GLOBAL STATUS OF MDR-TB/XDR-TB:

CHALLENGES, SOLUTIONS, AND CONSEQUENCES OF INACTION

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OVERVIEW

I. GLOBAL CHALLENGES
   • EPIDEMIOLOGY OF MDR-TB
   • SUCCESSES OVER LAST DECADE
   • CHALLENGES

II. SOLUTIONS
   • LABORATORY
   • DRUG SUPPLY
   • DELIVERY OF CARE

III. CONSEQUENCES OF INACTION
SECTION I: GLOBAL CHALLENGES
EPIDEMIOLOGY OF MDR-TB
### Global TB estimates (2008)

<table>
<thead>
<tr>
<th>All forms of TB</th>
<th>Estimated number of cases</th>
<th>Estimated number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidrug-resistant TB (MDR-TB)</td>
<td>9.4 million</td>
<td>1.3 million*</td>
</tr>
<tr>
<td>Extensively drug-resistant TB (XDR-TB)</td>
<td>~500,000</td>
<td>130,000</td>
</tr>
<tr>
<td>HIV-associated TB</td>
<td>1.4 million (15%)</td>
<td>520,000</td>
</tr>
</tbody>
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*excluding deaths among HIV+ people

Source: Adapted from Dr. Ernesto Jaramillo and Dr. Fuad Mirzayev, Stop TB Department, WHO, Geneva
Distribution of proportion of MDR-TB among new TB cases, 1994-2009

Source: WHO/HTM/TB/2010.3
Distribution of proportion of MDR-TB among previously-treated TB cases, 1994-2009

Source: WHO/HTM/TB/2010.3
Estimated number of MDR-TB cases (primary and acquired in 2008) divided by WHO region

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Estimated number of MDR-TB cases (primary and acquired) in 2008 (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African</td>
<td>69 000 (53 000–110 000)</td>
</tr>
<tr>
<td>Americas</td>
<td>8 200 (7 300–9 300)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>24 000 (11 000–81 000)</td>
</tr>
<tr>
<td>European</td>
<td>81 000 (73 000–90 000)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>130 000 (110 000–170 000)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>120 000 (100 000–140 000)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>440 000 (390 000–510 000)</strong></td>
</tr>
</tbody>
</table>

Source: WHO/HTM/TB/2010.3
Estimated number of MDR-TB cases in 27 high-burden countries (2008)

Source: WHO/HTM/TB/2010.3
SUCCESSES OVER THE LAST DECADE
THE 1990s…

- Outbreak in New York
- Reluctance by WHO to treat
- Poor countries without options

“MDR-TB is too expensive to treat in poor countries; it detracts attention and resources from treating drug-susceptible disease.”

- World Health Organization Groups at Risk, 1996
August 1996
DOTS-Plus project initiated in Lima’s Northern Cone by PIH/SES and Harvard Medical School, with the Peruvian National TB Program
The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis

International Edition

Partners In Health
Program in Infectious Disease and Social Change, Harvard Medical School
Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital
IMPORTANT FUNDING

1. Mr. Tom White (1995)
   Boston Philanthropist
   Funded treatment in Peru

2. Soros Foundation (1998)
   NGO
   Funded work in Russian prisons

   NGO
   Funded Russia, Peru
   Funded Partners coalition

Photo: Partners In Health (with permission)
1 Building international consensus

- A meeting was convened by Professor Howard Hiatt (BWH) and Dr. Arata Kochi (Director, WHO Stop TB Initiative) in Cambridge, USA, in 1998 to bring together key global TB decision-makers.

- This group developed the concept of “DOTS-Plus”, a programmatic approach for the treatment of MDR-TB.
The creation of a mechanism to enable “DOTS-Plus”:

- Professor Jim Kim and others at Harvard Medical School and Partners In Health, working with international partners and the World Health Organization, created the Green Light Committee (GLC) in 2000.
PARADIGM SHIFT...

Mandate:

- Ensure access to *quality-assured second-line drugs at affordable prices*
- Monitoring and evaluation of *second-line drug use* in approved projects
- Promotion of *technical assistance* for MDR-TB projects to ensure programs in keeping with WHO guidelines (“quality-assured programs”)

*DOTS-Plus & the Green Light Committee*
*Improving access to second-line anti-TB drugs*
PARADIGM SHIFT...

Models for MDR-TB care:

- “DOTS-Plus” pilot projects:
  - Lima, Peru
  - Tomsk, Russian Federation
  - Latvia
  - Manila, Philippines
  - Estonia
PARADIGM SHIFT...

The creation of international guidelines for the treatment of MDR-TB using the models
"To help contain resistance to second-line anti-TB drugs and consistent with the policies of other international funding sources, all procurement of medications to treat MDR-TB must be conducted through the Green Light Committee (GLC)"

-Third Board Meeting, 10-11 October, 2002

Second-line drugs for low and lower-middle income countries; thousands of patients to be enrolled in 2007-2011; creation of a Global Buffer Stock of SLDs and a Revolving Fund
OUTCOMES…

Patients Approved For Enrollment in GLC Projects 2000-2009

- 166 approved applications
- 108 projects
- 67 countries
- 59,282 patients

Source: GLC Secretariat, Slide adapted from Dr. Ernesto Jaramillo, WHO, Geneva
GLC Initiative
Treatment outcomes by year

Source: Dr. Fuad Mirzayev, WHO, Geneva
CHALLENGES
CHALLENGE: DIAGNOSIS OF MDR-TB

Need rapid culture and drug-sensitivity testing

- Liquid bacterial culture → 2 weeks
- Molecular tests → 2 days
- Both require laboratory infrastructure; need an approach that requires less infrastructure

Need rapid point-of-care test

- Diagnose patients at health points/clinics
- Start treatment immediately to reduce transmission and increase successful treatment outcomes
CHALLENGE: SECOND-LINE DRUG SUPPLY

- Not enough manufacturers
- Not enough quality-assured drugs
- Opaque market; insufficient forecasting
- Prices are very high for some drugs
- Serious delivery delays
- Countries use tender process
- Countries want local manufacturers
CHALLENGE: MDR-TB TREATMENT DELIVERY

• Global Plan to stop TB called for the treatment of 1.6 million patients with MDR-TB between 2006 and 2015; this is far from being achieved.

• Lack of health system capability to deliver complex health interventions

• Lack of funds

• Lack of political commitment
~500,000 estimated cases in 2008

CHALLENGE: MDR-TB TREATMENT DELIVERY

No treatment reported. Some treatment probably obtained, quality unknown

Countries report treatment, standard unknown

Treated in GLC approved programmes

<1%
CHALLENGE: MDR-TB TREATMENT DELIVERY

GLC Patients Treatment As Proportion of Total Patients

YEAR

MORTALITY

PATIENTS

2000
2001
2002
2003
2004
2005
2006
2007
2008
2009

0
1000000
2000000
3000000
4000000
5000000
6000000

Total Cumulative New Patients
GLC-Approved Treatments
CHALLENGE: MDR-TB TREATMENT DELIVERY

GLC Patients Treated As Proportion of Total Patients

- Total Cumulative New Patients
- GLC-Approved Treatments

YEAR

Treated by GLC
Gap between the Global Plan, 2006-2015 and GLC projections

* 62,000 expected by year-end 2009.

Source: Dr. Ernesto Jaramillo, WHO, Geneva
SECTION II:
SOLUTIONS
DIAGNOSTICS
The Lesotho Example (2006): Built laboratory capacity for mycobacterial culture and drug susceptibility testing
In 2007, the WHO and the Stop TB Partnership created the Global Laboratory Initiative

- laboratory capacity development and coordination

- accelerate laboratory development based on the model piloted by FIND and PIH in the Kingdom of Lesotho (EXPAND-TB)
LAB CAPACITY BUILDING: EXPAND-TB

EXPAND-TB is implemented by WHO-GLI, WHO-GDF and FIND under a Grant from UNITAID

2009: 6 countries
2010: 18 countries including India (43 labs)
2011: 3 countries

Source: Dr. Fuad Mirzayev, WHO, Geneva
EXPAND-TB Project Targets

* Targets calculated as a % of the estimated MDR-TB burden, 80% for most countries; 35% for India and 60% for Zambia and Cameroon

Source: Dr. Fuad Mirzayev, WHO, Geneva
5 in Western Pacific
13 in Europe
6 in Americas
2 in Africa
2 in SE Asia
1 in Eastern Mediterranean

Source: Dr. Fuad Mirzayev, WHO, Geneva
Priority must be given to research on—and funding for—the immediate development and rapid deployment of point-of-care testing for drug-susceptible and drug-resistant tuberculosis.
MDR-TB DRUG SUPPLY
WHO prequalification programme approved new sources for cycloserine, capreomycin, and ofloxacin: from two prequalified suppliers for 11 products in 2007 to 8 suppliers in 2009

Global drug facility established a
- Strategic Rotating Stockpile (SRS) of second-line drugs (UNITAID funded; 5,800)
- forecasting tool with support from Clinton Foundation
- price negotiation task force (GDF/GLC)
SOLUTIONS — DRUG SUPPLY

• Access to quality-assured second-line anti-TB drugs remains a major barrier as countries increase their pace of enrolment
  – Need to explore other mechanisms

• Some new drugs are in clinical development for TB treatment (e.g. moxifloxacin, PA-824, TMC 207), but more will be needed
MDR-TB TREATMENT DELIVERY
SOLUTIONS — TREATMENT DELIVERY

Infection control has to be made a priority
SOLUTIONS — TREATMENT DELIVERY

Ambulatory care costs less

Figure 3
Average cost per patient treated in the DOTS-Plus programme by item and source of funding, GLC prices scenario, 2003 US$

- Regional:
  - DOT visits: 1,117
  - Day stay ward: 2,545
  - Inpatient care, diagnostic tests & consultations: 4,444

- External:
  - Programme costs: 2,157
  - Drug costs at GLC prices: 3,718

*External sources means funding from both federal level and international agencies.

Source: WHO 2005
Hospital can be a major nidus for transmission of TB bacilli

- Retrospective study of the role of non-adherence and default and the acquisition of MDR-TB in Tomsk (in 2000)

- Substance abuse was a strong predictor of non-adherence (OR 7.3 (2.89-18.46))
  - Non-adherence NOT associated with MDR-TB

- MDR-TB occurred among adherent patients who had been hospitalized in the course of therapy compared to those treated as out-patients
  - OR 6.34 (1.34 – 29.72) – began treatment in hospital
  - OR 6.26 (1.02 – 38.35) – hospitalized later during treatment

Community based care allows patients to receive care in their own communities; essential when treatment is up to two-years long.
Universal access—and transmission interruption—has to be a priority

Ambulatory care and community based approaches provide a way to treat large numbers of patients rapidly, and safely

Source: WHO 2010
1. URGES all Member States:

(1) to achieve universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis as part of the transition to universal health coverage, thereby saving lives and protecting communities, by means of:

(a) developing a comprehensive framework for management and care of multidrug-resistant and extensively drug-resistant tuberculosis, that includes directly-observed treatment, community-based and patient-centered care, and which identifies and addresses the needs of persons living with HIV, the poor and other vulnerable groups, such as prisoners, mineworkers, migrants, drug users, and alcohol dependants, as well as the underlying social determinants of tuberculosis and multidrug-resistant and extensively drug-resistant tuberculosis;
The system of international technical assistance provision is currently inadequate. It must be transformed in order to better draw on the experience of successful regional MDR-TB treatment programs, to include the provision of on-site, long-term technical assistance, and where necessary, to involve on-site implementation teams.
SOLUTIONS — TREATMENT DELIVERY

Need to use existing knowledge-hubs to help countries/regions scale up
SOLUTIONS — TREATMENT DELIVERY

Need long-term on-site technical assistance in some settings

Many of the successful GLC Pilot projects had strong technical partners:

- Latvia worked with US CDC
- Tomsk (Russia) worked with PIH
- LHL worked with Arkhangelsk
- Orël (Russia) worked with CDC and WHO
- PIH assisted the NTP in Peru with national scale-up
- TDF is the NTP’s main technical partner in the Philippines
- Lesotho received technical assistance from PIH and FIND
- MSF worked with Uzbekistan, Georgia, Armenia
Large global health initiatives—such as PEPFAR—and bilateral and institutional donors for global health should make improving the capacity to deliver MDR-TB treatment an important priority. The Global Fund and UNITAID have done so, and others should follow this lead with their influence and resources.
The number of individuals receiving antiretroviral treatment in PEPFAR’s 15 focus-countries

Source: PEPFAR 2008; WHO 2008

Countries included: Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam (added in 2004), Zambia
**SOLUTIONS — TREATMENT DELIVERY**

**COUNTRY INITIATIVES TO EXPAND MDR-TB TREATMENT**

1. **GEOGRAPHICAL EXPANSION OF MDR TB TREATMENT**

   - **2001-2004**
     - Lima and Callao
     - 85.2%
   - **2005-2007**
     - Lima and Callao + 7 regions
     - 97.0%
   - **2008**
     - Included 5 more regions
     - 98.7%

2. **FINANCIAL SUPPORT FOR MDR TB TREATMENT EVOLUTION**

   ![Bar chart showing financial support for MDR TB treatment from 2001 to 2008]

   - **Source:** Dr. Oscar Ugarte, Minister of Health of Peru, Presented in Beijing, China
SECTION III: CONSEQUENCES OF INACTION
CONSEQUENCES OF INACTION

~500,000 estimated cases in 2008

No treatment reported. Some treatment probably obtained, quality unknown

→ AMPLIFICATION OF RESISTANCE
→ DEATH
→ CONTINUED TRANSMISSION

Source: Adapted from Dr. Ernesto Jaramillo and Dr. Fuad Mirzayev, WHO, Geneva
CONSEQUENCES OF INACTION

Source: WHO 2010
Countries/Settings with Prevalence of any drug-resistance higher than 30% among new cases (2002-2007)

Source: WHO 2008
CONSEQUENCES OF INACTION

Countries/Settings with Prevalence of MDR-TB higher than 5% among new cases (2002-2007)

Source: WHO 2008
Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Laloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

Summary
Background The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in a rural area in KwaZulu Natal, South Africa.

Methods We undertook enhanced surveillance for drug-resistant tuberculosis with sputum culture and drug susceptibility testing in patients with known or suspected tuberculosis. Genotyping was done for isolates resistant to first-line and second-line drugs.

Results From January, 2005, to March, 2006, sputum was obtained from 1539 patients. We detected MDR tuberculosis
Distribution of countries and territories reporting at least one case of XDR-TB as of January 2010

Source: WHO/HTM/TB/2010.3
THANK YOU