Multidrug-resistant Tuberculosis – A Challenge to Global TB Control

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National Jewish Health
Chair, Global GLC, WHO and Stop TB Partnership
Disclosures

• World Health Organization – Chair, Global Green Light Committee
• Otsuka – Chair, Data Monitoring Committee for clinical trials of delaminid
Outline

• The problem – epidemiology of M/XDR-TB
• The challenges – diagnosis, drugs, delivery of care
• The solution?
Transmission and Pathogenesis of Drug-resistant TB

1. Mutation
   - Resistant mutants
2. Selection due to inadequate treatment
   - Acquired (M)DR-TB
3a. Transmission
   - Primary (M)DR-TB
3b. More primary (M)DR-TB

Nature → Man

HIV
Inadequate infection control
Diagnostic delay

Definitions for Multidrug and Extensively Drug Resistant TB

**MDR-TB**: Resistance to at least isoniazid and rifampin

**XDR-TB**: MDR plus resistance to fluoroquinolones and one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin)

Source: Peter Cegielski
The Global TB Situation

Estimated incidence and case notification rates by WHO region, 1990–2010

The Global TB Situation

### Estimated number of cases, 2010

**All forms of TB**
- 8.8 million (8.5–9.2 million)

**HIV-associated TB**
- 1.1 million (1.0–1.2 million)

**Multidrug-resistant TB**
- ~650,000 out of 12 million (11-14 million) prevalent TB cases

### Estimated number of deaths, 2010

**All forms of TB**
- 1.1 million* (0.9–1.2 million)

**HIV-associated TB**
- 350,000 (320,000–390,000)

* Excluding deaths attributed to HIV/TB

MDR-TB Notification and Enrollment

Estimated MDR-TB cases among notified TB patients in 2010

Percentage of Previously Treated TB Cases with MDR-TB

* Figures are based on the most recent year for which data have been reported, which varies among countries.

## MDR-TB Notification and Enrollment
MDR cases reported vs estimated among notified TB, 2010

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>2010</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated</td>
<td>Reported</td>
<td>Ratio</td>
</tr>
<tr>
<td>African</td>
<td>32,000</td>
<td>9,504</td>
<td>30%</td>
</tr>
<tr>
<td>American</td>
<td>6,200</td>
<td>2,158</td>
<td>35%</td>
</tr>
<tr>
<td>East Med.</td>
<td>14,000</td>
<td>829</td>
<td>6%</td>
</tr>
<tr>
<td>European</td>
<td>53,000</td>
<td>32,616</td>
<td>62%</td>
</tr>
<tr>
<td>S-E Asian</td>
<td>88,000</td>
<td>3,779</td>
<td>4%</td>
</tr>
<tr>
<td>West Pacific</td>
<td>77,000</td>
<td>4,222</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td><strong>290,000</strong></td>
<td><strong>53,108</strong></td>
<td><strong>18%</strong></td>
</tr>
</tbody>
</table>
Key Challenges in Scale-up of MDR-TB Control

- Strengthening basic TB control
- Health workforce crisis: numbers and quality
- Laboratory capacity
- Complexity of MDR/XDR-TB care
- Collaboration with HIV/AIDS programs
- Quality, price, availability of second line drugs
- Sustainable financing
- Ethical, legal and human rights environment
Major Obstacles to Control of DR-TB

**DIAGNOSIS**
- Appropriate and timely diagnostics

- Programs need help to build laboratory capacity for diagnosis of patients and monitoring of treatment. This includes the implementation of available new diagnostics (GLI and partners).

**DRUGS**
- Uninterrupted access to quality-assured second-line drugs

- Programs need help in the area of drug supply management (TB and ancillary drugs) and forecasting
- Global supplies of drugs and procurement mechanisms need to be strengthened

**CARE DELIVERY**
- Delivery of care for two years with appropriate management of adverse events

- Programs need help with pilot program implementation, DR-TB treatment integration into national TB control strategies, capacity building (HR), and scale-up
History of the WHO/GLC Response to MDR-TB

- 1994  Global DRS project launched
- 2000  Green Light Committee established
- 2000  The 1st DOTS-Plus project launched
- 2002  The Global Fund decides that all proposals for MDR-TB treatment must be approved by the GLC
- 2005  MDR-TB control proven feasible and cost-effective intervention
- 2006  The first WHO MDR-TB guidelines
- 2009  The emergency edition of MDR-TB Guidelines
- 2009  Ministerial meeting in Beijing: "Call for Action"
- 2009  50,000 (63,107) patients approved by GLC for treatment
- 2009  62nd WHA resolution on MDR-TB
- 2010  100,000 (104,537) patients approved by GLC for treatment.
- 2010  Ongoing discussion on revision of framework for MDR-TB scale-up for countries
- 2011  New framework for the programmatic management of MDR-TB
Green Light Committee Initiative
Notified MDR-TB cases (2007-2009) and projected numbers of patients to be enrolled on treatment (2010-2011), compared with Global Plan 2010 targets for MDR-TB cases to receive treatment (2011-2015)
Rationale for the New Global Framework

• Very few MDR-TB patients on treatment
  Only 11% of people with MDR receiving *any* treatment
  Less than 3% of people receiving care of known quality
• Revision of the global framework was urgently required

‘Shift from a controlling to a supporting mode’

Three Task Forces:

I. Provision of technical assistance
II. Availability of quality assured second-line TB drugs (SLDs)
III. Monitoring and evaluation, and the governance structure for MDR-TB management scale-up
WHO

Country Office
Regional Office
Stop TB Dept - HQ

STP Coordinating Board
STB Partnership Secretariat

MDR-TB Focal point
GDF
GLI

MDR-TB WG Core Group

rGLC Secretariat
gGLC Secretariat
MDR-TB WG

rGLC
gGLC

Data/Analysis
Technical dilemmas

MDR- TB Focal point

MDR-TB WG Secretariat

NTP National TBTEAM
Technical partners

Monitoring
Advocacy
Support
Current gGLC Members

• Public "Call for applications" for 9 gGLC members, 20 April to 16 May 2011
• 129 applications received from individuals of 46 countries
• gGLC Selection Committee (STP, Core Group of MDR-TB WG & WHO) recommended following 9 applicants:

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Country/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rich, Dr Michael</td>
<td>USA (PIH)</td>
</tr>
<tr>
<td>2</td>
<td>Chiang, Dr Chen-Yuan</td>
<td>Province of China, Taiwan (UNION)</td>
</tr>
<tr>
<td>3</td>
<td>Keravec, Joel</td>
<td>France (MSH)</td>
</tr>
<tr>
<td>4</td>
<td>Satti, Dr Hind</td>
<td>Sudan (PIH)</td>
</tr>
<tr>
<td>5</td>
<td>Caminero, Dr Jose A.</td>
<td>Spain (UNION)</td>
</tr>
<tr>
<td>6</td>
<td>Daley, Dr Charles</td>
<td>USA (National Jewish Health)</td>
</tr>
<tr>
<td>7</td>
<td>Pending election</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Cirillo, Dr Daniela M.</td>
<td>Italy (Fondazione San Raffaele IRCSS)</td>
</tr>
<tr>
<td>9</td>
<td>Chesire, Ms Lucy</td>
<td>Kenya (TB Action Group)</td>
</tr>
</tbody>
</table>
Laboratories doing culture for TB per 5 million population
Countries with high burden of TB, MDR-TB or both, 2010

*No data

Diagnostic DST for Rifampicin and Isoniazid
Among New TB cases, by Region, 2010

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>0.2%</td>
</tr>
<tr>
<td>AMR</td>
<td>5.0%</td>
</tr>
<tr>
<td>EMR</td>
<td>0.6%</td>
</tr>
<tr>
<td>EUR</td>
<td>30.4%</td>
</tr>
<tr>
<td>SEAR</td>
<td>0.1%</td>
</tr>
<tr>
<td>WPR</td>
<td>0.4%</td>
</tr>
<tr>
<td>Global</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Diagnostic DST for Rifampicin and Isoniazid Among Previously Treated TB cases, by Region, 2010

- AFR: 2.8%
- AMR: 18.5%
- EMR: 6.3%
- EUR: 50.7%
- SEAR: 0.3%
- WPR: 1.6%
- Global: 6.4%
DST coverage for second-line drugs among MDR-TB cases, 2010
Global Laboratory Initiative (GLI)
Supranational Reference Laboratories (n=32)
Expanding Access to New Diagnostics for TB (EXPAND-TB)

The EXPAND-TB Project aims to diagnose at least 119,032 patients with multidrug-resistant TB. Specific operational objectives are to:

- Improve control of MDR-TB
  - by introducing rapid, quality-assured WHO-endorsed tests
- Improve market dynamics
  - by increasing market size and decreasing test price
- Integrate tools in TB control programmes
  - by supporting close to 100 TB laboratories in 27 countries
Evolution of M/XDR Testing

Decentralization
M/XDR Testing on Different Health Care Levels
GeneXpert Instrument Modules and Cartridges
Procured under Concessional Pricing

Data provided by FIND
### Antituberculosis Drugs

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Isoniazid</th>
<th>Rifampin/Rifabutin</th>
<th>Ethambutol</th>
<th>Pyrazinamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>Streptomycin</td>
<td>Kanamycin</td>
<td>Amikacin</td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td>Viomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>Levofloxacin</td>
<td>Moxifloxacin</td>
<td>Ofloxacin</td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>Ethionamide</td>
<td>Protonamide</td>
<td>Cycloserine</td>
<td>Terizidone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P-aminosalicylic acid</td>
</tr>
<tr>
<td>Group 5</td>
<td>Clofazimine</td>
<td>Imipenem</td>
<td>Thioacetazone</td>
<td>Amoxacillin/Clavulanate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Macrolides</td>
<td>Linezolid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High-dose INH</td>
</tr>
</tbody>
</table>
## Building a Treatment Regimen

<table>
<thead>
<tr>
<th>Step</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethambutol</td>
<td>Streptomycin</td>
<td>Levofloxacin</td>
<td>Ethionamide</td>
<td>Clofazimine</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>Kanamycin</td>
<td>Moxifloxacin</td>
<td>Protonamide</td>
<td>Imipemen</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Amikacin</td>
<td>Ofloxacin</td>
<td>Cycloserine</td>
<td>Amoxacillin/Clavulanate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Linezolid</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thioacetzone</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High-dose INH</td>
</tr>
</tbody>
</table>

4+ likely effective drugs
Treatment Outcomes in MDR-TB Patients by WHO Region, 2009 cohorts

WHO Global TB Report , 2012
Global Drug Facility (GDF)

- The GDF is an independent, organization within the Stop TB Partnership that operates a unique procurement system
  - Low prices
  - Quality control
  - Standardization
  - Pool procurement
  - Transparency
  - Procurement and supply management
# Second-line Drug Shortages

**TABLE.** Number and percentage of local, state, and territorial health departments experiencing challenges in obtaining second-line drugs (SLDs)* for tuberculosis treatment in the past 5 years, by selected characteristics — National Tuberculosis Controllers Association member survey, United States, 2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faced any challenges obtaining SLDs in the past 5 years</td>
<td>21/33</td>
<td>(64)</td>
</tr>
<tr>
<td>Nationwide shortages</td>
<td>21/21</td>
<td>(100)</td>
</tr>
<tr>
<td>Shipping delays</td>
<td>15/21</td>
<td>(71)</td>
</tr>
<tr>
<td>Medications too expensive for their program</td>
<td>13/21</td>
<td>(62)</td>
</tr>
<tr>
<td>Medications too expensive for uninsured</td>
<td>10/21</td>
<td>(48)</td>
</tr>
<tr>
<td>Delays caused by IND protocol submission</td>
<td>10/21</td>
<td>(48)</td>
</tr>
<tr>
<td>Medications too expensive for insured patients</td>
<td>8/21</td>
<td>(38)</td>
</tr>
<tr>
<td>Payer bureaucracy</td>
<td>7/21</td>
<td>(33)</td>
</tr>
<tr>
<td>Adverse effects and other problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substantial staff time diverted by drug procurement</td>
<td>13/19</td>
<td>(68)</td>
</tr>
<tr>
<td>Delay in starting treatment</td>
<td>11/19</td>
<td>(58)</td>
</tr>
<tr>
<td>Treatment lapse and interruption</td>
<td>6/19</td>
<td>(32)</td>
</tr>
<tr>
<td>Inadequate regimen</td>
<td>6/19</td>
<td>(32)</td>
</tr>
</tbody>
</table>

Abbreviation: IND = investigational new drug.
* Including capreomycin, kanamycin, amikacin, moxifloxacin, levofloxacin, para-aminosalicylate sodium, cycloserine, ethionamide, linezolid, and clofazimine.

CDC. MMWR 2012
Global TB Drug Pipeline

**Chemical classes:**
- fluoroquinolone
- rifamycin
- oxazolidinone
- nitroimidazole
- diarylquinoline
- benzothiazinone


2. Combination regimens: first clinical trial (NC001) of a novel TB drug regimen testing the three drug combination of PA-824, moxifloxacin, and pyrazinamide.

**Lead Optimization**
- Mycobacterial Gyrase Inhibitors
- Riminophenazines
- Diarylquinoline
- Translocase-1 Inhibitor
- MGYrX1 inhibitor
- InhA Inhibitor
- GyrB inhibitor
- LeuRS Inhibitor
- Pyrazinamide Analogs

**Discovery**
- CPZEN-45
- SQ641
- SQ609
- DC-159a
- Q201
- THPP
- TBA-354

**Preclinical Development**
- BTZ043
- AZD5847

**GLP Tox.**
- Bedaquiline (TMC-207)
- PA-824
- Linezolid
- Sutezolid (PNU-100480)
- SQ-109
- Rifapentine
- Novel Regimens

**Clinical Development**
- Gatifloxacin
- Moxifloxacin
- Rifapentine
- Delamanid (OPC67683)

[www.newtbdrugs.org](http://www.newtbdrugs.org)

*Updated: November 2, 2011*
The Global Plan to Stop TB, 2011-2015
Goal: To reduce the global burden of DR-TB

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Activities</th>
<th>Indicators</th>
<th>Baseline (2009)/Target (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scale up access to DST to FLD</td>
<td>Testing for MDR-TB using culture, DST, and molecular technologies</td>
<td>Percentage of previously treated TB patients tested for resistance</td>
<td>7%/100%</td>
</tr>
<tr>
<td>Scale up access to DST to SLD</td>
<td>Testing for susceptibility to SLD using culture, DST</td>
<td>Percentage of confirmed MDR-TB patients who have a SLD DST result</td>
<td>15%/100%</td>
</tr>
<tr>
<td>Scale up access to effective treatment</td>
<td>Procurement and supply of SLD</td>
<td>Percentage of cases with confirmed MDR-TB started on therapy</td>
<td>36%/100%</td>
</tr>
<tr>
<td>Scale up TB infection control</td>
<td>Development of national IC plans for MDR-TB</td>
<td>Ratio of TB among HCWs/general population</td>
<td>n/a/1</td>
</tr>
<tr>
<td>Strengthen surveillance of DR-TB</td>
<td>Surveillance of drug resistance</td>
<td>Number of countries with electronic MDR-TB database</td>
<td>10/27</td>
</tr>
<tr>
<td>Expand country capacity through advocacy</td>
<td>Resource mobilization</td>
<td>Number of high-level missions to countries with high MDR-TB rates</td>
<td>1/10</td>
</tr>
</tbody>
</table>
Funding requirements 2009-2015
27 MDR-TB high-burden countries

Most of the funding required is in the European Region, followed by Asia. In Asia the funding is mainly required in China and India.
Funding Gaps for TB Care and Control

![Graph showing funding gaps from 2006 to 2013.](image)

a Funding available for a given line item may exceed that required for the same line item under a country's plan and budget.

WHO Global TB Report, 2012
What do you expect in your lifetime?

Stop TB in my lifetime

What will you do?

Stop TB in my lifetime

Stop TB in my lifetime

Stop TB in my lifetime

WORLD TB DAY  24 MARCH 2013