How best to structure a laboratory network with new technologies

Cristina Gutierrez, MD, PhD

Uniting to scale up TB care in Central Asia
14 and 15 April 2011
Tashkent, Uzbekistan

Partnering for better diagnosis for all
## New laboratory diagnostics for TB and MRD-TB

<table>
<thead>
<tr>
<th>WHO endorsement</th>
<th>Technology</th>
<th>Detects</th>
<th>Turnaround time</th>
<th>Sensitivity Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 2007</td>
<td>ZN microscopy</td>
<td>TB</td>
<td>2-3 days</td>
<td>Baseline</td>
</tr>
<tr>
<td>Before 2007</td>
<td>Solid Culture &amp; DST</td>
<td>TB &amp; MDR-TB</td>
<td>30-60 days</td>
<td>Baseline</td>
</tr>
<tr>
<td>2007</td>
<td>Liquid Culture &amp; DST</td>
<td>TB &amp; MDR-TB</td>
<td>15-30 days</td>
<td>+10% compared to LJ</td>
</tr>
<tr>
<td>2008</td>
<td>Line Probe Assay (1st line, Rif-INH)</td>
<td>TB &amp; MDR-TB</td>
<td>2-4 days</td>
<td>At this time for smear + only</td>
</tr>
<tr>
<td>2009</td>
<td>LED-based FM</td>
<td>TB</td>
<td>1-2 days</td>
<td>+10% compared to ZN</td>
</tr>
<tr>
<td>Conditional 2009</td>
<td>In house DST (MODS, CRI, NRA)</td>
<td>TB &amp; MDR-TB</td>
<td>15-30 days</td>
<td>1st line only</td>
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<tr>
<td>2010</td>
<td>GeneXpert</td>
<td>TB &amp; Rif R-TB</td>
<td>2 hours</td>
<td>+40% compared to ZN</td>
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**Importance for** early diagnosis & care | smear-negative TB | rapid MDR detection
Introducing high tech in low tech settings

Major advantages in workflow

- fully automated with 1-step external sample prep.
- time-to-result 1.5 h (walk away test)
- throughput: up to 16 tests/module/day
- no bio-safety cabinet
- closed system (lower contamination risk)

Performance

- specific for MTB
- sensitivity close to culture
- detection of rif-resistance via rpoB gene

Automated Sample Prep, Amplification and Detection

<120 minutes

A technology platform:

- TB & Rif Resistance
- Potential for HIV viral load
- Potential for HPV STD
The slow road to TB diagnosis

Threshold for visibility of AFB by smear microscopy

Infection of healthy patient
Patient visits clinic: no diagnosis made
First smear: AFB negative
Patient visits pharmacy
AFB+: TB diagnosis made

Number of TB bacilli per millilitre (ml) of sputum

Patient feels unwell
Night cough begins
Cough worsens: patient returns to clinic
Blood appears in sputum; infant daughter infected with TB
Too weak to work

first month  second month  third month  fourth month  fifth month
Importance of early diagnosis: Sensitivity (cfu/ml) of pulmonary TB tests

- **MGIT**: 10-100/ml
- **LAMP-TB**: 50-150/ml
- **Xpert MTB**: 50-150/ml
- **iLED fluorescent microscope**: 10,000/ml
- **Line-probe**: 10,000/ml
- **Capilia speciation dipstick (of culture)**: 1,000,000/ml
Integration of new tools in the tiered health system

- Surveillance
- Reference methods
- Network supervision

- Resolution testing (screening-test negative drug resistance)

- Screening
- Passive case finding
- Detect and treat

- Clinical Screening
- Primary care

Fraction of patients seen

2007

Reference Labs

Regional Labs

District Level

SubDistrict Level

Microscopy Level

Community Level

Surveillance
Reference methods
Network supervision

Resolution testing (screening-test negative drug resistance)

Screening
Passive case finding
Detect and treat

Clinical Screening
Primary care

5%
10%
25%
60%

SC / DST 30d / 60d

ZN 2-3d

Fraction of patients seen
Integration of new tools in the tiered health system

**SubDistrict Level**
- Microscopy Level
- Community Level

**District Level**
- SubDistrict Level

**Regional Labs**
- Reference Labs

**2010**
- Integrated NAAT +40% / 2h
  - Sputum neg./HIV pos.
- HPV STD 2012
- LC / DST 15d / 30d
- LPA Rif / INH 2d
- Early Infant DX HIV

**Surveillance**
- Reference methods
- Network supervision

**Resolution testing**
- (screening-test negative drug resistance)

**Screening**
- Passive case finding
- Detect and treat

**Clinical Screening**
- Primary care

**Fraction of patients seen**
- 60%
- 25%
- 10%
- 5%
Integration of new tools in the tiered health system

- Surveillance
- Reference methods
- Network supervision

• Resolution testing (screening-test negative drug resistance)

- Screening
- Passive case finding
- Detect and treat

- Clinical screening
- Primary care

Fraction of patients seen

Expected 2012-14

Integrated NAAT +40% /2h
Sputum neg./HIV pos. HIV Viral Load – 2012
HPV STD 2012

LC / DST
15d/ 30d

LPA  Rif / INH 2d
Early Infant DX HIV

RDT Gen1 / Gen 2

Manual NAAT+25%
EID HIV – 2011
Malaria HAT

LED FM +10%

Integrated NAAT +40% /2h
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Decentralization of molecular diagnostics

1st generation MDR

2nd generation automated MDR

1st generation manual detection

2nd generation manual detection

LPA

2008

Xpert

2010

2011

LAMP

POC test

2015

Less complexity, more robustness
Expanding the access to new diagnostics (2009-2013)

- Integrating new tools in national TB control programs
- Improving MDR-TB control
- Improving market dynamics

Assessment visit
Memorandum of understanding
Infrastructure and equipment
Training
Technical validation
Reporting
Mentor ship

- Liquid culture and DST
- Rapid MTB speciation
- Line Probe Assay

27 countries
101 laboratories (42 in India)
30% MDR-TB cases
Impact evaluation
The rational for introducing new TB tests in a network

- Disease burden, size of the country, level of decentralization
- Eligible patient to be tested and diagnostic algorithm
  - Smear + and/ or –
  - Any case or only any drug resistant suspect or only MDR suspects
  - Low and high HIV settings
  - Low and high MDR settings
- Specimen/patient referral
- Linkage to treatment
- Costs and donors support
- Technical realities and implementation challenges
Challenges of implementing new diagnostics

- A functional laboratory requires more than commodities

Logistics and supplies

Human Resources
   - Guidelines
   - Technology transfer

Infrastructure

Quality Assurance

Linked referral systems and reporting

Essential instruments, reagents, supplies

Additional components to ensure quality diagnostic services
Challenges of implementing new diagnostics are tool-dependent

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Laboratory infrastructure

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- BSL2 and molecular rooms
- BSL3
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<td>✔</td>
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</tr>
<tr>
<td>Waste management</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Laboratory Information Management System</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Communication of results</td>
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<td>Quality management system, with EQA, proficiency testing, IQC</td>
<td>✓</td>
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To maintain good performance and to assure high quality results
### Internal Quality Controls, NTRL Lesotho

#### Tuberculosis

- **Liquid culture (MGIT)**
- **Drug susceptibility testing**
- **Smear microscopy**
- **Media batch testing with H37Rv**
- **MRC cultures as internal standards - H37Rv and one mono ‘rif’ (mainly)**
- **Temperature logs, equipment maintenance sheets for all tests**
- **Batch testing of stains with known positive and negative slides - Centralized supply**
- **IQC slides - One 1+ positive and one negative, every day before patients samples checking**
- **NRL Onsite EQA activities for all microscopy centers**

#### HIV-EID

- **Line Probe assay**
- **Mfg. run controls (CC, AC, TUB)**
- **Water used in DNA extraction step and master-mix step controls (negative)**
- **Mfg. run controls (one high positive and one negative DBS)**
- **AmpliCor HIV 1-DNA**
- **CDC/GAP internal controls - (one high positive and one negative DBS)**
- **For all HIV-1 DNA positive, test is repeated, before providing results**
- **Monitoring of statistics of test results and trends, monthly (to check what kind of samples are processed and what is TAT)**
### External Proficiency Testing at NTRL Lesotho

#### Tuberculosis

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<td>Solid/Liquid culture (MGIT) &amp; AFB smears</td>
<td>NHLS, South Africa (SA)</td>
<td>3 blinded cultures isolates 1 lyophilized sample for culture, id and DST and 10 blinded smears (Quarterly) 100% concordance with smear and culture results (2nd quarter 2010)</td>
</tr>
<tr>
<td>Line Probe assay</td>
<td>MRC, Pretoria, SA</td>
<td>10 culture isolates for DST (Annual) Achieved 95% concordance with rifampicin and 100% for isoniazid (2009)</td>
</tr>
<tr>
<td>HIV-EID</td>
<td>Amplicor HIV 1- DNA</td>
<td>10 Dried Blood spot specimens sent by GAP (quarterly) Achieved 100% concordance (1st and 2nd PT rounds, 2010)</td>
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<td>GAP/CDC, Atlanta</td>
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National TB Programs implementing new technologies

- Coordination with local stakeholders
- Internal and external quality assurance
- Technology transfer and training
- Specimen referral mechanisms
- Monitoring, evaluation and impact assessment
- Long-term, on-site mentoring
- Laboratory management SOPs
- Procurement
- Supply chain management
- Internal and external quality assurance
- Policy reform and adoption
- Biosafety standards
Thank you!