th>
<th>Line probe assay: Laboratories per 5 million population</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 high TB burden countries</td>
<td>1.1</td>
<td>1.5</td>
<td>0.4</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>27 high MDR-TB burden countries</td>
<td>0.9</td>
<td>1.3</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Global</td>
<td>1.1</td>
<td>3.9</td>
<td>0.8</td>
<td>0.2</td>
</tr>
</tbody>
</table>

- 15 of the 22 high TB burden countries have ≥1 microscopy centre per 100,000 population
- 17 of the 36 high TB / MDR-TB burden countries have ≥1 culture and DST laboratories per 5 million population
Tools in tiered health services

Surveillance
Reference methods
Network supervision

Case finding
Treatment

Screening
Referral

Central Reference Level

District & Sub-district Level

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

**Tools in combination**

- early diagnosis & care
- smear-negative TB
- rapid resistance detection
Tools in different algorithms

One size no longer fits all
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
EXPanding Access to New Diagnostics for TB

$87M (total $350M)

Integrate tools in TB control
Increase MDR diagnosis
Improve market dynamics

Diagnose ~129,000 MDR patients

Strengthen >100 Labs
Commodities
Know-how

EXPANDx-TB
Project countries and partners

Contributing own funds for essential non-commodity components of laboratory strengthening and for technical assistance.
Project Status

Laboratory preparedness
- Laboratory assessment
- Memorandum of Understanding
- Infrastructure upgrade
- Creation of SOPs
- Policy reform

6-12 months
- Mozambique
- Rwanda
- Senegal
- Peru
- Viet Nam

18-24 months
- Belarus
- Indonesia
- Kazakhstan

Routine testing and monitoring
- Monitoring and evaluation
- Impact assessment
- Market dynamics

Up to year 5
- Azerbaijan
- Bangladesh
- Cameroon
- Côte d’Ivoire
- Djibouti
- Ethiopia
- Georgia
- India
- Uganda
- Haiti
- Kenya
- Kyrgyzstan
- Lesotho
- Myanmar
- Tajikistan
- Rep Moldova
- UR Tanzania
- Uzbekistan
- Swaziland

- Labs established: 58 out of 101
- 19 countries reporting MDR-TB cases
- More that 21,000 MDR-TB cases already diagnosed
TBXpert Project

- USD 25.9 million UNITAID-funded project for procurement of GeneXperts and Xpert MTB/RIF cartridges
  - Consortium: WHO Stop TB Department, Stop TB Partnership, Global Laboratory Initiative (GLI), TB REACH, EXPAND-TB, African Society for Laboratory Medicine (ASLM), Interactive Research and Development (IRD)

- Project objectives:
  - To reduce the cartridge price from 16.86 USD to 9.98 USD to generate demand and create a sustainable market
  - To rapidly scale-up implementation of Xpert MTB/RIF in target countries using effective diagnostic algorithms
  - To develop and establish innovative PPM models to accelerate uptake and increase demand
TBXpert Project

- >200 GeneXpert devices and 1.4 million Xpert MTB/RIF cartridges in 21 countries, 2013-2015
**Impact of Xpert MTB/RIF**

- **Early** and **rapid** case detection
- **Increase** in number of TB and R-resistant cases
- Reduced need (**but not eliminated**) for conventional laboratory services
- **Urgent need to match diagnosis with treatment and care delivery**

**Rapid TB test with higher sensitivity, used widely**

- More TB patients are found **earlier in the course** of their disease
- Allow for rapid detection of TB patients with lower bacterial load
- Early and rapid case finding allows earlier intervention and management

- Reduction in mortality, suffering from and disease transmission
- **Low bio-safety requirement**
- Sensitivity close to culture
- High specificity
- Rapid (< 2 hrs)
- Portable
- Easy to use

- Running costs
- Infrastructure needs
- R resistance ≠ MDR-TB
- No use for treatment monitoring

**World Health Organization**
DST coverage and enrolment on MDR-TB treatment compared to Global Plan

Coverage among new cases and enrollment on MDR-TB treatment compared with the targets in the Global Plan to Stop TB, 2011-2015

Lines indicate the planned targets, blue squares show the situation in 2009-2011 and green circles the projected enrolments 2012-2015
Enrolment on MDR-TB treatment, 2011

- India [68000, 5%]
- China [61000, 2%]
- Russian Federation [44000, 43%]
- Philippines [11000, 22%]
- Pakistan [10000, 3%]
- Ukraine [9300, 53%]
- Kazakhstan [8200, 64%]
- South Africa [8100, 70%]
Scaling up quality management of MDR-TB
- Only if all pieces fit together -