Can Tuberculosis Be Eradicated?

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Eradication, elimination or control?

- **Eradication** – complete absence of the disease from the planet.

- **Elimination** – ending the disease as a public health problem.
  - Defined as TB incidence of <1 per million and TB deaths <1 per 10 million

- **Control** – making it a much smaller problem than it currently is.
Global Burden of Disease Estimates of Incidence, Prevalence and Mortality from HIV and TB

HIV

1.3 million deaths in 2012

Tuberculosis

1.4 million deaths in 2012

CJL Murray et al., Lancet, Sept 12, 2014
The World in 2 Acts
“Controlled” and Uncontrolled TB

Dye, et al., Ann Rev Publ Health 2013
Tools to Control of Tuberculosis
Why hasn’t TB already been eliminated?

• Global failure to apply biomedical tools effectively
  – Weaknesses in health systems
• Inadequacies of existing tools
  – Smear detection of cases ~50%
  – Adherence to regimens is poor
  – BCG vaccine does not prevent adult TB
• Changing epidemiological situation
  – HIV epidemic
  – MDR
• Global policies that lack understanding of best epidemiologic approaches
The Path to Elimination

Dye, et al., Ann Rev Publ Health 2013
Drivers of tuberculosis

• Population level drivers
  – Force of infection (transmission)
  – Crowding and mixing
  – Inadequate diagnostic/treatment services
  – (Drug resistance)

• Individual level drivers
  – HIV/immunosuppression
  – Diabetes
  – Smoking
  – Silicosis
  – Malnutrition
TB Case Detection: Mind the Gap

Global trends in case notification (black) and estimated TB incidence (green) rates, 1990–2012. Case notifications include new and relapse cases (all forms).

Every year 9 million people get sick with TB.

Reach the 3 million. Find. Treat. Cure TB. Help us to reach them.

World TB Day 24 March 2014

WHO Global Tuberculosis Report 2013
Tuberculosis in South African Adults Dying at Home without a Medical Diagnosis

- Adults dying at home, no diagnosis
- (18% excluded, known to have TB)
- Consent from family
- Bilateral axillary Tru-Cut biopsy
- Modified bronchoalveolar lavage

<table>
<thead>
<tr>
<th>Post-Mortem Diagnosis</th>
<th>N=85 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB on ≥1 lab test</td>
<td>29 (34.1)</td>
</tr>
<tr>
<td>TB on ≥2 lab tests</td>
<td>22 (25.9)</td>
</tr>
<tr>
<td>Biopsy</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>16/29 (55.2)</td>
</tr>
<tr>
<td>AFB positive (ZN)</td>
<td>13/16 (81.3)</td>
</tr>
<tr>
<td>Xpert</td>
<td>13/29 (44.8)</td>
</tr>
<tr>
<td>MGIT</td>
<td>18/29 (62.1)</td>
</tr>
<tr>
<td>BAL</td>
<td></td>
</tr>
<tr>
<td>AFB+ (Auramine)</td>
<td>9/29 (31.0)</td>
</tr>
<tr>
<td>Xpert</td>
<td>20/29 (69.0)</td>
</tr>
<tr>
<td>MGIT</td>
<td>19/29 (65.5)</td>
</tr>
</tbody>
</table>

Martinson et al., CROI 2013
Estimated HIV prevalence among new TB cases, 2012
TB Incidence and Prevalence of Diabetes, 2010 and 2030

Dooley and Chaisson, Lancet Infect Dis, 2009; 9: 737–46
Global Prevalence of Tobacco Smoking by Men

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

Hanrahan et al., AIDS 2010
Population-level Control Strategies for TB

Latent TB
(Global ~ 2 billion)

Active TB
(Global ~ 9 million)

Uninfected/Susceptible

Treatment of TB

Vaccination

Primary TB
Population-level Control Strategies for TB

Latent TB
(Global ~ 2 billion)

Active TB
(Global ~ 9 million)

Uninfected/Susceptible

Treatment of TB

Vaccination

TB Preventive Rx

Primary TB
Modeled approaches to reaching TB elimination

Dye, et al., Ann Rev Publ Health 2013
Control of TB: Historical Precedents

• Remembering how it was done!
THE MONUMENTAL CITY.

GEORGE PAPANICOLA
BORN 1907
DIED 1939
REST IN PEACE

BALTIMORE HAS HIGHEST DEATH RATE
FROM TUBERCULOSIS
OF TEN LARGEST
CITIES.

SLUMS

VOTE FOR BROWNLEY CIRCUS.
Impact of DOT and Rigorous TB Control in Baltimore


Keys to success in reducing TB in Baltimore

- Essentially complete case-finding
- Community-based directly observed therapy
- High rates of contact evaluation
- High rates of completion of IPT for contacts
- Outreach program to drug treatment centers and injection drug users
- 20 years later, Baltimore’s rate = national rate (~4-5 cases/100,000), 90% reduction
  - 80+% in foreign-born individuals
DOTS Results in TB Incidence Decline

DOTS Results in TB Incidence Decline: The Case of Peru

7-fold increase in case-finding

Pulmonary TB Falling at 6%/year

George W. Comstock and the Conquest of Tuberculosis in Alaskan Eskimos
INH Preventive Therapy in an Undeveloped Area: The Bethel Study

• the Bethel [trial] was designed to test the prophylactic usefulness of isoniazid among entire communities in an undeveloped area with a serious tuberculosis problem.”

• 28 villages, ~7000 residents

• Pertinent features of the Bethel area in 1957:
  • High rate of poverty
  • 2% prevalence of active TB
  • Annual risk of TB infection ~8 percent
  • Average household size 6, 2/3rd of homes 1 room
  • “a climate that discourages ventilation”

TB Rates in the 6 Years After Treatment with INH or Placebo in the Bethel Trial

Cumulative reduction 5.1% → 2.1% = 60%

Tuberculosis in Alaska, 1970: The Continued Decline of the Tuberculosis Epidemic

Prevalence of Positive Skin Test Reactions in Children, 1949-1970

Kaplan GJ, Fraser RI, Comstock GW. ARRD 1972,105:920
Interventions and impact: Bethel 1950s & 60s
Annual Risk of Infection (%) and incidence rates per 100,000

Intensive Case Finding

INH RCT: 42% pop INH 12mos
INH all residents

ARI
TB incidence
A Platform for Controlling Global Tuberculosis

• **FIND** the TB that is there
  – Passive case detection is not sufficient
  – Intensified (active case finding essential)
  – Improved diagnostic technologies

• **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
  – Control susceptibility (antiretrovirals, diabetes control)
  – New vaccine
Preventive Interventions in TB

Prevent Infection
Reduce Susceptibility
Chemoprophylaxis

TB and HIV vaccines obvious additional strategies, but not currently available
The March of Diagnostic Technology

- LED Microscopy*
- Line probe assays for MDR
- Urine LAM dipstick**
- GeneXpert TB/RIF*

*BSL-3 not required
** Point of care test
Campaigns to detect prevalent, untreated TB cases?
Rocinha *favela*, Rio de Janeiro
A cluster-randomized trial of door-to-door active case finding for TB in Rio de Janeiro (14 neighborhoods, 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
TB in Rocinha before and after intervention – 16% decline in incidence

DETECTB Community-Based TB Case Finding in Harare, Zimbabwe

- Multiple rounds of ACF in community
  - Door to door vs mobile vans
- Findings after 6 rounds:
  - 59% reduction in HIV- TB prevalence
  - 22% reduction in HIV+ TB prevalence

Corbett et al. Lancet 2010
Community-Randomized Trial of Household Contact Evaluation and Preventive Therapy (DOTS-A) vs DOTS in Rio de Janeiro

TB Incidence/100,000

Year

15% difference

p=0.04, 1999 vs. 2004

Cavalcante et al., Int J TB Lung Dis 2010:14:203-9
Cluster-randomized trial of TB control interventions

TB/HIV at the clinic: 257,698
Enhanced Case Finding: 148,090

Household: 257,729
ECF & Household: 299,138

H. Ayles, et al., Lancet, 2013
Impact of Household Contact Evaluations for New TB Patients or Community Active TB Case (ECF) Finding in High Burden Areas

Household Evaluations: Impact on TB prevalence

Household Evaluations: impact on transmission in children

ECF impact on TB prevalence

ECF impact on transmission in children

Risk ratios (for prevalence) and Rate ratios (for transmission)

H. Ayles, et al., Lancet, 2013
Impact of Improving Case Finding and Treatment on Tuberculosis Control: A Mathematical Model

Dowdy and Chaisson, Bull WHO 2009, 87:296–304
Preventive Interventions in TB
Impact of ART on TB Incidence in HIV+ People

<table>
<thead>
<tr>
<th></th>
<th>ART</th>
<th>Control</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TB cases</td>
<td>PY at risk</td>
<td>TB cases</td>
</tr>
<tr>
<td>All baseline CD4 counts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Badri (2002) *</td>
<td>9</td>
<td>375.1</td>
<td>82</td>
</tr>
<tr>
<td>Cohen (2011) *, †</td>
<td>17</td>
<td>1661.9</td>
<td>33</td>
</tr>
<tr>
<td>Golub (2007)</td>
<td>221</td>
<td>11627</td>
<td>155</td>
</tr>
<tr>
<td>Golub (2009)</td>
<td>44</td>
<td>952</td>
<td>200</td>
</tr>
<tr>
<td>Jerene (2006)</td>
<td>6</td>
<td>162.6</td>
<td>9</td>
</tr>
<tr>
<td>Lannoy (2008)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Miranda (2007)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Samandari (2011) †</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Santoro-Lopes (2002)</td>
<td>1</td>
<td>-</td>
<td>42</td>
</tr>
<tr>
<td>Severe (2010) †</td>
<td>18</td>
<td>-</td>
<td>36</td>
</tr>
<tr>
<td>Zhou (2009)</td>
<td>57</td>
<td>5186</td>
<td>40</td>
</tr>
<tr>
<td>All studies</td>
<td></td>
<td></td>
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</table>

Effect: Z = 9.19, p < 0.001; Heterogeneity: $I^2 = 31\% \ (22\% - 44\%) \ , \ p = 0.151$

Reduce Susceptibility

TB rates in relation to ART scale up in rural Malawi

Zachariah, et al., 2011, Int J Tuberc Lung Dis
Preventive Interventions in TB

Prevent Infection

Reduce Susceptibility

Chemoprophylaxis
The THRio Study: Implementation of TB Screening and INH Preventive Therapy in HIV Clinics

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases</th>
<th>Crude HR (95% CI)</th>
<th>p-value</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent To Treat TB</td>
<td>475</td>
<td>0.87 (0.69-1.10)</td>
<td>0.24</td>
<td>0.73 (0.54-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>TB or Death</td>
<td>1313</td>
<td>0.76 (0.66-0.87)</td>
<td>&lt;0.001</td>
<td>0.69 (0.57-0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Per-protocol (Stayers) TB</td>
<td>399</td>
<td>0.43 (0.31-0.58)</td>
<td>&lt;0.001</td>
<td>0.42 (0.31-0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TB or Death</td>
<td>1055</td>
<td>0.50 (0.41-0.60)</td>
<td>&lt;0.001</td>
<td>0.50 (0.41-0.60)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Stayers – per-protocol - Among those remaining in clinic contact (Patients censored after one year without a clinic contact)

Durovni et al., Lancet Infect Dis. 2013;10:852-8
Long term efficacy of IPT in HIV-infected persons in a medium TB burden setting: Rio de Janeiro

(Golub, CID, 2014, In press)
5-Year Impact of IPT for HIV+ Patients in Rio de Janeiro on Population TB Incidence

(Annual rate of IPT delivery: 20%/year to fit study data)

Population TB/HIV Mortality, per 100,000/yr

Population TB/HIV Incidence, per 100,000/yr

Year Since Initial Roll-Out

No IPT
IPT

IPT: 15.6% reduction
IPT: 14.3% reduction

6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial

Lancet. 2011;377:1588-1598.
Thibela TB: durability of IPT effect at individual level

<table>
<thead>
<tr>
<th>Interval</th>
<th>Arm</th>
<th>Adjusted IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9mth (IPT period)</td>
<td>IPT</td>
<td>0.37 (0.19-0.72)</td>
</tr>
<tr>
<td>9-18mths</td>
<td>IPT</td>
<td>0.94 (0.57-1.54)</td>
</tr>
<tr>
<td>&gt;18mths</td>
<td>IPT</td>
<td>0.79 (0.54-1.17)</td>
</tr>
</tbody>
</table>

Churchyard et al., NEJM 2014
Thibela TB: what will it take to control TB in gold mines?

Mining population - Scale up over 1 year

- No intervention
- ART
- Doing the basics better
- Improved diagnostics
- Treat. latent MTB in HIV+s
- Treat. latent MTB in HIV-s

Reid, et al., Int J. Tuberc Lung Dis. 2014. In press
Short-course, sterilizing regimen for latent TB: Rifapentine/INH x 12 weekly doses vs INH x 9 mos. Cumulative TB Rates

Log-rank P-value: 0.06
Preventive Interventions in TB

Prevent Infection

Reduce Susceptibility

Chemoprophylaxis

TB and HIV vaccines urgently needed
Can TB be eliminated? Probably not by 2050.

Can TB be controlled? Yes, with investment in epidemiologically sound strategies and tools.
Strategies and tools to control TB

- Improved diagnostics (↑ case finding, ↓ transmission)
  - Better tests
  - Campaigns to find prevalent cases (e.g., contacts)
- Improved therapy (↑ treatment completion)
  - Shorter duration regimens to assure adherence
  - New drugs for MDR/XDR TB
- Prevention
  - INH or novel preventive therapy
  - Reduction of susceptibility (ART, diabetes, smoking)
  - Effective vaccine
- Combination of approaches essential
Tuberculosis:
The Nemean Lion
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