SETTING THE STAGE:
GLOBAL CHALLENGES IN DRUG-RESISTANT TUBERCULOSIS AND POTENTIAL SOLUTIONS

SALMAAN KESHAVJEE, MD, PHD

HARVARD MEDICAL SCHOOL
BRIGHAM AND WOMEN’S HOSPITAL
PARTNERS IN HEALTH

INSTITUTE OF MEDICINE/
INDIAN COUNCIL OF MEDICAL RESEARCH

DELHI, INDIA
APRIL 18, 2011
OVERVIEW

I. CURRENT STATE OF AFFAIRS

II. WHY THE SLOW PACE OF TREATMENT SCALE-UP?

III. CONSEQUENCES OF INACTION
CURRENT STATE OF AFFAIRS
Gap between the Global Plan, 2006-2015 and GLC projections

Source: Dr. Ernesto Jaramillo, WHO, Geneva
~5 million cases

10 YEAR PICTURE (2000-2009)

~3.5 million patients
No treatment reported.
Some treatment probably obtained, quality unknown.
Continued transmission
Many are DEAD

0.5%
Treated in GLC approved programmes

~1.5 million patients – DEAD
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
WHY THE SLOW PACE OF TREATMENT SCALE-UP?
I. DELAY FROM EVIDENCE TO POLICY CHANGE
TREATMENT OF 171 PATIENTS WITH PULMONARY TUBERCULOSIS RESISTANT TO ISONIAZID AND RIFAMPIN

Marian Goble, M.D., Michael D. Iseman, M.D., Lorie A. Madsen, R.N.-C., B.S.N., Dennis Waite, M.D., Lynn Ackerson, Ph.D., and C. Robert Horsburgh, Jr., M.D.

SPECIAL ARTICLE

TUBERCULOSIS IN NEW YORK CITY — TURNING THE TIDE

Thomas R. Frieden, M.D., M.P.H., Paula I. Fujiwara, M.D., M.P.H., Rita M. Washko, M.D., and Margaret A. Hamburg, M.D.

Abstract  Background. From 1978 through 1992, the number of patients with tuberculosis in New York City nearly tripled, and the proportion of such patients who had drug-resistant isolates of Mycobacterium tuberculosis more than doubled.

Methods. We reviewed, confirmed, and analyzed data obtained during the surveillance of patients with tuberculosis.

Results. From 1992 through 1994, there was a 21 percent decrease in reported cases of tuberculosis in among elderly and foreign-born persons, in whom the disease is likely to result from the reactivation of an infection acquired many years earlier. Enrollment in a program of directly observed therapy, in which health workers watch patients take their medications, increased from fewer than 100 patients to nearly 1300, with more than 32,000 patient-months of observation from 1992 through 1994.

Conclusions. Epidemiologic patterns strongly suggest that the decrease in cases resulted from an interruption in the ongoing spread of M. tuberculosis infection, primar-
“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
MDR-TB treatment initiated in Lima’s Northern Cone by PIH/SES and Harvard Medical School, with the Peruvian National TB Program

Early 2000s
Dissemination of the example of community-based delivery of MDR-TB treatment as feasible in resource-limited settings
THE
STOP TB
STRATEGY
Building on and enhancing DOTS to meet the TB-related Millennium Development Goals
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;
II. INADEQUATE DIAGNOSTIC CAPACITY
Need rapid culture and drug-sensitivity testing

- Liquid bacterial culture ‡ 2 weeks
- Molecular tests ‡ 2 hours to 2 days
- Require laboratory infrastructure; need an approach that requires less infrastructure
- Need something that works on children and those with HIV

Need rapid point-of-care test

- Diagnose patients at health points/clinics
- Start treatment immediately to reduce transmission and increase successful treatment outcomes
SOLUTION: BUILD CAPACITY

Lesotho example demonstrates what can be achieved in resource-limited settings
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
III. INADEQUATE DRUG SUPPLY
The creation of a mechanism to enable “DOTS-Plus”

Created by Jim Kim and colleagues (PIH/Harvard), working with international partners and the WHO in 2000.

**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”)
## Reduced prices of second-line TB drugs

Result of negotiations based on plans for pooled procurement

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>1997 price</th>
<th>2000 price</th>
<th>% Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>1gm vial</td>
<td>$9.00</td>
<td>$0.90</td>
<td>90</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>250mg tab</td>
<td>$3.99</td>
<td>$0.50</td>
<td>87</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>250mg tab</td>
<td>$0.90</td>
<td>$0.14</td>
<td>84</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>1gm vial</td>
<td>$2.50</td>
<td>$0.39</td>
<td>84</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>1gm vial</td>
<td>$29.90</td>
<td>$0.90</td>
<td>97</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>200mg tab</td>
<td>$2.00</td>
<td>$0.05</td>
<td>98</td>
</tr>
</tbody>
</table>
CHALLENGES

• Not enough manufacturers of quality-assured 2\textsuperscript{nd} line drugs
• No pooled procurement
• Opaque market; insufficient forecasting
• Prices are very high for some drugs
• Serious delivery delays
• Overly centralized system
• Countries want local manufacturers
Situation with second-line anti-TB drugs

- Competition tends to lower prices and allows affordable access to medical technologies... second-line anti-TB drugs have been an exception.
## Prices available for GLC - approved programmes, in US$

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin 500mg</td>
<td>0.11</td>
<td>1.20</td>
<td>+991%</td>
</tr>
<tr>
<td>Kanamycin 1g</td>
<td>0.36</td>
<td>2.58</td>
<td>+617%</td>
</tr>
<tr>
<td>Cycloserine 250mg</td>
<td>0.14</td>
<td>0.59</td>
<td>+321%</td>
</tr>
<tr>
<td>Capreomycin 1gr</td>
<td>1.02</td>
<td>4.00</td>
<td>+292%</td>
</tr>
<tr>
<td>Ethionamide 250mg</td>
<td>0.10</td>
<td>0.09</td>
<td>Stable</td>
</tr>
<tr>
<td>Prothionamide 250mg</td>
<td>0.10</td>
<td>0.10</td>
<td>Stable</td>
</tr>
<tr>
<td>PAS 4g sachet</td>
<td>1.51</td>
<td>1.57</td>
<td>Stable</td>
</tr>
</tbody>
</table>

Source: MSF/IUATLD 2011
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
IV. INADEQUATE CARE-DELIVERY CAPACITY IN COUNTRIES
Delivery of treatment

Lack of infection/transmission control

Lack of systems to deliver care to patients over the 2-year period of treatment and to manage adverse events

Lack of systems to help countries scale-up treatment rapidly
SOLUTIONS — TREATMENT DELIVERY

Infection control has to be made a priority
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: 772
  - Day stay ward: 1117
  - Inpatient care, diagnostic tests & consultations: 2545

- External
  - Programme costs: 2167
  - Drug costs at GLC prices: 3718

*External sources means funding from both federal level and international agencies.
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
IV. INSUFFICIENT TECHNICAL ASSISTANCE
U.S. IOM RECOMMENDATION (2008):

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 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
### Table: Number of MDR-TB cases, health system ranking, and poverty in the 27 MDR-TB high-burden countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of MDR-TB patients (2008)*</th>
<th>Health system overall performance ranking (N = 191; 1997)†</th>
<th>Living on &lt;$2/day (2000–2007)² %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>5600</td>
<td>188</td>
<td>74.4</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>5200</td>
<td>180</td>
<td>77.5</td>
</tr>
<tr>
<td>Nigeria</td>
<td>11000</td>
<td>187</td>
<td>83.9</td>
</tr>
<tr>
<td>South Africa</td>
<td>13000</td>
<td>175</td>
<td>42.9</td>
</tr>
<tr>
<td>Europe &amp; Eastern Mediterranean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armenia</td>
<td>480</td>
<td>104</td>
<td>43.4</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>4000</td>
<td>109</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Belarus</td>
<td>800</td>
<td>72</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>460</td>
<td>102</td>
<td>2.4</td>
</tr>
<tr>
<td>Estonia</td>
<td>94</td>
<td>77</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Georgia</td>
<td>670</td>
<td>114</td>
<td>30.4</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>8100</td>
<td>64</td>
<td>17.2</td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>1400</td>
<td>151</td>
<td>51.9</td>
</tr>
<tr>
<td>Latvia</td>
<td>170</td>
<td>105</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Lithuania</td>
<td>330</td>
<td>73</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Pakistan</td>
<td>15000</td>
<td>122</td>
<td>60.3</td>
</tr>
<tr>
<td>Republic of Moldova</td>
<td>2100</td>
<td>101</td>
<td>28.9</td>
</tr>
<tr>
<td>Russia</td>
<td>38000</td>
<td>130</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Tajikistan</td>
<td>4000</td>
<td>154</td>
<td>50.8</td>
</tr>
<tr>
<td>Ukraine</td>
<td>8700</td>
<td>79</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>8700</td>
<td>117</td>
<td>76.7</td>
</tr>
<tr>
<td>South-East Asia &amp; Western Pacific</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td>9800</td>
<td>88</td>
<td>81.3</td>
</tr>
<tr>
<td>China</td>
<td>100000</td>
<td>144</td>
<td>36.3</td>
</tr>
<tr>
<td>India</td>
<td>99000</td>
<td>112</td>
<td>75.6</td>
</tr>
<tr>
<td>Indonesia</td>
<td>9300</td>
<td>92</td>
<td>53.8</td>
</tr>
<tr>
<td>Myanmar (Burma)</td>
<td>9300</td>
<td>190</td>
<td>—</td>
</tr>
<tr>
<td>Philippines</td>
<td>13000</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>Vietnam</td>
<td>5900</td>
<td>160</td>
<td>48.4</td>
</tr>
</tbody>
</table>

Source: Keshavjee and Farmer, *IJTLD*, 2010
USING TECHNICAL ASSISTANCE CENTERS/KNOWLEDGE HUBS AS A NIDUS FOR IMPLEMENTATION
INTENSE MODELS OF ON-SITE TECHNICAL ASSISTANCE

FOR EXAMPLE (and/or):
• Country manager
• Laboratory consultant
• Community organizer
• Clinician
• Other

Technical Assistance Centers/Knowledge Hubs

In-country support team

GLOBAL TECHNICAL PARTNERS

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

Source: WHO 2008
MAP 7  Distribution of countries and territories reporting at least one case of XDR-TB as of January 2010

Source: WHO/HTM/TB/2010.3
Time to rethink the global approach

• Constraining structures and lack of innovative thinking
  – Stop TB Partnership/World Health Organization
  – Global Drug Facility
  – Limited involvement of the private sector
  – Limited focus on advocacy in countries

• Lack of engagement with key partners such as PEPFAR, UNICEF, UNDP, and others

• Limited focus on implementation
THANK YOU