STEMMING THE TIDE OF MULTIDRUG-RESISTANT TUBERCULOSIS:

MAJOR BARRIERS TO ADDRESSING THE GROWING EPIDEMIC

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WASHINGTON DC
NOVEMBER 5, 2008
OVERVIEW

I. THE PROBLEM OF DRUG-RESISTANT TUBERCULOSIS

II. DIAGNOSIS OF MDR-TB

III. MDR-TB DRUG SUPPLY

IV. MDR-TB TREATMENT DELIVERY
SECTION I:

THE PROBLEM OF DRUG-RESISTANT TUBERCULOSIS
Notified cases of MDR-TB (2004-2006) and projected patients to be treated (2007-2008) compared to estimated burden of MDR-TB

An estimated 40,000 cases of XDR-TB each year

Source: WHO 2008
SECTION II: DIAGNOSIS OF MDR-TB
In 2005, the World Health Assembly passed a resolution requesting the Director General to:

“...to implement and strengthen strategies for the effective control of, and management of persons with drug-resistant tuberculosis.”

In 2007, the WHO and the Stop TB Partnership created the Global Laboratory Initiative (GLI)
Countries need one culture facility per 5 million population and one DST facility per 10 million population.

- Out of 22 select high-burden countries:
  - only six had one culture facility per 5 million population (China, South Africa, the Russian Federation, Brazil, Thailand and Cambodia)
  - only nine had one DST facility per 10 million population (China, Indonesia, South Africa, the Russian Federation, Viet Nam, Uganda, Brazil, Thailand and Cambodia)

- Excess capacity exists in economically developed nations
LESOTHO MODEL
Built laboratory capacity for mycobacterial culture and drug susceptibility testing
16 GLI-FIND-UNITAID project countries

74,000 MDR-TB patients diagnosed (and provided with treatment) by 2011

Source: GLI 2008
1. Sustainable funding from bilateral and multilateral donors must be increased to support construction of in-country drug-sensitivity testing/rapid-testing laboratories and ongoing external quality assessments by supranational reference laboratories.
RECOMMENDATIONS

DIAGNOSIS OF MDR-TB:

2. Creation of a system of long-term on-site technical assistance would help countries build and/or rapidly expand their capacity to perform mycobacterial culture, DST, and rapid molecular genetic tests for drug-resistant tuberculosis.
3. In-country laboratory networks for: specimen transport, data management, and certification and coordination of private laboratories need improvement.
4. Use of excess laboratory capacity for mycobacterial culture and drug-susceptibility testing in wealthy nations should be encouraged while laboratories are being built in poorer regions.
## Risk factors for delay in TB diagnosis and treatment

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>N</th>
<th>Delay &gt; 6 days</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;35 years</td>
<td>53</td>
<td>23 (49)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Male sex</td>
<td>59</td>
<td>29 (50)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Rural residence</td>
<td>13</td>
<td>8 (62)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>No salary</td>
<td>57</td>
<td>28 (49)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Health insurance</td>
<td>68</td>
<td>36 (54)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Negative HIV serology</td>
<td>34</td>
<td>17 (50)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Out-patient</td>
<td>22</td>
<td>13 (59)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Antibiotic Trial</td>
<td>72</td>
<td>39 (54)</td>
<td>0.083</td>
</tr>
<tr>
<td>EPTB/ SNPTB</td>
<td>76</td>
<td>43 (57)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

## TB Treatment Delays

<table>
<thead>
<tr>
<th></th>
<th>Median delay Day</th>
<th>Median delay Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Delay</strong></td>
<td>25</td>
<td>0-216</td>
</tr>
<tr>
<td><strong>Health service delay</strong></td>
<td>28</td>
<td>1-194</td>
</tr>
<tr>
<td>At primary and/or secondary level</td>
<td>18</td>
<td>0-191</td>
</tr>
<tr>
<td>At referral hospital</td>
<td>6</td>
<td>0-45</td>
</tr>
<tr>
<td><strong>Treatment delay</strong></td>
<td>1</td>
<td>0-6</td>
</tr>
<tr>
<td><strong>Total delay</strong></td>
<td>57</td>
<td>8-240</td>
</tr>
</tbody>
</table>

5. 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.
SECTION III:

MDR-TB DRUG SUPPLY

Photo: Open Society Institute/Pep Bonet
1. The WHO and international partners should take immediate and rapid steps to increase the number of manufacturers of quality-assured second-line anti-tuberculosis drugs. A mechanism needs to be developed to make these drugs available at pre-negotiated prices to programs purchasing via the GDF and through direct-purchase by countries.
2. The GDF should create a tiered system of approval for manufacturers of second-line drugs—and purchase of product by the GLC mechanism—consistent with a manufacturer’s progress in the EDM prequalification process.

Large countries operating within the GLC mechanism should be allowed to purchase second-line anti-tuberculosis drugs from domestic manufacturers who have entered the WHO’s Essential Drugs Monitoring (EDM) prequalification process.
3. The GLC mechanism should institute a transparent system for quantification of demand for second-line drugs.
4. The GDF should maintain a second-line anti-tuberculosis drug buffer stock (at minimum, enough to treat 5,000 patients) in order to facilitate rapid delivery of drugs to programs (less than one month).
Multi-drug Resistant Tuberculosis (MDR-TB)

- INH (H)
- RIF (R)
- EMB (E)
- PZA (Z)

Other 2nd-line Injectable
- Fluoroquinolone
  - OFLOX
  - LEVO
  - CPX
  - MOXI
  - GATI

- SM
- KM
- AMK
- CM
- ETH
- CS
- PAS

- AMX/CLV
- Clofazamine
- Clarithromycin
- Thiacetazone

Third-line Other agents

- 18 to 24 months of treatment, including 9 months with an injectable agent
- monitoring is required
- Numerous adverse events that need to be aggressively managed
- Nausea and vomiting
- Diarrhea
- Nephrotoxicity
- Hepatotoxicity
- Hypokalemia
- Hypothyroidism
- Depression
- Psychosis
- Seizure
- Ototoxicity
- Arthralgia
- Rash
- Neuropathy

- Complete blood count
- Electrolytes
- Liver function tests
- Urea and creatinine
- HIV ELISA
- Audiometry
- Psychiatrist evaluation
- Pregnancy testing
- Nausea and vomiting
- Diarrhea
- Nephrotoxicity
- Hepatotoxicity
- Hypokalemia
- Hypothyroidism
- Depression
- Psychosis
- Seizure
- Ototoxicity
- Arthralgia
- Rash
- Neuropathy
MDR-TB DRUG SUPPLY

Global Plan Investment Targets 2006

Source: Treatment Action Group
5. There should be a global effort to increase the options available for treating MDR-TB and XDR-TB, by optimizing current regimens and by developing at least three new anti-TB drugs.
SECTION IV:

MDR-TB TREATMENT DELIVERY
MDR-TB TREATMENT DELIVERY:
Absolute number and proportion of MDR-TB in Baltic Countries (1997-2007)

Source: WHO 2008
MDR-TB TREATMENT DELIVERY:

Absolute number and proportion of MDR-TB in Russian Oblasts (1997-2007)

Source: WHO 2008
1. Universal treatment for drug-resistant tuberculosis within national TB control strategies—side by side with drug-susceptible disease—has to be clearly and actively promoted by the WHO, the Stop TB Partnership, and global funding/technical assistance/implementation partners.
2. Transmission control, especially in high-risk congregate settings such as hospitals, prisons/jails, refugee camps, and residential care settings, has to be made a key programmatic priority.
MDR-TB TREATMENT DELIVERY:

MODELS THAT HAVE WORKED

Many successful projects have had technical partners:

- Latvia worked with CDC
- Tomsk (Russia) worked with PIH
- Orël (Russia) worked with CDC
- PIH assisted the NTP in Peru with national scale-up
- TDF is the NTP’s main technical partner in the Philippines
- Uzbekistan and Georgia worked with MSF
- Azerbaijan prison worked with ICRC
- Lesotho received technical assistance from PIH and FIND
- Gorgas TB Initiative worked in Kazakhstan
- Harvard School of Public Health worked in Cambodia
WHAT APPEARS TO HELP:

- ongoing, on-site assistance
- working closely, daily, with the NTP
- facilitating immediate solutions
- providing ongoing local capacity-building

KEY FACTOR FOR SUCCESS:

- IMPLEMENTATION STRATEGY
- SUFFICIENT FUNDING (LOCAL AND INTERNATIONAL)
- ONGOING/ON-SITE ASSISTANCE
- LINKAGE WITH GOVERNMENT AND LOCAL NGOs
CASE EXAMPLE: LESOTHO
Lesotho: Basic Data

- Ranks 120 out of 140 on Human Development Index
- Only 7% of households have electricity
- Only 11.9% of households have running water
- 0.043 physicians per 1,000 population
- Life expectancy has dropped to 35 years
- HIV prevalence 25%
- In 2005, reported more than 10,000 cases of TB (One of the highest TB prevalence in the world; ~600/100,000)
The extent of drug-resistant TB

**PROGRAMMATIC CHALLENGES:**

- Living in remote areas/far from health clinics
- Limited health services infrastructure
- Severe human-resource limitations
MDR-TB TREATMENT DELIVERY:

WHAT ARE THE BARRIERS TO CARE?

- Diagnosis of TB and MDR-TB in patients with HIV
- Having facilities to care for very sick patients
- Infection control in a high HIV setting
- Having second-line drugs to give to patients
- Having a mechanism to deliver MDR-TB care (± HIV treatment) in urban and rural areas
- Shortage of trained human resource
- Extreme poverty (the social and economic devastation—legacy of colonialism and apartheid)
- Migration of workers to South Africa to work in the mines
MDR-TB TREATMENT DELIVERY:

**Diagnosis:** Built laboratory capacity for mycobacterial culture and drug susceptibility testing
MDR-TB TREATMENT DELIVERY:

Drugs: quality-assured drug supply at an affordable price funded by UNITAID

DOTS-Plus & the Green Light Committee

Improving access to second-line anti-TB drugs
MDR-TB TREATMENT DELIVERY:

Facility to care for the very sick: refurbishment of an existing hospital at Botsabelo to create an MDR-TB referral facility and center of excellence.
Infection control in a high HIV setting: masks for all staff and state-of-the-art ventilation in facilities
MDR-TB TREATMENT DELIVERY:

Mechanism to deliver MDR-TB care and shortage of trained human resources: trained community health workers making home visits to patients on a daily basis
MDR-TB TREATMENT DELIVERY:

Poverty: assistance with food, housing, fuel and transportation
3. 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.
4. The WHO, the Stop TB Partnership, and global funding/technical assistance/implementation partners should actively promote the provision of ambulatory-based MDR-TB treatment, and, where appropriate, active collaboration with private-sector laboratories and tuberculosis treatment providers.
EXPANDING THE VISION

WE WANT THE TREATMENT
Number of patients approved by the GLC annually (01/2000 – 09/2008)

Source: WHO 2008
MDR-TB TREATMENT DELIVERY:

GLC-Project Patients approved by WHO Region from 2000 to 2008

WHO estimates of the number of new patients each year (% in GLC-approved projects as of September 2008)

Source: WHO 2008
MDR-TB TREATMENT DELIVERY:

Expected project impact from GLI / FIND / UNITAID collaboration

- 74,000 MDR-TB patients diagnosed (and provided with treatment) by 2011
- 15% of global MDR-TB burden
- At least 3-fold increase over current situation

Adapted from a slide from Karin Weyer, WHO, Geneva
MDR-TB TREATMENT DELIVERY:

The number of individuals receiving antiretroviral treatment in PEPFAR’s 15 focus-countries

Countries included: Botswana, Cote d’Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam (added in 2004), Zambia

Source: PEPFAR 2008; WHO 2008
MDR-TB TREATMENT DELIVERY:

TREATING MORE PATIENTS

Diagnostics

Drugs

Patients

Adapted from a slide from Karin Weyer, WHO, Geneva
5. 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.
ACKNOWLEDGEMENT

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Alexei Prorekhin
Steven Reynolds
John Ridderhof
William Rodriguez
Tamara Russell
Nina Schwalbe
Alex Sloutsky
Thelma Tupasi
Karin Weyer
Abigail Wright

Acknowledgements
Jaime Bayona
Ernesto Jaramillo
Kitty Lambregts
Oksana Ponomarenko
Mario Raviglione
Hind Satti
Peter Stephens
Gail Cassell
Institute of Medicine
PIH Lesotho
THANK YOU