Outline

- Natural history
- Global Trends
- Policy & Governance
- Millennial Challenges
Leading causes of death

*All ages*

- Ischemic heart disease: 12.5%
- Stroke, CVD: 11.4%
- Lower Resp Infections: 6.2%
- COPD: 4.9%
- Diarrheal Diseases: 3.2%
- HIV/AIDS: 2.1%
- Tuberculosis: 2.1%
- Respiratory Cancers: 2.1%
- Diabetes Mellitus: 2.1%
- Traffic Accidents: 2.1%

*World Bank, “Investing in Health”, 1993*
TB Facts

► 9.4 million new cases/year
  - 44% AFB smear+
  - 7.7% HIV+
  - ~500,000 multi-drug resistant (5.4%)

► 14.4 million prevalent cases
  - 1 million children <14 (7%)

► 1.6 million deaths *(1 every 16 sec)*
  - 22% w/ HIV

► 1/3 world’s population infected
  - 10% lifetime risk of TB
Natural History

**Risk factors for progression**
- Malnutrition
- HIV (21-33X risk)
- Diabetes (3x risk)
- Renal failure, smoking, anti-TNF, gastric bypass, silicosis

50% may survive w/ out Rx
50,000 years of co-evolution

R. Herschberg et al, PLOS Biology, 2008
Dynamics of TB Epidemics

Reactivation epidemics
Primary/progressive

Why must we all die?

As a nation, we owe it to ourselves… Humanity demands it, treaty obligations require it, and self-interest ought to prompt it.

Gov. Lyman Knapp, Alaskan Territory, 1892
Reported TB Cases*
United States, 1982–2009

*Updated as of July 1, 2010.
Trends in TB Cases in Foreign-born Persons, United States, 1989–2009*

*Updated as of July 1, 2010.
Modern TB epidemics

FIGURE 1.3
Estimated TB incidence rates, by country, 2006

- Poverty/Immunology
- Control/Adherence
- Political Instability

Drug Resistance

Diabetes

AIDS

80% cases in 22 high burden countries
# TB control

*(US and developing world)*

<table>
<thead>
<tr>
<th>Program</th>
<th>US</th>
<th>Developing world</th>
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<tbody>
<tr>
<td>BCG vaccination</td>
<td>No</td>
<td>~80%</td>
</tr>
<tr>
<td>Contact tracing</td>
<td>Yes</td>
<td>Ad hoc</td>
</tr>
<tr>
<td>LTBI Mass Screening</td>
<td>Targeted</td>
<td>No</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Diagnostics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB Smear</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CXR</td>
<td>Yes</td>
<td>When available</td>
</tr>
<tr>
<td>Culture</td>
<td>Routine</td>
<td>Seldom</td>
</tr>
<tr>
<td>DST</td>
<td>Routine</td>
<td>Seldom</td>
</tr>
<tr>
<td>Treatment Modality</td>
<td>Individualized</td>
<td>Standardized</td>
</tr>
<tr>
<td>Treatment Funding</td>
<td>Ambulatory</td>
<td>Residential/Amb.</td>
</tr>
<tr>
<td></td>
<td>Public-private</td>
<td>Public</td>
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</table>
THE STOP TB STRATEGY

Building on and enhancing DOTS to meet the TB-related Millennium Development Goals

- Clinical & Programmatic Guidelines
- Monitoring & Evaluation
- Multi-lateral financing
- Drug & Diagnostic Procurement
- Research & Development
Directly observed therapy – short course (DOTS)

$30-$50/1st line course
55 million TB patients since 1995
84% success rate
How is TB control financed?

$4 billion/year
85% Domestic
10% Stop TB programs
5% Foundations/NGO

Global TB Control Report, 2011
Key 2015 Targets (vs. 1990)

- Negative Incidence trend
- Halve prevalence
- Halve mortality

<1/1M by 2050

Global Plan to STOP TB 2006-2015
Millennial Challenges

Laboratory Infrastructure
HIV
MDR
Health System Restructuring
Prevention/Prophylaxis
Research/Development
## I. Laboratory Infrastructure Needs

### Coverage Quality Assurance

<table>
<thead>
<tr>
<th>Country</th>
<th>Labs (Thousands)</th>
<th>Labs (NRL)</th>
<th>Sputum Smear (Number/100,000 Pop)</th>
<th>Culture (Number/5 Million Pop)</th>
<th>DST (Number/10 Million Pop)</th>
<th>Laboratories for Sputum Smear Microscopy</th>
<th>EQA Included</th>
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<tr>
<td>India</td>
<td>1,169,016</td>
<td>Y</td>
<td>12,184</td>
<td>11</td>
<td>11</td>
<td>11,386</td>
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<tr>
<td>China</td>
<td>1,328,630</td>
<td>Y</td>
<td>3,294</td>
<td>327</td>
<td>187</td>
<td>3,294</td>
<td>100</td>
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<tr>
<td>Indonesia</td>
<td>231,627</td>
<td>N</td>
<td>4,855</td>
<td>41</td>
<td>11</td>
<td>4,855</td>
<td>100</td>
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<tr>
<td>Nigeria</td>
<td>148,093</td>
<td>Y</td>
<td>794</td>
<td>2</td>
<td>1</td>
<td>347</td>
<td>44</td>
</tr>
<tr>
<td>South Africa</td>
<td>48,577</td>
<td>Y</td>
<td>249</td>
<td>15</td>
<td>10</td>
<td>241</td>
<td>97</td>
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<td>Bangladesh</td>
<td>158,665</td>
<td>Y</td>
<td>753</td>
<td>4</td>
<td>2</td>
<td>753</td>
<td>100</td>
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<tr>
<td>Ethiopia</td>
<td>83,099</td>
<td>Y</td>
<td>833</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
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<td>Pakistan</td>
<td>163,902</td>
<td>N</td>
<td>1,131</td>
<td>3</td>
<td>1</td>
<td>360</td>
<td>32</td>
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<tr>
<td>Philippines</td>
<td>87,960</td>
<td>Y</td>
<td>2,374</td>
<td>3</td>
<td>3</td>
<td>2,374</td>
<td>100</td>
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<tr>
<td>DR Congo</td>
<td>62,636</td>
<td>Y</td>
<td>1,205</td>
<td>1</td>
<td>1</td>
<td>1,023</td>
<td>85</td>
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<td>Russian Federation</td>
<td>142,499</td>
<td>Y</td>
<td>4,048</td>
<td>965</td>
<td>280</td>
<td>–</td>
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<td>Viet Nam</td>
<td>87,375</td>
<td>Y</td>
<td>737</td>
<td>17</td>
<td>2</td>
<td>–</td>
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<td>Kenya</td>
<td>37,538</td>
<td>Y</td>
<td>930</td>
<td>5</td>
<td>1</td>
<td>37</td>
<td>40</td>
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<td>Brazil</td>
<td>191,791</td>
<td>Y</td>
<td>4,044</td>
<td>193</td>
<td>38</td>
<td>1,819</td>
<td>45</td>
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<td>Tanzania</td>
<td>40,454</td>
<td>Y</td>
<td>717</td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Uganda</td>
<td>30,884</td>
<td>Y</td>
<td>716</td>
<td>3</td>
<td>2</td>
<td>716</td>
<td>100</td>
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<tr>
<td>Zimbabwe</td>
<td>13,349</td>
<td>Y</td>
<td>180</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Thailand</td>
<td>63,884</td>
<td>Y</td>
<td>1,023</td>
<td>65</td>
<td>14</td>
<td>1,023</td>
<td>100</td>
</tr>
<tr>
<td>Mozambique</td>
<td>21,397</td>
<td>Y</td>
<td>252</td>
<td>1</td>
<td>1</td>
<td>252</td>
<td>100</td>
</tr>
<tr>
<td>Myanmar</td>
<td>48,798</td>
<td>Y</td>
<td>324</td>
<td>2</td>
<td>1</td>
<td>54</td>
<td>17</td>
</tr>
<tr>
<td>Cambodia</td>
<td>14,444</td>
<td>Y</td>
<td>201</td>
<td>3</td>
<td>1</td>
<td>186</td>
<td>93</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>27,145</td>
<td>Y</td>
<td>500</td>
<td>1</td>
<td>–</td>
<td>360</td>
<td>72</td>
</tr>
</tbody>
</table>

*High-burden countries (22) 420,1761 20 16,672,20 570,14 29,080,70*
New Diagnostics

Hains Genotype MTB-DR Plus

*M. tuberculosis* Complex and its Resistance to Rifampicin and/or Isoniazid

Example Results with the GenoType MTBDRplus

- Conjugate Control
- Amplification Control
- *M. tuberculosis* complex
- *rpoB* Locus Control
- *rpoB* wild type probe 1
- *rpoB* wild type probe 2
- *rpoB* wild type probe 3
- *rpoB* wild type probe 4
- *rpoB* wild type probe 5
- *rpoB* wild type probe 6
- *rpoB* wild type probe 7
- *rpoB* wild type probe 8
- *rpoB* mutation probe 1
- *rpoB* mutation probe 2
- *rpoB* mutation probe 3
- *katS* Locus Control
- *katS* wild type probe
- *katS* mutation probe 1
- *katS* mutation probe 2
- *inhA* Locus Control
- *inhA* wild type probe 1
- *inhA* wild type probe 2
- *inhA* mutation probe 1
- *inhA* mutation probe 2
- *inhA* mutation probe 3A
- *inhA* mutation probe 3B
- colored marker

Resistance:
- -
- R+1
- 1
- R+1
- R+1

R = Rifampicin
1 = Isoniazid
II. MDR/XDR TB

- ~450,000 cases
- Rx 2000-3,000/course
- 3% new/20% previous
- <1% tested (7% previously treated)
- 16% tested on Rx
- By 2015
  - Rx 270,000
  - Dx 100% previously treated
III. HIV/TB

34% tested
46% on ART
IV. Health Care Restructuring
V. Contact tracing & Prophylaxis

Borgdorff et al, Bull WHO, 2002
VI. Research & Development

The development pipeline for new drugs, 2011

- Lead identification
  - Nitroimidazoles
  - Mycobacterial Gyrase Inhibitors
  - RKR inhibitors
  - Diaryquinolines
  - Translocase-1 Inhibitor
  - MGyX1 Inhibitor
  - IHa Inhibitor
  - QyrB Inhibitor
  - LeurS Inhibitor
  - Prazinamide Analogs

- Lead optimization
  - OZKEN-45
  - SQ641
  - SQ609
  - DC-159a
  - Benzothiazinone
  - Q201

- Preclinical development
  - AZD6847

- Phase I
  - TMC-207
  - OPC-67483
  - Pa-824
  - Linezolid
  - Rifapentine
  - SG-109
  - PNU-100480
  - Novel Regimen

- Phase II
  - Catifloxacin
  - Morifloxacin
  - Rifapentine

- Phase III
  - Sulfonamides

Note: This table only includes projects that have identified a promising molecule (known as a "lead" compound).

The development pipeline for new vaccines, 2011

- Preclinical development
  - Mtb [AlsyA ΔpanCD ΔsecA2]
  - MTBvac01 [AphoD, Δfad D26]
  - HBHA
  - Hybrid 5e+IC31
  - HG85 A/B
  - Spray-dried BCG

- Phase I
  - VPM 1002
  - AERAS-422
  - AdAg85A
  - Hyvac 4/AERAS-404

- Phase II
  - M72
  - RUTI
  - MVAb8A/AERAS-485

- Phase IIb
  - MVAb8A/AERAS-482/ Crucell Ad35

- Phase III
  - Hybrid 1+IC31

Preclinical vaccine candidates are not yet in clinical trials, but have been manufactured under GMP for clinical use and have undergone some preclinical testing that meets regulatory standards.
Funding needs

Components

- DOTS (48%)
- DOTS-plus (15%)
- TB/HIV (6%)
- Lab Strengthening (8%)
- Research/Dev’t (21%)
  - New Diagnostics
  - New Vaccines
  - New Drugs

2006 - 2015

Funding gap
US$30.8 billion; 55%
Available funding
US$25.3 billion; 45%

Stop TB Plan 2006-2015; new projections account for 9B shortfall 2006-2010
Recap

Healthy human beings are substantially equipped to control TB infection

Control requires stable primary health care systems

Key Challenges

- Diagnostics
- MDR and HIV
- Health system structuring
- Political Commitment
Useful Web sites

► WHO/TB & Stop TB Partnership
  http://www.who.int/tb/en/

► IUATLD
  http://www.theunion.org/

► CDC/TB Elimination
  http://www.cdc.gov/tb/

► Global Fund
  http://www.theglobalfund.org/en/

► Global Laboratory Initiative
  http://www.stoptb.org/wg/gli/

► Organization for Economic Development
  http://www.oecd.org/
### TABLE 1.1
Summary of main indicators, baselines and targets set in the Global Plan to Stop TB 2011–2015

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOTS/laboratory strengthening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases diagnosed, notified and treated according to the DOTS approach (per year)</td>
<td>5.8 million</td>
<td>6.9 million</td>
</tr>
<tr>
<td>Treatment success rate (in annual cohort)</td>
<td>86%</td>
<td>90%</td>
</tr>
<tr>
<td>Number of countries with ≥1 laboratory with sputum-smear microscopy services per 100 000 population</td>
<td>≥75</td>
<td>149</td>
</tr>
<tr>
<td><strong>Drug-resistant TB/laboratory strengthening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of previously treated TB patients tested for MDR-TB</td>
<td>7%</td>
<td>100%</td>
</tr>
<tr>
<td>Percentage of new bacteriologically-positive patients tested for MDR-TB</td>
<td>7%</td>
<td>20%</td>
</tr>
<tr>
<td>Number of countries among the 22 HBCs and 27 high MDR-TB burden countries with ≥1 culture laboratory per 5 million population</td>
<td>18–21</td>
<td>36</td>
</tr>
<tr>
<td>Percentage of confirmed cases of MDR-TB enrolled on treatment according to international guidelines</td>
<td>36%</td>
<td>100%</td>
</tr>
<tr>
<td>Number of confirmed cases of MDR-TB enrolled on treatment according to international guidelines</td>
<td>11 000</td>
<td>~270 000</td>
</tr>
<tr>
<td>Treatment success rate among confirmed cases of MDR-TB</td>
<td>60%</td>
<td>≥75%</td>
</tr>
<tr>
<td><strong>TB/HIV/laboratory strengthening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of AFB smear-negative, newly notified TB cases screened using culture and/or molecular-based test</td>
<td>&lt;1%</td>
<td>≥50%</td>
</tr>
<tr>
<td>Percentage of TB patients tested for HIV</td>
<td>26%</td>
<td>100%</td>
</tr>
<tr>
<td>Percentage of HIV-positive TB patients treated with CPT</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td>Percentage of HIV-positive TB patients treated with ART</td>
<td>37%</td>
<td>100%</td>
</tr>
<tr>
<td>Percentage of people living with HIV attending HIV care services who were screened for TB at their last visit</td>
<td>~25%</td>
<td>100%</td>
</tr>
<tr>
<td>Percentage of people living with HIV attending HIV care services who were enrolled on IPT; among those eligible</td>
<td>&lt;1%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Laboratory strengthening</strong> (additional to those above)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of national reference laboratories implementing a quality management system (QMS) according to international standards</td>
<td>&lt;5%</td>
<td>≥50%</td>
</tr>
</tbody>
</table>

AFB, acid-fast bacilli; ART, antiretroviral therapy; CPT, co-trimoxazole preventive therapy; HBC, high TB burden country; HIV, human immunodeficiency virus; IPT, isoniazid preventive therapy; MDR-TB, multidrug-resistant tuberculosis.
Professional Organizations

INTERNATIONAL STANDARDS FOR TUBERCULOSIS CARE

Diagnosis  Treatment  Public Health

World Health Organization
International Union Against Tuberculosis and Lung Disease
Stop TB Partnership
CDC 24/7
American Thoracic Society