New frontiers: changing diagnostic paradigms

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Poor diagnosis: Impact on individuals, communities and global health programmes

- Lack of diagnosis
  - Syndromic treatment
  - Potential mis- or overtreatment
  - Continued illness
- Individual health
- Public health
  - Continued transmission
  - Waste of resources
  - Development of drug resistance
- Overall impact
  - Growing incidence & prevalence
  - Increasing burden of disease
  - Misallocation of resources
  - Increasing difficulty to control disease
The 5 essential components of the DOTS strategy:
1. Sustained political commitment
2. Quality-assured sputum smear microscopy
3. Direct-observed treatment, short-course
4. Uninterrupted supply of quality-assured anti-TB drugs
5. Recording and reporting system
"The impact of HIV on the epidemiological situation of TB is so large that the tools available at present for TB control will fail to restrain the increase in the incidence of TB caused by HIV infection."

Karel Styblo - Bull. IUATLD, Vol.65, N 1, March 1990
The shortfalls of DOTS (II): MDR-TB


* Australia, Democratic Republic of the Congo, Fiji, Guam, New Caledonia, Solomon Islands and Qatar reported data on combined new and previously treated cases.
Evolution in TB diagnosis

Koch | 1882
X-ray | 1895
Tuberculin | 1907
Culture | 1936
1st TB drugs | 1950
Short-course therapy | 1980s
Smear & X-ray | 1960-80
HIV / MDR-TB | 2006 - 2010

Sanatoria

Centralised programs

Decentralisation to district level *(based on Styblo model)*

Need for new tools & strategies
DOTS (II): 6 additional crucial elements in new strategy

1. Sustaining, improving and accelerating quality DOTS expansion
2. Addressing TB-HIV, MDR-TB and other special challenges
3. Contributing to health system strengthening
4. Engaging all care providers
5. Empowering patients and communities
6. Enabling and promoting research
The slow road to TB diagnosis

Infection of healthy patient

Patient visits clinic: no diagnosis made

First smear: AFB negative

Patient visits pharmacy

Threshold for visibility of AFB by smear microscopy

Blood appears in sputum; infant daughter infected with TB

Too weak to work

Patient returns to clinic

AFB+: TB diagnosis made

Number of TB bacilli per millilitre (ml) of sputum

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

Target sensitivity range of antigen antibody detection tests:
- LAMP-TB: 50-150/ml
- Xpert MTB*: 50-150/ml
- MGIT*: 10-100/ml
- iLED* fluorescent microscope: 10,000/ml
- Line-probe*: 10,000/ml
- Capilia* speciation dipstick (of culture): 1,000,000/ml

* Development completed
## WHO recommendations 2006-2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Technology and Changes</th>
</tr>
</thead>
</table>
| 2006 | - Smear-positive case definition from 2 to 1 positive smears  
      - Screening for TB with 2 instead of 3 smears  
      - Conventional FM |
| 2007 | - Commercial liquid culture / DST  
      - Rapid speciation (MPT64) |
| 2008 | - Line probe assay (Rif & INH) |
| 2009 | - LED-based FM  
      - Non-commercial culture (MODS, CRI, NRA) |
| 2010 | - Cartridge-based Automated NAAT: Pending |
A changing landscape

Expected 2012 (Gen 1) / 2014 (Gen 2)

- Surveillance
- Reference methods
- Network supervision

- Resolution testing (screening-test negative drug resistance)

- Screening
- Passive case finding
- Detect and treat

- Clinical Screening
- Primary care

SubDistrict Level
- ZN 2-3d
- LED FM +10%
- Manual NAAT+25%

Microscopy Level
- Single step NAAT +40% /2h

District Level
- In house DST (MODS, NRA, CRI)
  Special settings and conditions

Regional Labs
- LC / DST 15d / 30d
- LPA Rif / INH 2d

Reference Labs
- RDT Gen1 / Gen 2

Community Level
- D/ DST 30d / 60d / 30d

A changing landscape
Decentralization of molecular diagnostics

1st generation MDR

2nd generation automated MDR

1st generation manual detection

Less complexity, more robustness

LPA
Automated NAAT
LAMP
POC test

2008
2010
2011
2013
Integration of technologies lead to breakthrough in 2010

- Molecular beacons
- RT PCR
- Resistance-associated mutations
- Fluorimetric probes
- Microfluidics
- Sonic bacterial lysis

Real-Time PCR

Microfluidics

TB DNA sequence

GeneXpert Xpert C. difficile

foundation for innovative new diagnostics
Introducing high tech in low tech settings

Major advantages in workflow

- fully automated with 1-step external sample preparation
- time-to-result 1 1/2 h (walk away test)
- throughput: up to 16 tests / module / run
- no bio-safety cabinet
- closed system (no contamination risk)

Performance

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

Automated Sample Prep, Amplification and Detection

A technology platform:
- TB & Rif Resistance
- Potential for HIV viral load
- Potential for HPV STD
GeneXpert as a scalable platform
### Table 34: Existing test cartridges on the GeneXpert platform

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cartridge</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphlococcus aureus</em> colonization</td>
<td><em>Bordetella pertussis</em></td>
</tr>
<tr>
<td>Vancomycin resistance</td>
<td><em>Bordetella parapertussis</em></td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>HSV Type 1</td>
</tr>
<tr>
<td>MRSA from tissue or blood</td>
<td>HSV Type 2</td>
</tr>
<tr>
<td>Group B <em>Streptococcus</em></td>
<td>RSV Type A</td>
</tr>
<tr>
<td>Enteroviral meningitis</td>
<td>RSV Type B</td>
</tr>
<tr>
<td>Coagulation disorders</td>
<td>Norovirus GI</td>
</tr>
<tr>
<td>Anthrax</td>
<td>Norovirus GII</td>
</tr>
<tr>
<td></td>
<td>Flu A</td>
</tr>
<tr>
<td></td>
<td>Flu B</td>
</tr>
<tr>
<td></td>
<td>Leukemia (BCR-ABL)</td>
</tr>
</tbody>
</table>
Expanding technology platform = increased cost-effectiveness

<table>
<thead>
<tr>
<th>Technology platform</th>
<th>“Menu”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional Laboratories (line probe assay)</td>
<td>1. TB Rif / INH</td>
</tr>
<tr>
<td></td>
<td>2. TB Fluoroquinolones/Inject</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td></td>
<td>3. EID/HIV</td>
</tr>
<tr>
<td>District/Subdistrict Laboratories (automated</td>
<td>1. TB Rif</td>
</tr>
<tr>
<td>NAAT)</td>
<td>2. TB Fluoroquinolones/Inject</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td></td>
<td>3. STDs</td>
</tr>
<tr>
<td></td>
<td>4. Viral load HIV</td>
</tr>
<tr>
<td></td>
<td>5. Others: Hepatitis B/C</td>
</tr>
<tr>
<td>Microscopy Centres (manual NAAT)</td>
<td>1. TB</td>
</tr>
<tr>
<td></td>
<td>2. Malaria</td>
</tr>
<tr>
<td></td>
<td>3. HAT</td>
</tr>
<tr>
<td></td>
<td>4. EID/HIV</td>
</tr>
<tr>
<td>Microscopy Centres (LED microscopy)</td>
<td>1. TB</td>
</tr>
<tr>
<td></td>
<td>2. HAT</td>
</tr>
<tr>
<td></td>
<td>3. Malaria</td>
</tr>
</tbody>
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Decreasing cost of new technologies over time

- Capital costs: Instruments, labs, QA, QC
- Cost to perform culture / DST (assume constant cost)
- Cost driven down due to increased volumes

Cost to introduce modern integrated platforms

Cost of reagents
Thank you!