How Research Can Help Control TB

Richard E. Chaisson, MD

Center for Tuberculosis Research
Consortium to Respond Effectively to the AIDS-TB Epidemic
Johns Hopkins University

A History of TB Control:
Mission Accomplished?

- 1882 – Koch discovers the tubercle bacillus*
- 1907 – von Pirquet adapts Koch’s tuberculin
- 1919 – Calmette and Guerin produce BCG
- 1943 – Schatz and Waksman discover streptomycin*
- 1948 – BMRC trial of streptomycin vs bed rest
- 1952 – Development of INH
- 1966 – Development of rifampin
- 1978 – Short-course chemotherapy – 6 months

*Awarded Nobel Prize
Federal Funding for Tuberculosis Research and Control, 1962 - 1990

BR Bloom and CJL Murray, Science 1992;257:1055-64

Estimated Global Incidence and Burden of Tuberculosis

WHO Estimates of Global Burden of Tuberculosis as of December 31, 2008

- All forms of TB: 9.4 million cases, 1.3 million deaths
- MDR-TB: 511,000 cases, ~150,000 deaths
- XDR-TB: 50,000 cases, 30,000 deaths
- HIV-related TB: 1.4 million cases (15% of TB), 500,000 deaths (23% of TB deaths, 22% of AIDS deaths)
Control of Tuberculosis

What went wrong?

• Inadequacies of existing tools
  – Smear detection of cases ~50%
  – Adherence to regimens is very poor
  – BCG vaccine does not prevent adult TB

• Changing epidemiological situation
  – HIV epidemic
  – MDR

• Failure to apply tools broadly
  – Weaknesses in health systems

• Lack of ongoing research enterprise

US NIH Funding for Infectious Disease Research, 2005 – 2008

The Stop TB Strategy & Global Plan

1. Pursue high-quality DOTS expansion
2. Address TB-HIV, MDR-TB, and needs of the poor and vulnerable
3. Contribute to health system strengthening
4. Engage all care providers
5. Empower people with TB and communities
6. Enable and promote research
Biomedical Tools and Public Health

Control of infectious diseases requires:
- biomedical tools (diagnostics, drugs and vaccines),
- public health strategies for applying and utilizing the tools at the population level to reduce disease burden, and
- effective health systems to implement tools and strategies

Tools for Treating and Preventing TB

<table>
<thead>
<tr>
<th>Target</th>
<th>Available tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostics</td>
<td>Sputum smear, culture, x-rays, IGRAs, molecular (new)</td>
</tr>
<tr>
<td>Drugs</td>
<td>Isoniazid, rifampin, PZA, ethambutol, 2nd line drugs</td>
</tr>
<tr>
<td>Vaccine</td>
<td>BCG (&gt;10 strains)</td>
</tr>
</tbody>
</table>

Current Global Strategies for Controlling TB

- Passive case finding (DOTS)
  - Reliance on sputum smear (<50% sensitivity)
  - No drug susceptibility testing
  - Poor adherence to therapy
- INH preventive therapy
  - Rarely used outside US and Europe
- BCG Vaccination
  - Most widely used vaccine, but doesn’t prevent infectious TB
- Infection control
  - Newly ‘discovered’ and largely ignored
Challenges in TB Research

• Development of new tools
  – Rapid, accurate diagnostics
  – Effective drugs to cure faster, treat M/XDR
  – New, effective vaccine
• Development of better strategies
  – Earlier case finding
  – Deploy preventive therapy
  – Infection control
• Strengthen health systems
  – Delivery of new tools to populations in need
  – Improve performance of systems

Epidemiologic Basis for TB Control:
Key Questions for Developing Control Strategies

• Where are the seedbeds of tuberculosis?
  – Who has latent infection?
• What are the determinants of tuberculosis?
  – Comorbidities, poverty, malnutrition
• Who has active TB?
  – What proportion of cases are detected, and when?
• Where is TB transmission occurring?
  – Who is becoming infected?
• What can be done to reduce susceptibility?
  – Vaccination
  – Control of co-morbidities, e.g., HIV and diabetes
  – Tobacco control

The Origin of TB Cases:
Prevalence of Risk Factors in Patients with Culture-Confirmed Pulmonary TB in Baltimore, MD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (Total = 139)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign born</td>
<td>12</td>
<td>9%</td>
</tr>
<tr>
<td>HIV Infection</td>
<td>31</td>
<td>24%</td>
</tr>
<tr>
<td>IDU</td>
<td>28</td>
<td>20%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18</td>
<td>14%</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>12</td>
<td>9%</td>
</tr>
<tr>
<td>Recent Cancer</td>
<td>8</td>
<td>6%</td>
</tr>
<tr>
<td>Steroid Use</td>
<td>7</td>
<td>6%</td>
</tr>
</tbody>
</table>

Oursler et al., CID 2002;34:729-9
TB Incidence and Prevalence of Diabetes, 2010 and 2030

Dooley and Chaisson, Lancet Infect Dis, 2009; 9: 737–46

Association of Body Mass Index with Risk of Tuberculosis in HIV+ Patients in Soweto, South Africa

Hanrahan et al., AIDS 2010, epub

Smoking and incident TB in HIV-infected adults in Soweto, South Africa

<table>
<thead>
<tr>
<th>Pack years of tobacco</th>
<th>TB Incidence Per 100 Person-years</th>
<th>Incidence Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>6.5 (5.9-7.4)</td>
<td>REF</td>
</tr>
<tr>
<td>1-5</td>
<td>9.0 (6.8-11.7)</td>
<td>1.36 (1.01-1.82)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>12.8 (9.7-16.7)</td>
<td>1.95 (1.44-2.60)</td>
</tr>
</tbody>
</table>

Martinson et al, CROI 2008
A Platform for Controlling Global Tuberculosis

- **FIND the TB that is there**
  - Passive case detection is not sufficient
  - New approaches to detect TB ‘often and early’

- **TREAT the TB that is found**
  - Treatment success is unacceptably low
  - Treatment for M/XDR is abysmal
  - New drugs and treatment strategies urgently needed

- **Prevent the TB that hasn’t occurred yet**
  - Preventive therapy essential for high risk populations
  - Infection (transmission) control critical
  - Reduce susceptibility (diabetes, ESRD, smoking)

Factors Associated with Transmission of TB Infection to Contacts of US-Born TB Cases in Maryland

<table>
<thead>
<tr>
<th>Source Case Variable</th>
<th>% Contacts TST+</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitary CXR: No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Sputum smear: –</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>+</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Dx Delay: ≤ 60 days</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>&gt; 60 days</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Dx Delay: ≤ 90 days</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&gt; 90 days</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>

Golub et al, Int J Tub Lung Dis, 2006;10:24-30
FIND TB Questions

• How can we improve TB case-finding?
  – Screening in health facilities
    • HIV clinics
    • Prenatal clinics
    • Primary health clinics → screening for high risk patients
      – Diabetes, End Stage Renal Disease, Immigrants
  – Community-based active case finding
  – Household contact evaluation

• What are the best clinical approaches to identify TB suspects?
  – Symptom screening
  – CXRs
  – Smear, culture, new technologies?

Rocinha favela, Rio de Janeiro

A cluster-randomized trial of door-to-door active case finding for TB in Rio de Janeiro
(14 clusters, 58,587 residents)

<table>
<thead>
<tr>
<th></th>
<th>Household Case Finding</th>
<th>Pamphlet Only</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB incidence during intervention</td>
<td>9.34/1000 py</td>
<td>6.04/1000 py</td>
<td>1.55 (1.10, 1.99)</td>
</tr>
</tbody>
</table>

Miller et al., IJTLD 2010
Should we consider campaigns to detect prevalent, untreated TB cases?

Active case finding at clinics – Open Access/Fast-track Community-based active case finding

ZAMSTAR Study Preliminary Results

- Baseline surveys of TB prevalence
  - 900/100,000 in Zambia
  - 2,200/100,000 in South Africa!
- Enhanced Case Finding
  - 24-33% of all TB cases in intervention communities detected by ECF
- Household evaluations
  - >2-5% of households have secondary TB case
  - ~50% contacts HIV tested
    - HIV prevalence high - ~50%
    - >50% HIV+ started on ART
FIND TB Questions

• How can we better detect \textit{M. tbc}?  
  – Better use of existing technologies  
    • LED microscopy  
    • Wider use of liquid culture  
  – New technologies  
    • Capilia, Hain/Inno-Lipa, Gene-Xpert, LAMP, LAM

• How can we improve the processes for laboratory diagnosis of TB?

Using lab results for patient care: a ‘no-brainer?’

Dowdy et al., PLoS One. 2008;3(12):e4057

TREAT TB

• Assure treatment completion for all patients  
• Identify optimal regimens for M/XDR TB  
• Determine risk factors for treatment failure and development of resistance  
  – Reinfection?  
  – Impact of suboptimal drugs (e.g., ofloxacin)  
• New drugs to improve therapy  
  – M/XDR TB treatment  
  – Treatment-shortening regimens
Effectiveness of DOT for TB/HIV Patients in Baltimore

- Observational cohort study of TB/HIV patients in Baltimore
- Patients in City DOT program or given self-administered therapy compared
  - DOT patients more likely to be IDU, uninsured
- Treatment success and survival significantly better in DOT patients
  - Successful Rx – 96% vs. 76% (p=.02)
  - Death – 15% vs. 43% (p=.01)

Alwood et al., AIDS 1994;8:1103-8


Chaulk et al., JAMA 1995;274:945-951

Improving treatment outcomes for TB/HIV and retreatment patients is essential

WHO Global TB Report, 2009
Outcomes of Treatment for MDR TB in the South African DOTS-Plus Program, 2002-2004

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HIV + (N=327)</th>
<th>HIV –/unknown (N=875)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful Rx</td>
<td>38.5%</td>
<td>49.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Failed</td>
<td>4.3%</td>
<td>11.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Defaulted</td>
<td>21.4%</td>
<td>22.6%</td>
<td>0.65</td>
</tr>
<tr>
<td>Died</td>
<td>35.8%</td>
<td>16.7%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Overall treatment success ~ 47%!

Farley et al., IJTLID, in press

New Drugs for TB

- Fluoroquinolones
  - Moxifloxacin
- Rifapentine
- TMC 207 (ATP synthase inhibitor)
  - In Phase 2 trials for MDR TB in Africa
- Nitroimidazopyrans
  - PA-824
  - OPC-67683
  - Phase 2 trial for MDR TB beginning in January 2008
- Diamines (SQ-109)
  - Phase 1 studies complete, awaiting Phase 2
- Oxazolidinones
- >12 other new compounds in development

Moxifloxacin vs. Ethambutol as 4th Drug in Initial Phase of TB Therapy:
Culture Conversion by Week

Marcus Conde et al., Lancet 2009; 373:1183-9
TMC 207 for MDR TB
Culture conversion at 2 months


Impact of Improving Case Finding and Treatment on Tuberculosis Control: A Mathematical Model

Dowdy and Chaisson, Bull WHO 2009: 87:296–304

PREVENT TB

- TB preventive therapy for high-risk individuals without active TB
- New drugs to shorten duration and treat latent MDR TB
- Contact evaluation and treatment
- Community-based preventive therapy
- Prevention of nosocomial transmission
- TB vaccine that actually works
WHO recommendations for INH preventive therapy in HIV+ people

• “INH preventive therapy should be provided as part of the package of care for people living with HIV/AIDS when active tuberculosis is safely excluded”

• Uptake of IPT is scandalously low

TB screening, treatment and IPT 2002-2008

By 2008, 1 out of 4 estimated HIV positive TB patients were identified and put on TB treatment.

TB Rates by ARV and INH Treatment Status in 2 Cohorts of South African Adults with HIV

<table>
<thead>
<tr>
<th>Exposure Category</th>
<th>Person-years</th>
<th>TB cases</th>
<th>Incidence rate (per 100 PYs) (95% CI)</th>
<th>Incidence rate ratio (95% CI)</th>
<th>Adjusted hazard ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>2815</td>
<td>200</td>
<td>7.1 (6.2-8.2)</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>HAART only</td>
<td>952</td>
<td>44</td>
<td>4.6 (3.4-6.2)</td>
<td>0.65 (0.46-0.91)</td>
<td>0.36 (0.25-0.51)</td>
</tr>
<tr>
<td>INH only</td>
<td>427</td>
<td>22</td>
<td>5.2 (3.4-7.8)</td>
<td>0.73 (0.44-1.13)</td>
<td>0.87 (0.55-1.36)</td>
</tr>
<tr>
<td>Both</td>
<td>93</td>
<td>1</td>
<td>1.1 (0.2-7.6)</td>
<td>0.15 (0.004-0.85)</td>
<td>0.11 (0.02-0.78)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>4287</td>
<td>267</td>
<td>6.2 (5.5-7.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, CD4, prior history of TB, urban/rural

Golub et al, AIDS 2009;23:631-6
Isoniazid Preventive Therapy and TB in the ALIVE Cohort of IDUs in Baltimore

<table>
<thead>
<tr>
<th>IPT experience</th>
<th># of TB cases</th>
<th>Person-years</th>
<th>Incidence Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IPT</td>
<td>20</td>
<td>24,585</td>
<td>0.81 (0.50-1.26)</td>
</tr>
<tr>
<td>Started IPT</td>
<td>2</td>
<td>4,185</td>
<td>0.48 (0.06-1.72)</td>
</tr>
<tr>
<td>IPT ≥ 30 days</td>
<td>1</td>
<td>3,358</td>
<td>0.29 (0.01-1.66)</td>
</tr>
<tr>
<td>Completed IPT</td>
<td>0</td>
<td>2,385</td>
<td>0 (0-1.55)</td>
</tr>
</tbody>
</table>

Golub et al., JAIDS 2008

Operational Studies of TB Prevention in HIV+ Patients and IDUs in Baltimore

- Voucher system and nurse education to improve PPD reading
- DOPT better than education and incentives to promote adherence to preventive Rx
- Use of the needle exchange van to provide TB screening and preventive services to injection drug users

Questions and issues about IPT

- Ruling out active TB
- Impact of HAART
- Drug interactions and toxicity
- INH resistance
- Adherence
- Implementation in health system
  - ART clinics, TB clinics, primary care clinics, private practices
Research for Reducing the Global Burden of TB

• Improved diagnostics (↑ case finding)
  – Better tests
  – Find prevalent cases earlier
• Improved therapy (↑ treatment success)
  – Shorter duration regimens to assure adherence
  – New drugs for MDR/XDR TB
  – Improved adherence and treatment completion
• Preventive therapy
• Infection control
• Community level interventions
• Health services research

“We will know we have performed enough research into controlling TB only when we have controlled it.”

“It ain’t over till it’s over.”
- Yogi Berra