TB Epidemiology

Richard E. Chaisson, MD
Johns Hopkins University
Center for Tuberculosis Research
Richard E. Chaisson, MD

- Professor of medicine, epidemiology, and international health
- Director of the Johns Hopkins University Center for Tuberculosis Research
- Co-founded the Johns Hopkins HIV Clinic cohort
- Interests focus on tuberculosis and HIV infection, including global epidemiology and control, prevention, clinical trials, and public health interventions
- Principal investigator of the Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE)
Section A

General Epidemiology and Natural History
“There are two kinds of statistics. The kind you look up and the kind you make up.”

— Archie Goodwin in Rex Stout’s Nero Wolfe mystery *Death of a Doxy*, 1966
About 9 million new cases in 2004
  - Sixteen million prevalent cases
  - Ninety-eight percent in developing countries
More than 10% increase since 1997
Increasing rates in Africa and Eastern Europe
  - Decreasing elsewhere
1.9 million deaths
  - Leading cause of death in people with HIV
Progress in case detection, but >50% still not diagnosed and treated!
Growth of TB in Africa and Eastern Europe

Growth of TB in Africa and Eastern Europe

- Eastern Europe
- Africa - low HIV
- Africa - high HIV

Year


Standardized Notification Rate

0 100 200 300
Estimated Number of TB Cases by Country, 2004

Estimated number of new cases (all forms)
- 0–999
- 1,000–9,999
- 10,000–99,999
- 100,000–999,999
- >1,000,000–999,999
- >1,000,000,000
- No estimate
Twenty-Two High-Burden Countries"
Reported TB Cases, United States, 1982–2003

Reported TB Cases in the United States
1982 - 2003

Year

Number of Cases

28000
24000
20000
16000
12000
TB Case Rates* by Age Group and Sex, United States, 2003

*Cases per 100,000
Cohort Analysis of Effect of Age on TB Incidence

TB Case Rates* by Race/Ethnicity

United States, 1993-2003

Cases per 100,000

Year

'93 '94 '95 '96 '97 '98 '99 '00 '01 '02 '03

*Cases per 100,000
Number of TB Cases in U.S.-Born Versus Foreign-Born Persons
United States, 1993-2003
Length of U.S. Residence Prior to TB Diagnosis, U.S.

Length of U.S. Residence Prior to TB Diagnosis, United States, 2003

<table>
<thead>
<tr>
<th></th>
<th>&lt;1 Year</th>
<th>1-4 Years</th>
<th>≥5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philippines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viet Nam</td>
<td></td>
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</tr>
</tbody>
</table>
Epidemiology of TB Fundamentals

- Reservoir of infection → humans (cattle)
  - Virtually all transmission is person to person
- Two-stage process
  - Initial infection with *M. tuberculosis*
  - Progression from infection to disease
Epidemiology of TB Fundamentals

- Risks for initial infection
  - Source case factors
  - Environmental factors
  - ? Recipient factors
- Risks for disease once infected
  - Inoculum size
  - Cellular immunity
  - Body habitus
  - Genetics
Risk of Infection and Disease among Exposed Individuals

Exposure (close contact)

No infection 70%

Infection ~30%

Risk factors
- Close contact, BR>HH>Casual
- Duration of contact
- Severity of disease, cough, cavities
TB Infection in Children by Type of Contact

Tuberculous Infection Among Children by Type of Contact and Bacteriologic Status of Index Case, British Columbia and Saskatchewan, 1966-1971

Adapted by CTLT from Grzybowski S, et al. Bull Int Union Tuberc 1975;50;90-106
TB Infection among Inflight Personnel

Prevalence of Tuberculous Infection Among Inflight Personnel in Contact with a Tuberculous Staff Member

Risk of Infection and Disease among Exposed Individuals

Exposure (Close Contact)

- No Infection (70%)
- Infection (~30%)

Infection

- Containment (90-95%)
- Early Progression
  - Recent TB ≤2 Yrs (5-10%)

Containment

- Continued Containment (85-90%)
- Late Progression-Reactivation TB (5%)
HIV and Risk of TB Disease among Infected Individuals

Exposure (Close Contact)

- No Infection (70%)
- Infection (~30%)

Infection

- Containment (60-95%)
- Early Progression (HIV Neg., 2-5%)
  (HIV Pos., 40+%) (HIV Pos., 40+%)

Containment

- Continued Containment (?-90%)
- Late Progression (HIV Neg., 5%)
  (HIV Pos., 3-14% per year)
Diagnostic Standards for Tuberculosis

<table>
<thead>
<tr>
<th>Latent TB</th>
<th>Active TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin skin test</td>
<td>CXR</td>
</tr>
<tr>
<td>– PPD-S</td>
<td>Sputum smear</td>
</tr>
<tr>
<td>– Cutpoints for positive</td>
<td>– Sensitivity 50%</td>
</tr>
<tr>
<td>– Nonspecific</td>
<td>Sputum culture</td>
</tr>
<tr>
<td>Interferon-gamma assays</td>
<td>Clinical criteria</td>
</tr>
</tbody>
</table>
### Quantifieron for Latent and Active TB Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>TST</th>
<th>Quantifieron PPD</th>
<th>Quantifieron Gold</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cx+ TB pts</td>
<td>65.7% 50/76 ≥5 mm</td>
<td>82.1% 92/112+</td>
<td>89.0% 105/118+</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG-vaccinated new nurses</td>
<td>35.4% 40/113 &lt;10 mm</td>
<td>56.0% 108/192-</td>
<td>98.1% 213/216-</td>
</tr>
</tbody>
</table>

Comparison of Elispot and TST in School Contacts of Infectious TB Cases

<table>
<thead>
<tr>
<th>Group</th>
<th>ELISPOT+</th>
<th>TST+</th>
<th>ELISPOT-</th>
<th>TST-</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Class 9C)</td>
<td>100%</td>
<td>90%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>T+</td>
<td>18</td>
<td>2</td>
<td>E+</td>
<td>0</td>
</tr>
<tr>
<td>E-</td>
<td>0</td>
<td>0</td>
<td>E-</td>
<td>0</td>
</tr>
<tr>
<td>B (Classes 9R, 9O, 9W, 9N)</td>
<td>53%</td>
<td>51%</td>
<td>47%</td>
<td>49%</td>
</tr>
<tr>
<td>T+</td>
<td>36</td>
<td>7</td>
<td>E+</td>
<td>5</td>
</tr>
<tr>
<td>E-</td>
<td>5</td>
<td>33</td>
<td>E-</td>
<td>6</td>
</tr>
<tr>
<td>C (Classes 9H, 9f, 9L, 9S)</td>
<td>38%</td>
<td>40%</td>
<td>62%</td>
<td>60%</td>
</tr>
<tr>
<td>T+</td>
<td>13</td>
<td>5</td>
<td>E+</td>
<td>6</td>
</tr>
<tr>
<td>E-</td>
<td>6</td>
<td>23</td>
<td>E-</td>
<td>5</td>
</tr>
<tr>
<td>D (Years 7, 8 and 10)</td>
<td>17%</td>
<td>20%</td>
<td>83%</td>
<td>80%</td>
</tr>
<tr>
<td>T+</td>
<td>53</td>
<td>13</td>
<td>E+</td>
<td>23</td>
</tr>
<tr>
<td>E-</td>
<td>0</td>
<td>0</td>
<td>E-</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted by CTLT from Ewer et al., Lancet 2003, 361:1168
Response to ELISPOT or TST by BCG Vaccination Status

Response to ELISPOT or TST by BCG vaccination status in a school TB outbreak

<table>
<thead>
<tr>
<th></th>
<th>Vaccinated (n = 467)</th>
<th>Unvaccinated (n = 68)</th>
<th>p for vaccinated vs. unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISPOT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>131 (28.1%)</td>
<td>16 (23.5%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Negative</td>
<td>336 (71.9%)</td>
<td>52 (76.5%)</td>
<td></td>
</tr>
<tr>
<td>Heaf grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>52 (11.1%)</td>
<td>10 (14.7%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>81 (17.6%)</td>
<td>2 (2.9%)</td>
<td>0.002*</td>
</tr>
<tr>
<td>2</td>
<td>110 (23.6%)</td>
<td>10 (14.7%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>116 (24.8%)</td>
<td>13 (19.1%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>108 (23.1%)</td>
<td>33 (48.5%)</td>
<td></td>
</tr>
</tbody>
</table>

*χ² test for trend across all five Heaf grades

Section B

Epidemiologic Basis for TB Control
Strategies for Control of Tuberculosis

- Detection and treatment of cases
- Treatment of latent infection
- Vaccination
Definitions of Tuberculosis Control

- Diagnosis of 70% of all cases, with cure rates of 85% (WHO/IUATLD)
- $R_0 < 1$
  - Less than one secondary case for each new case (Frost, 1937, Anderson and May, 1982)
- The incidence of tuberculosis goes down
Control Strategies for TB

- **Latent TB**
  - TB Preventive Rx

- **Active TB**
  - Treatment of TB, Vaccination
  - TB Preventive Rx

- **Uninfected/Susceptible**

- **Primary TB**
Use Dots More Widely
DOT vs. DOTS

- **Directly Observed Therapy**
  - Supervision of all doses of TB medication by a health team member

- **Directly Observed Therapy, Short Course**
  - WHO policy for TB control, with programmatic imperatives to strengthen TB control efforts
What Is DOTS?

- Governmental commitment to TB control
- System for registration and follow-up of TB cases
- Reliable supply of TB drugs
- Microbiologic confirmation of TB diagnosis
- Supervision of at least the initial phase of TB therapy
Treatment Outcomes by WHO Region

DOTS vs. Non-DOTS Treatment Outcomes, 1999 Cohort

AFR  AMR  EMR  EUR  SEAR  WPR

Treated Successfully
Not Treated Successfully
Not Evaluated

Adapted by CTLT from WHO
DOTS Results in TB Incidence Decline: The Case of Peru

- Pulmonary TB Cases per 100,000
- Year

DOTS Results in TB Incidence Decline

- Case Finding
- Pulmonary TB Falling at 6%/year
AFB Smears Performed by the TB Program, Peru, 1987-1997

AFB Smears (Thousands)

Year


Adapted by CTLT from Tuberculosis en el Peru, Informe 1997, Ministerio de Salud, Lima, 1998
Full DOTS Implementation in Vietnam

TB in Vietnam Under Full DOTS Implementation

Adapted by CTLT from Global Tuberculosis Control, WHO Report 2004
What Can DOT(S) Do?

- Increase treatment completion rates
- Reduce the emergence of drug-resistant TB
- Improve cost-effectiveness of TB control
- In conjunction with other interventions, reduce TB incidence
Section C

Challenges in TB Control
Challenges in the Control of Tuberculosis

- HIV epidemic
- MDR tuberculosis
- Health system weaknesses and lack of political will
  - Poor infrastructure and lack of support
  - Weak organization of primary health services
  - Private practitioners
  - Prisons
Tuberculosis and HIV

The prevalence of HIV in TB patients as measured in national surveys (blue dots) and sub national surveys (red dots; data reported to WHO), plotted against the prevalence of HIV in adults (data from UNAIDS).
Rising TB incidence in setting of falling HIV prevalence in Uganda

UNAIDS Fact Sheet, WHO Global TB Report
TB in Botswana: Pre- and Post-DOTS, HIV

Adapted by CTLT from Global Tuberculosis Control, WHO Report 2004

Reported TB Cases, United States, 1979-1999

Year

Cases


Increase in TB Funding
(About 10-Fold)

Introduction of HAART
Major Challenges in HIV-Related TB

- Case detection
  - High prevalence of active TB in community
    - 3% of HIV+ pregnant women
    - 8% of HIV VCT clients
  - Negative smears more common
- Treatment of TB and HIV
  - Drug interactions
  - Drug toxicity and adverse reactions
- Prevention
  - Use of preventive therapy

- Primary drug resistance—median 10.7%
  - Primary MDR—median 1%
- Acquired drug resistance—median 23%
  - Acquired MDR—median 9.3%
- MDR “hot spots” widespread

Primary MDR TB, United States, 1993–2002

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
41% of hospitalized patients in rural KwaZulu-Natal had MDR-TB

25% of these had XDR-TB
- Resistant to first- and second-line TB drugs

All HIV+

52 of 53 died

Median survival: 16 days

Global Approaches to MDR TB Control

- Expansion and strengthening of DOTS
  - Prevent creation of MDR cases through mismanagement
  - Assure access to drug supply
- DOTS-Plus
  - Second-line drugs for TB in setting of DOTS
  - Green Light Committee of WHO
    - Approves proposals for national DOTS+ programs
- New drug development
  - Global Alliance for TB Drug Development
**BCG* for Prevention of TB**

- Live attenuated vaccine derived from *M. bovis* early 1900s by Calmette and Guérin
- Most widely used vaccine in the world
- Efficacy shown in clinical trials in 1930s–1950s
- Recent trials show lack of benefit
- Genetic evidence of attenuation of strain over years of laboratory passage
- New vaccines in development, but will need to be compared with BCG

*Bacillus of Calmette and Guérin (BCG)*
## Meta-Analysis of BCG Effectiveness in 26 Studies

<table>
<thead>
<tr>
<th>Outcome/design</th>
<th>Relative odds or risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB prevention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical trials</td>
<td>0.49</td>
<td>0.34–0.70</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>0.50</td>
<td>0.39–0.64</td>
</tr>
<tr>
<td>Prevention of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical trials</td>
<td>0.29</td>
<td>0.16–0.53</td>
</tr>
</tbody>
</table>

Relationship to Lab Passage to BCG Efficacy

Relationship of Lab Passage to BCG Efficacy

Adapted by CTLT from Behr and Small, Nature 1997, 389: 133.
Strategies for Control of Tuberculosis: Limitations

- Detection and treatment of cases
  - Poor diagnostic capabilities
  - Poor compliance with treatment
  - Emergence of drug resistance
  - HIV epidemic
- Treatment of latent infection
  - Resources for screening and treatment
- Vaccination
  - Current vaccine doesn’t prevent disease or transmission
Imperatives for Controlling TB in the Coming Years

- Expand DOTS
- Increase case finding
- Evaluate and treat contacts of cases
- Treat high-risk patients with latent TB
- Decrease HIV prevalence
- Provide effective treatment for HIV
- Develop effective HIV and TB vaccines