WHERE DO WE GO FROM HERE?

WHAT WILL BE REQUIRED TO ACHIEVE ZERO DEATHS FROM TUBERCULOSIS?

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INTERNATIONAL WORKSHOP ON MDR-TB
BEIJING, PEOPLES REPUBLIC OF CHINA
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Why have we not been successful in the struggle against tuberculosis?

1. We have not used correct and optimized biomedical approaches

2. We have not used optimal delivery systems
CORRECTING AND OPTIMIZING
THE BIOMEDICAL STRATEGY
THE PAST
“MINIMALIST VS. OPTIMALIST”

1. Political commitment
   - Limited engagement with private sector

2. Diagnosis with sputum-smear microscopy
   - Low sensitivity in patients with paucibacillary disease (pediatric populations, patients infected with HIV)
   - Sub-optimal for patients with smear-negative or extra-pulmonary TB
   - Incapable of identifying resistant strains

3. Standardized short-course chemotherapy
   - Does not work for drug resistant disease
   - Ignored the role of surgery in advanced cases

4. Regular supply of high-quality drugs
   - Lack of integration with country procurement systems
   - Second-line drugs not included
   - Drugs for adverse events were not considered

5. Standardized recording and reporting
   - Unable to capture complex data
Also missing from minimalist strategies…

- **Focus on transmission/infection control**
  - Little emphasis on health system strengthening, including the design of appropriate health facilities and systems to prevent transmission
  - Assumption that MDR was not virulent enough for transmission
  - One-size-fits-all approach to treatment

- **Strategies for active case detection**
  - Relied on patients appearing when they were sick
  - One-size-fits-all approach to diagnosis

- **Strategy for latent disease**
  - Majority of people have latent disease; reactivation as a source of continued transmission
  - Proven transmission and mortality benefit

- **Proper integration with other health services**
  - Drug procurement independent of general procurement systems
  - Independent clinic and delivery operations

- **Active engagement with the private sector**
  - Critical for R&D as well as diagnosis/delivery

- **FLEXIBILITY:** slow response to change in light of new evidence
CAN WE IMPROVE OUR APPROACH?

ZERO TB
Deaths/Infections/Suffering
Find TB cases

Active case finding

Separate safely and reduce exposure

Treat effectively based on rapid DST
Find TB cases

Active case finding
Search for cases among people living with HIV

Intensified TB case-finding among HIV-positive people, 2005–2009. The percentage of estimated HIV-positive people who were screened for TB is shown above the line.

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*a* Numbers under years show the number of countries reporting data followed by the percentage of total estimated HIV-positive people accounted for by reporting countries.

Source: WHO, Tuberculosis Control Report, 2010
Search for cases among children

Between 10% and 30% of patients

- Diagnostics poor; often not done
- Need appropriate diagnostics
- Need appropriate case-finding strategies
Low case detection:
- one third of patients (over 3 million) are not detected each year
- mortality has stayed roughly the same

Potential solutions:
- true point-of-care test for TB/DR-TB
- help programs improve performance
- integration with other parts of the public health system
- partnership with the private sector
Innovative mechanisms/Approaches (E.g. TB Reach)

Engaging the private sector to increase tuberculosis case detection: an impact evaluation study

Aamir J Khan, Saira Khowaja, Faisal S Khan, Fahad Qazi, Ismat Lotia, Ali Habib, Shama Mohammed, Uzma Khan, Farhana Amanullah, Hamidah Hussain, Mercedes C Becerra, Jacob Creswell, Salmaan Keshavjee
Challenges

DIAGNOSTICS

POC tests
- identification of TB at clinic so that treatment can be initiated immediately

Molecular tests
- one size does not fit all
- need to reliably determine second-line drug resistance

Children
- Need an approach that can work effectively
Separate safely and reduce exposure

Treat effectively based on rapid DST
Need to diagnose drug-resistance

Source: WHO, Tuberculosis Control Report, 2010
Start patients on an effective regimen as soon as possible.

When patients are started on an effective treatment regimen, they become less infectious

TREATMENT = REDUCED TRANSMISSION

Relative infectivity of patients*:

- Susceptible TB
  - 61 Untreated (29 GPs) 100%
  - 29 Treated (1 GP) 2%

- Drug-resistant TB
  - 6 Untreated (14 GPs) 28%
  - 11 Treated (6 GPs) 5%

*all smear positive patients, relative to the amount of time on the ward

Treat as many patients as possible to prevent transmission

Universal access to care—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, outside of congregate settings

Source: MULTIDRUG AND EXTENSIVELY DRUG-RESISTANT TB (M/XDR-TB): 2010 GLOBAL REPORT ON SURVEILLANCE AND RESPONSE
Treating tuberculosis: a crash course

**First-line**
- INH (H)
- RIF (R)
- EMB (E)
- PZA (Z)
- SM (S)

**Second-line**
- Injectable
  - KM
  - AMK
  - CM

- Fluoroquinolone
  - OFLOX
  - LEVO
  - MOXI

- Other 2nd-line
  - S*

**Third-line**
- AMX/CLV
- Clofazamine
- Linezolid
- Carbapenems

Ancillary drugs for adverse events

Have a reliable, affordable supply of QA drugs so that patients can be put on an effective treatment regimen.
A comprehensive solution is required

Fixing this will require a reconfiguration of the global procurement system

**DRUG SUPPLY**

High quality, reliable, affordable, drug supply

**DELIERY GAP**

System capable of finding and diagnosing patients and delivering care

Fixing this will require a reconfiguration of the way countries are assisted

Demand will only be ensured if systems to deliver the drugs to patients are in place
Preventive therapy for TB (including MDR-TB)

Comstock’s studies in Alaska 1960s

• Isoniazid preventive therapy effective in preventing TB in different populations

• protective effect persistent for more than 19 years (as of 1979); perhaps lifelong

INH prophylaxis in patients infected with HIV

• highly effective in preventing mortality

• greater effect seen in PPD+ people

• 36 month therapy (continuous IPT) was more effective for prevention of TB than 6 month IPT in people with HIV (2011)

Urgent need to test prophylaxis of MDR-TB contacts

• children?
• people infected with HIV?
• all contact?
Table 1  Risk factors for the development of active tuberculosis among persons infected with *Mycobacterium tuberculosis*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Estimated risk for TB relative to persons with no known risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk (testing and treatment for LTBI recommended for all ages&lt;sup&gt;1&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>110–170</td>
</tr>
<tr>
<td>HIV</td>
<td>50–110</td>
</tr>
<tr>
<td>Transplantation (related to immune-suppressant therapy)</td>
<td>20–74</td>
</tr>
<tr>
<td>Silicosis</td>
<td>30</td>
</tr>
<tr>
<td>Chronic renal failure requiring hemodialysis</td>
<td>10–25</td>
</tr>
<tr>
<td>Carcinoma of head and neck</td>
<td>16.0</td>
</tr>
<tr>
<td>Recent TB infection (&lt;2 years)</td>
<td>15.0</td>
</tr>
<tr>
<td>Abnormal chest x-ray—with upper lobe fibronodular disease typical of healed</td>
<td>6–19</td>
</tr>
<tr>
<td>TB infection</td>
<td></td>
</tr>
<tr>
<td>TNF-alpha inhibitors</td>
<td>1.7–9.0</td>
</tr>
<tr>
<td>Moderate risk (testing and treatment for LTBI recommended if age &lt;65 years&lt;sup&gt;1&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>Treatment with glucocorticoids</td>
<td>4.9</td>
</tr>
<tr>
<td>Diabetes mellitus (all types)</td>
<td>2–3.6</td>
</tr>
<tr>
<td>Young age when infected (0–4 years)</td>
<td>2.2–5</td>
</tr>
<tr>
<td>Slightly increased risk (testing and treatment for LTBI recommended if age</td>
<td></td>
</tr>
<tr>
<td>&lt;50 years&lt;sup&gt;1&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;90% ideal body weight; for most persons, this is a BMI ≤ 20)</td>
<td>2–3</td>
</tr>
<tr>
<td>Cigarette smoker (1 pack/day)</td>
<td>2–3</td>
</tr>
<tr>
<td>Abnormal chest x-ray—granuloma</td>
<td>2</td>
</tr>
<tr>
<td>Low risk (testing and treatment for LTBI recommended if age &lt;35 years&lt;sup&gt;1&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>Infected person, no known risk factor, normal chest x-ray (‘low-risk reactor’)</td>
<td>1</td>
</tr>
<tr>
<td>Very low risk (treatment of LTBI not usually recommended)</td>
<td></td>
</tr>
<tr>
<td>Person with positive two-step (booster), no other known risk factor, and</td>
<td>0.5</td>
</tr>
<tr>
<td>normal chest x-ray</td>
<td></td>
</tr>
</tbody>
</table>
Adjunct therapies

• Autologous mesenchymal stromal cells?
• Other immunomodulators/anti-inflammatories?
• Therapeutic vaccines?
OPTIMIZING CARE DELIVERY SYSTEMS ("ENABLING PLATFORMS")
Need to fill the implementation gap

- Diagnosis of drug Resistance
- Supply of Second-line drugs

IMPLEMENTATION GAP
<table>
<thead>
<tr>
<th>Country</th>
<th>Number of MDR-TB patients (2008)*</th>
<th>Health system performance ranking (N = 191; 1997)$^\dagger$</th>
<th>Living on &lt;$2/day (2000–2007)$^\dagger$ %</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>
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<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
COMMUNITY-BASED CARE

• USE OF WRAP AROUND SERVICES
  (food and other enablers help patients complete treatment successfully)

• NO CO-PAYMENTS

• PATIENT ACCOMPANIMENT

• STRENGTHENING OF PUBLIC SECTOR
Cash transfer and microfinance interventions for tuberculosis control: review of the impact evidence and policy implications

D. Boccia,* J. Hargreaves,* K. Lönnroth,† E. Jaramillo,‡ J. Weiss,‡ M. Uplekar,§ J. D. H. Porter,‡ C. A. Evans§

Figure Conceptual framework. In this review we focus on tuberculosis (TB) disease and interventions targeting socio-economic position at household level. It is hypothesised that cash transfer, either conditional or unconditional, and microfinance interventions can support TB control by improving a household's socio-economic position and thereby reducing the exposure to biological risk factors (such as human immunodeficiency virus and malnutrition) and improving the household food security and health-seeking behaviour.
The innovative socio-economic interventions against tuberculosis (ISIAT) project: an operational assessment

C. Rocha,†† R. Montoya,†† K. Zevallos,†† A. Curatola,†† W. Ynga,‡‡ J. Franco,†† F. Fernandez,††
N. Becerra,†† M. Sabaduche,† M. A. Tovar,‡‡ E. Ramos,‡‡ A. Tapley,†† N. R. Allen,†† D. A. Onifade,††
C. D. Acosta,†† M. Maritz,†† D. F. Concha,§ S. G. Schumacher,†‡‡ C. A. Evans††

The socio-economic interventions were associated with increases in household contact TB screening (from 82% to 96%); successful TB treatment completion (from 91% to 97%); patient human immunodeficiency virus testing (from 31% to 97%); and completion of preventive therapy (from 27% to 87%; all \( P < 0.0001 \)).

CONCLUSIONS: Socio-economic interventions can strengthen TB control activities.
Investing in Improved Performance of National Tuberculosis Programs Reduces the Tuberculosis Burden: Analysis of 22 High-Burden Countries, 2002–2009

Yoko Akachi,1 Alimuddin Zumla,2 and Rifat Atun3

1Strategy, Performance and Evaluation Cluster, The Global Fund to Fight AIDS, Tuberculosis, and Malaria, Geneva, Switzerland; 2Division of Infection and Immunity, Centre for Clinical Microbiology, University College London Medical School, and 3Imperial College London, United Kingdom

Objective. To assess the impact of investment in national tuberculosis programs (NTPs) on NTP performance and tuberculosis burden in 22 high-burden countries, as determined by the World Health Organization (WHO).

Data Source/Study Setting. Estimates of annual tuberculosis burden and NTP performance indicators and control variables during 2002–2009 were obtained from the Organization for Economic Cooperation and Development, the WHO, the World Bank, and the Penn World Table for the 22 high-burden countries.

Study Design. Panel data analysis was performed using the outcome variables tuberculosis incidence, prevalence, and mortality and the key explanatory variables Partnership case detection rate and treatment success rate, controlling for gross domestic product per capita, population structure, and human immunodeficiency virus (HIV) prevalence.

Results. A $1 per capita (general population) higher NTP budget (including domestic and external sources) was associated with a 1.9% (95% confidence interval, .12%–3.6%) higher estimated case detection rate the following year for the 22 high-burden countries between 2002 and 2009. In the final models, which corrected for autocorrelation and heteroskedasticity, achieving the STOP TB Partnership case detection rate target of >70% was associated with significantly ($P < .01$) lower tuberculosis incidence, prevalence, and mortality the following year, even when controlling for general economic development and HIV prevalence as potential confounding variables.

Conclusions. Increased investment in NTPs was significantly associated with improved performance and with a downward trend in the tuberculosis burden in the 22 high-burden countries during 2002–2009.
New Outpatient Attendances in Government of Uganda and Private Not for Profit Health Units

Government scraps health user fees just before the end of the financial year

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</thead>
<tbody>
<tr>
<td>Millions</td>
<td>8.2</td>
<td>8.8</td>
<td>9.3</td>
<td>9.6</td>
<td>13.4</td>
<td>17.7</td>
<td>20.2</td>
<td>24.5</td>
</tr>
</tbody>
</table>

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.
The number of individuals receiving antiretroviral treatment in PEPFAR’s 15 focus-countries compared to the GLC mechanism

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

367,000 TB/HIV Patients Treated

MDR-TB Patients

Source: PEPFAR 2008; WHO 2008
Brazil’s population living below $1.25 per day

% of total

Rural

Urban

Source: IPEA

GLOBAL: 15% drop between 1990 and 2011

BRAZIL: 50% drop between 1990 and 2011
THE WAY FORWARD
BRICS Country Leadership for Tuberculosis Treatment and Control

The Ministers agreed to establish platforms for collaboration within BRICS framework and with other countries with a view to realizing the goals and objectives outlined in the Delhi Communiqué

Source; R. Atun, International Workshop on Multi-Drug Resistant Tuberculosis, Beijing 2013
Delhi Communiqué (1)

Clause 7

The Ministers recognized that multi-drug resistant tuberculosis is a major public health problem for the BRICS countries due to its high prevalence and incidence mostly on the marginalized and vulnerable sections of society.

Source: R. Atun, International Workshop on Multi-Drug Resistant Tuberculosis, Beijing 2013
Delhi Communiqué (2)

Resolved to:

• collaborate and cooperate for development of capacity and infrastructure
• reduce the prevalence and incidence of tuberculosis through innovation for new drugs/vaccines, diagnostics and promotion of consortia of tuberculosis researchers
• collaborate on clinical trials of drugs and vaccines, strengthening access to affordable medicines and delivery of quality care.

Source; R. Atun, International Workshop on Multi-Drug Resistant Tuberculosis, Beijing 2013
The Ministers also recognized the need to cooperate for adopting and improving systems for

- notification of tuberculosis patients,
- availability of anti-tuberculosis drugs at facilities by improving supplier performance,
- procurement systems and logistics and management of HIV-associated tuberculosis in the primary health care system.

Source: R. Atun, International Workshop on Multi-Drug Resistant Tuberculosis, Beijing 2013
BRICS COUNTRY TUBERCULOSIS INITIATIVE?

• BRICS countries have a high proportion of the global burden of disease

• These countries are well poised to commit to scaling up the treatment of MDR-TB (in BRICS countries and their sphere of influence) through innovations in technology and health care delivery, technical cooperation
ZERO TB
Deaths/Infections/Suffering

www.treatmentactiongroup.org/tb/advocacy/zero-declaration
WE ASPIRE TO A WORLD WITH ZERO TB DEATHS

Thank you

Photo: Open Society Institute/Pep Bonet