MDR, XDR and Untreatable Tuberculosis and Laboratory Perspectives

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Introduction

• 2008 IOM Meeting in Washington the emerging threat of totally drug resistant tuberculosis was mentioned

• The purpose of my presentation is to highlight the challenges we face in diagnosing drug resistance and the realities of it in the African context.

• I have the sober opinion that untreatable tuberculosis will always be with us but depends on the setting.
Presentation outline

1. Prevalence of resistance against second-line drugs (SLD)
2. Rationale use of SLD sensitivity testing (ST) in programmatic management of drug resistant tuberculosis
3. Untreatable tuberculosis
1. Prevalence of resistance against second-line drugs

- **Tuberculosis control in 2012**
  - Gains made in reducing incidence, prevalence, mortality

- **Progress in responding to DR-TB remains low**
  - Numbers of MDR-TB in 27 high burden countries reached 60,000
  - Huge underestimation
  - Average rate of XDR-TB among MDR-TB is 9%
## Estimates of TB burden 2011

<table>
<thead>
<tr>
<th>Description</th>
<th>NUMBER (thousands)</th>
<th>RATE (per 100,000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (excludes HIV+TB)</td>
<td>720 (180–270)</td>
<td>26 (21–31)</td>
</tr>
<tr>
<td>Prevalence (includes HIV+TB)</td>
<td>2,500 (2,100–3,000)</td>
<td>203 (243–347)</td>
</tr>
<tr>
<td>Incidence (excludes HIV+TB)</td>
<td>2,300 (2,100–2,400)</td>
<td>262 (242–283)</td>
</tr>
<tr>
<td>Incidence (HIV+TB)</td>
<td>870 (500–950)</td>
<td>202 (193–211)</td>
</tr>
<tr>
<td>Case detection, all forms (%)</td>
<td>61 (56–66)</td>
<td></td>
</tr>
</tbody>
</table>

### TB case notifications 2011

<table>
<thead>
<tr>
<th>Category</th>
<th>NEW CASES (%)</th>
<th>RETREATMENT CASES (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear-positive</td>
<td>605,929 (46)</td>
<td>52,283 (41)</td>
</tr>
<tr>
<td>Smear-negative</td>
<td>357,811 (27)</td>
<td>9,271 (7.3)</td>
</tr>
<tr>
<td>Smear unknown/another done</td>
<td>109,258 (8.3)</td>
<td>13,498 (11)</td>
</tr>
<tr>
<td>Extrapulmonary/other</td>
<td>240,643 (18)</td>
<td>51,853 (42)</td>
</tr>
<tr>
<td>Other</td>
<td>1,069 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Total new</td>
<td>1,314,910</td>
<td>126,905</td>
</tr>
<tr>
<td>Other (history unknown)</td>
<td>18,951</td>
<td></td>
</tr>
<tr>
<td>Total new and relapse</td>
<td>1,367,753</td>
<td>1,460,765</td>
</tr>
</tbody>
</table>

### New cases

<table>
<thead>
<tr>
<th>Category</th>
<th>SMear-POSITIVE</th>
<th>SMear-NEGATIVE/UNKNOWN/NOT DONE</th>
<th>EXTRAPULMONARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F ratio</td>
<td>1.4</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Age &lt; 15</td>
<td>19,183</td>
<td>43,845</td>
<td>12,615</td>
</tr>
</tbody>
</table>

### Laboratories 2011

<table>
<thead>
<tr>
<th>Type</th>
<th>NUMBER OF MEMBER STATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear positive (per 100,000 population)</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Culture positive (per 5 million population)</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Drug susceptibility testing (per 5 million population)</td>
<td>≥ 1</td>
</tr>
</tbody>
</table>

### Treatment success rate 2010 (%)

- New smear-positive (and/or culture-positive): 82%
- New smear-negative/ extrapulmonary: 64%
- Retreatment: 54%
- MDR-TB (2009 cohort): 45%

### TB/HIV 2011

<table>
<thead>
<tr>
<th>Category</th>
<th>NUMBER (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB patients with known HIV status</td>
<td>1,001,972</td>
</tr>
<tr>
<td>HIV-positive TB patients</td>
<td>459,608 (46)</td>
</tr>
<tr>
<td>HIV-positive TB patients on co-trimoxazole preventive therapy (CPT)</td>
<td>353,306 (78)</td>
</tr>
<tr>
<td>HIV-positive TB patients on antiretroviral therapy (ART)</td>
<td>203,851 (46)</td>
</tr>
</tbody>
</table>

### Estimates of MDR-TB burden 2011

<table>
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<th>RETREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of TB cases with MDR-TB</td>
<td>20 (81.62)</td>
<td>11 (3.418)</td>
</tr>
<tr>
<td>MDR-TB cases among notified</td>
<td>31,000 (1,100–67,000)</td>
<td>14,000 (4,300–23,000)</td>
</tr>
<tr>
<td>Extrapulmonary MDR-TB cases</td>
<td>318,000 (1,100–67,000)</td>
<td>14,000 (4,300–23,000)</td>
</tr>
</tbody>
</table>

### Reported cases of MDR-TB 2011

- Cases tested for MDR-TB: 1,311 (<1%) |
- Laboratory-confirmed MDR-TB cases: 370 (2.9%) |
- Patients started on MDR-TB treatment: 1,183 |

### Financing TB control

- Total budget (US$ millions): 2012 500, 2013 500
- % of budget funded from development assistance: 11, 10
- % available funding from Global Fund: 51, 54

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* Ranges represent uncertainty intervals.

* Calculations exclude countries with missing numerators or denominators.

* Financing indicators exclude funding for general healthcare services provided outside NTPs. South Africa has been excluded due to lack of data.
Treatment outcomes

**FIGURE 4.8** Treatment outcomes for patients diagnosed with MDR-TB by WHO region, 2009 cohorts. The number of countries reporting outcomes for at least one case, followed by total cases with outcome data, shown beside each bar.
Prevalence of drug-resistance

Percentage of new TB cases with MDR-TB

Countries that had notified at least one case of XDR-TB by the end of 2011

TB Epidemiology

The 27 high MDR-TB and XDR-TB burden countries

Estimated TB incidence in 2009

Estimated proportion of HIV positives in incident TB cases in 2009

Estimated MDR-TB incidence
Only two laboratories in continent doing SL DST, both in SA
Some of the other countries do perform FL DST
Cost of DST and drugs prohibitive
Costs of SLD prohibitive
Experience in prescribing SLD limited
HIV coinfection and overlapping toxicity
Provincial distribution of TB cases 2004–2008:
only two laboratories doing SL DST

1,219,912 sq km
Population: 48.7 Mil
9 Provinces
52 districts
262 Sub districts
2. Rational use of SL DST in programmatic management of tuberculosis

- Rapid rifampicin testing
- Organisation and funding for laboratory network
- Biosafety and infection control
- Transportation of infectious material
- Surveillance and surveys using DST
- Hierarchy of DST under programmatic conditions
- Quality assurance
- Testing for SLD resistance in settings where drugs are not used
• Hierarchy of testing for SLD resistance

• When to test?
  – Monitoring of treatment and identification of patients with resistance - ?
    Clinical failure, high risk populations
  – Universal screening at case finding, treatment initiation or at month 4

• Which patients to test?
  – Defaulters, relapse, slow/no – conversion
  – All MDR? All XDR?
  – Full DST screening of all patients with Rif-resistance?
  – High risk populations (HCW)

• Turn-around-time of DST
  – SL DST is slow, cumbersome, contamination is a problem
  – Prognostic value drug sensitivity testing

• Empiric treatment or postponement?
• Ongoing transmission and generation of resistance during mono-therapy
Identification of specimens for further investigation
ALGORITHM FOR EARLY DETECTION OF MDR-TB

Return visit

New Suspect DAY 0

Facility (Clinic/Hospital)

TWO frontloaded sputum specimens

SPUTUM 1

SPUTUM 2

SPUTUM 3

Microscopy Laboratory

Smear POSITIVE

Smear NEGATIVE

Do LPA on POSITIVE with highest grade

Do LPA on POSITIVE specimen

No LPA if BOTH smears NEGATIVE

LPA Laboratory

Confirm TB and susceptible to INH & Rif

Confirm TB and resistant to INH &/or Rif

Confirm TB and susceptible to INH & Rif

Confirm TB and resistant to INH &/or Rif

Culture Laboratory

No Culture (Discard)

TREAT Regimen 1 or 2

Initiate MDR treatment

Adjust MDR treatment

Full phenotypic DST

SPUTUM 3

POSSITIVE: DO LPA

DO Culture

New Suspect DAY 7

ACTION
Patients at high risk: High default rates drive drug resistance

FIGURE 4.8 Treatment outcomes for patients diagnosed with MDR-TB by WHO region, 2009 cohorts. The number of countries reporting outcomes for at least one case, followed by total cases with outcome data, shown beside each bar.
Quality control

A high-quality laboratory system that uses modern diagnostics is a prerequisite for early, rapid and accurate detection of TB. Of the estimated 8.7 million incident TB cases in 2011, only 66% were diagnosed and notified to national TB control programmes, due in part to inadequate laboratory capacity in many low- and middle-income countries. Furthermore, of the notified cases of pulmonary TB, around one-third were not bacteriologically confirmed using a WHO-recommended laboratory method, and a proportion of the patients in whom TB was clinically diagnosed without laboratory confirmation may not have had TB.

These numbers do not capture the significant delay that many patients experience in receiving a diagnosis of TB because of poorly functioning laboratory systems, resulting in delays to the start of their treatment, additional suffering and expenses, and adverse treatment outcomes. Diagnosis of drug resistance remains a particular challenge for laboratory systems in many low- and middle-income countries.

Only 19% of the 310 000 cases of multidrug-resistant TB (MDR-TB) estimated to exist among patients with pulmonary TB received a laboratory-confirmed diagnosis of their disease and were notified in 2011.

Rapid and timely detection of TB cases and strengthened capacity to diagnose cases of drug-resistant TB are thus global priorities for TB care and control.
The TB Supranational Reference Laboratory Network (SRLN) was created in 1994 in order to support the WHO-IUATLD Global Project on TB drug resistance surveillance.

The objectives of the Global Project are to estimate the magnitude of drug resistance globally, determine trends and provide data to inform WHO policy decisions.

Monitor proficiency of National Reference Laboratories in susceptibility testing of anti-TB drugs and thereby ensuring quality assured diagnosis of drug resistance.

Conclusions

Quality-assured laboratory services constitute the backbone of programmes for drug-resistant TB. Implementation of such programmes necessitate that governments and donors adequately fund appropriate and safe laboratory infrastructures in which well-trained staff working to clear standard operating procedures are able to deliver accurate and timely drug-resistance results. The need remains to improve DST for second-line drugs and to configure screening and diagnostic algorithms into rational management programmes for drug-resistant TB. In addition, accelerated expansion and integration of laboratory services as a core component of TB control programmes is required to achieve the aims of the global MDR-TB response and maximize the potential of new technological developments.
If the drugs are not used testing is not necessary
(Affordability of SL drugs)

REGIONAL ACTION FOR THE ELIMINATION OF TB AND
CONTROL OF HIV IN THE MINING SECTOR OF
SOUTHERN AFRICA

South Africa’s half a million mine workers have the highest TB incidence in the world: an estimated 3000-7000 per 100 000 are infected, with many of these individuals also HIV positive.

With the mining industry in South Africa heavily dependent on migratory workers from rural areas and surrounding countries, particularly Lesotho, Swaziland and Mozambique, this problem is a sub-regional one.

All these countries are among the top seven worldwide for TB incidence and HIV-TB co-infection and all have cases of extremely drug resistant tuberculosis (XDR-TB).

During the Stop TB Board meeting which took place in South Africa in October 2010, the Governments of South Africa, Lesotho, and Swaziland have publically called for action to address the critical health concern of HIV/TB co-infection in mining communities in the sub-region.
3. Untreatable Tuberculosis

- Drug resistance is a reality in tuberculosis
- Drug resistance will be due to natural mutation frequency
  - Rates for new drugs?
- Drug resistance is a man-made problem – lessons from MDR-TB (XDR-TB)
  - Settings with high default rates and non-adherence
  - Drug toxicity
  - Inappropriate use
- Reliability of SL DST and designing individualised regimens
  - Low agreement between phenotypic resistance and genotypic markers
  - Agreement with clinical failure
- Ethical aspects of untreatable tuberculosis
Conclusion

- Standardisation of susceptibility testing urgently needed
- Expanded laboratory capacity to make DST universally available
- Relationship between phenotypic resistance, genotypic resistance and clinical resistance needed
Thank You