Global Strategy to Control Drug-resistant Tuberculosis

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Disclosures

• World Health Organization – I receive some salary support from WHO
• Otsuka – Chair, Data Monitoring Committee for Delamanid clinical trials.
Outline

• The problem – epidemiology of M/XDR-TB
• The Green Light Committee Initiative
• The new GLC Framework
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)

Definitions for Multidrug and Extensively Drug Resistant TB

9 million TB cases
Transmission and Pathogenesis of Drug-resistant TB

1. Mutation

2. Selection due to inadequate treatment

Acquired (M)DR-TB

3a. Transmission

Primary (M)DR-TB

HIV

Inadequate infection control

Diagnostic delay

3b. More primary (M)DR-TB

Nature

Man
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

# MDR-TB Notification and Enrollment

MDR cases reported vs estimated among notified TB, 2010

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>2010</th>
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<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>Global</td>
<td>290,000</td>
<td>53,108</td>
<td>18%</td>
</tr>
</tbody>
</table>
Countries With at Least one XDR-TB Case by End of 2011
Outcomes of MDR-TB Treatment

For MDR-TB patients started on treatment in 2008*

* In countries reporting outcomes for >200 MDR-TB cases with <20% unevaluated (cohort size shown below country names)
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
Created in 2000 by the WHO and the Stop TB Partnership

Objectives:

• Contribute to the progress towards meeting global tuberculosis control targets and prevent development of almost incurable forms of TB (XDR-TB)

• Increase access to quality-assured, affordable second-line drugs for the treatment of drug-resistant TB (DR-TB) among well-performing TB control programs in developing countries

Activities:

• Determines compliance of country MDR-TB programs with international standards set in the field of TB control and the WHO Guidelines for the Programmatic Management of DR-TB,

• Enables access to affordable, high-quality, second-line drugs for the treatment of DR-TB in developing countries

• Informing WHO of GLC findings, deliberations and recommendations, and assisting WHO with developing policy to control MDR-TB
The GLC was comprised of representatives from 9 institutions with specific programmatic, clinical, advocacy, scientific and managerial expertise. Its membership rests with institutions, not individuals.

Members during GLC existence:
- WHO (permanent member)
- IUATLD
- Centers for Disease Control and Prevention
- Latvian National TB Programme
- Partners In Health/Harvard Medical School
- Médecins Sans Frontières
- KNCV
- Hospital F.J. Muniz – Argentina
- American Thoracic Society
- Indus Hospital, Pakistan
GLC Governance, Operating and Financing

**GLC Governance**
- Green Light Committee
- Stop TB Partnership
- World Health Organization

**GLC Operations**
- GLC Initiative coordination (GLC Secretariat)
- Drug procurement and management (GDF Secretariat)
- Technical assistance to GLC programmes (WHO and partners)
- Monitoring and evaluation (Green Light Committee, WHO and partners)

**GLC Financing**
- The Global Fund to Fight AIDS, Tuberculosis and Malaria
- UNITAID
- World Health Organization
- Other donors

GLC Secretariat
Green Light Committee Initiative

- GLC Secretariat
- GLC Expert committee
- GDF: Procurement
- WHO: Technical Support / M&E
- Country/Project
- GDF Procurement Agent

2 months
• Evolution – quality of application and approval rate increased by years
Type of Applications Received, 2000-2010

- Evolution – proportion of expansion applications increased by years

- Evolution – proportion of expansion applications increased by years
Cumulative DRTB-Global Fund Proposals, GLC Approved And Actual Enrollments
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
Goal: Universal Access to DR-TB Management by 2015

1. Increased level of technical support to countries
2. Increased access to high-quality, affordable SLDs
3. Strengthen advocacy
4. Regular monitoring and evaluation of country performance
5. Regular updating of international policy and guidelines
6. Provision of advice to funding agencies upon their request
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>
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<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>
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<tr>
<td>4</td>
<td>Satti, Dr Hind</td>
<td>Sudan (PIH)</td>
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<tr>
<td>5</td>
<td>Caminero, Dr Jose A.</td>
<td>Spain (UNION)</td>
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<tr>
<td>6</td>
<td>Daley, Dr Charles</td>
<td>USA (National Jewish Health)</td>
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<tr>
<td>7</td>
<td>Mohan, Neeraj</td>
<td>India (CHAI)</td>
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<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>
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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
Diagnostic DST for Rifampicin and Isoniazid
Among New TB cases, by Region, 2010

World Health Organization
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%

World Health Organization
DST Coverage for Second-line Drugs Among MDR-TB Cases, 2010

World Health Organization
Evolution of M/XDR Testing
Decentralization

Global Laboratory Initiative
GeneXpert Expansion

Cumulative number of GeneXpert modules and Xpert MTB/RIF cartridges procured under concessional pricing.

- Q4 2010: 40,790
- Q1 2011: 86,320
- Q2 2011: 191,900
- Q3 2011: 329,350
- Q4 2011: 591,450

Global Laboratory Initiative
Guidelines for PMDT
Priority Topics

- Case finding
- Regimens for MDR-TB
- Duration of treatment
- Monitoring during treatment
- Models of care
### Building a Treatment Regimen

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Group 1</th>
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<tbody>
<tr>
<td></td>
<td>Ethambutol</td>
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<tr>
<td></td>
<td>Pyrazinamide</td>
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<thead>
<tr>
<th>Step 2</th>
<th>Group 2</th>
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<tbody>
<tr>
<td></td>
<td>Streptomycin</td>
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<tr>
<td></td>
<td>Amikacin</td>
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<td></td>
<td>Kanamycin</td>
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<td></td>
<td>Capreomycin</td>
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<thead>
<tr>
<th>Step 3</th>
<th>Group 3</th>
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<tr>
<td></td>
<td>Levofloxacin</td>
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<tr>
<td></td>
<td>Moxifloxacin</td>
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<td>Ofloxacin</td>
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<thead>
<tr>
<th>Step 4</th>
<th>Group 4</th>
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<tr>
<td></td>
<td>Ethionamide</td>
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<tr>
<td></td>
<td>Cycloserine</td>
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<tr>
<td></td>
<td>Protonamide</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
</tr>
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<td></td>
<td>P-aminosalicylic acid</td>
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<thead>
<tr>
<th>Step 5</th>
<th>Group 5</th>
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<tbody>
<tr>
<td></td>
<td>Clofazimine</td>
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<tr>
<td></td>
<td>Imipemen</td>
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<tr>
<td></td>
<td>Amoxacillin/Clavulanate</td>
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<td></td>
<td>Macrolides</td>
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<td></td>
<td>Linezolid</td>
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<tr>
<td></td>
<td>Thioacetzone</td>
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<td></td>
<td>High-dose INH</td>
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**Duration:**
- Intensive phase – 8 mos
- Total duration - ≥ 20 mos
Profile of New M/XDR-TB Regimens

- Shorter duration with increased efficacy
- Fewer medicines
- No drug-drug interactions with ARVs (TB-HIV)
- Orally bioavailable; maximum of once daily dosing
- Improved safety and tolerability
- Affordable cost of goods with quality assured products
- Standardized approaches
- Less intensive monitoring
Global TB Drug Development Pipeline

**Discovery**

- Mycobacterial Gyrase Inhibitors
- Riminophenazines
- Diarylquinoline
- Translocase-1 Inhibitor
- MGyrX1 inhibitor
- InhA Inhibitor
- GyrB inhibitor
- LeuRS Inhibitor
- Pyrazinamide Analogs

**Preclinical Development**

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

- BTZ043

**GLP Tox.**

- AZD5847

**Clinical Development**

**Phase I**

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

**Phase II**

**Phase III**

- Gatifloxacin
- Moxifloxacin
- Rifapentine
- Delamanid (OPC67683)

Global TB Alliance
The Global Plan to Stop TB, 2011-2015

Between 2011 and 2015 ...

- Increase in TB cases tested for R & H yearly from 0.8 million to 1.9 million
- 1 million multidrug-resistant TB (MDR-TB) patients detected and put on treatment
- USD 7.1 billion spent
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>
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</thead>
<tbody>
<tr>
<td>1. 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>2. 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>3. 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>4. 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>5. 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>6. 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 for MDR-TB

Funds available for MDR-TB, 2006-2012*

* In 106 countries with 96% of MDR-TB cases enrolled in 2010
Funding for MDR-TB

Funding required for MDR-TB*

BRICS=Brazil, the Russian Federation, India, China and South Africa. MICS=Middle-income countries (excluding BRICS). LICS=Low-income countries.

* As per Global Plan to Stop TB, 2011-2015
MDR-TB Notification and Enrollment
Notified cases of MDR-TB (2007–2010) and projected numbers of patients to be enrolled on treatment (2011-2012) compared with the targets included in the Global Plan to Stop TB 2011–2015.
Conclusions

- Even if most TB patients in the world are not drug-resistant, they present a formidable challenge to global TB control.
- Treatment of MDR-TB is longer, more complicated and less effective than for drug-susceptible TB.
- Coverage of DST for TB patients remains low and thus a minority of drug-resistant TB patients are detected and notified.
- To reach the Global Plan targets, substantial resource mobilization will be needed, both from domestic and from external sources. The price of treating a patient needs to be reduced.