The Area of the “Magic Mountain”

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Gumbo lab
History of TB
History of TB

• Historically known by a variety of names, including:
  – Consumption
  – Wasting disease
  – White plague
  – Sanatorium was part of treatment
  – Those who could not afford died at home

• TB was a death sentence for many
1865: Jean-Antoine Villemin proved TB is contagious

1884: First TB sanatorium established in U.S.

1882: Robert Koch discovers M. tuberculosis

1943: Streptomycin (SM) a drug used to treat TB is discovered

1943-1952: Two more drugs are discovered to treat TB: INH and PAS

1993: TB cases decline due to increased funding and enhanced TB control efforts

Mid-1970s: Most TB sanatoriums in U.S. closed

Mid-1980s: Unexpected rise in TB cases
“It seems likely that the tubercle is surrounded with a special wall of unusual properties, and that the penetration of a dye through this wall can occur when alkali, aniline, or similar substance is present.”

Robert Koch
Nobel Prize-Medicine (1905)
Epidemiology of TB
Significance for Global Health: TB

• TB is a disease of poverty; affecting mostly young adults in their most productive years. The vast majority of TB deaths are in the developing world, with more than half of all deaths occurring in Asia.

• More than 2 billion people, equal to 1/3 of the world population, are latently infected with TB (LTBI)
  – 1 in 10 people with LTBI bacilli will become sick with active TB in their lifetime; those with HIV are at much greater risk
  – Africa accounted for 85% of estimated global HIV positive TB cases in 2006.

• 1.7 million people died from TB in 2006 including 231,000 people with HIV. This is equal to 4,500 deaths a day.
The global population structure and geographical distribution of M. tuberculosis

Gagneux S. et.al. PNAS 2006;103:2869-2873
U.S. TB Resurgence
1986 - 1992

20% increase

Reported TB Cases, U.S., 1982-2008
Reported Tuberculosis Cases Among Blacks and Whites, United States, 1980 - 1992

US Centers for Disease Control and Prevention
Tuberculosis Statistics in the United States, 1992
TB Transmission
Types of Mycobacteria

- *M. tuberculosis* causes most TB cases in U.S.

- Mycobacteria that cause TB:
  - *M. tuberculosis*
  - *M. bovis*
  - *M. africanum*
  - *M. microti*
  - *M. canetti*

- Mycobacteria that do not cause TB
  - e.g., *M. avium complex*
TB Transmission

• TB is spread person to person through the air via droplet nuclei

• *M. tuberculosis* may be expelled when an infectious person:
  – Coughs
  – Sneezes
  – Speaks
  – Sings

• Transmission occurs when another person inhales droplet nuclei
TB Transmission

Dots in air represent droplet nuclei containing \textit{M. tuberculosis}
TB Transmission

• Probability that TB will be transmitted depends on:
  – Infectiousness of person with TB disease
  – Environment in which exposure occurred
  – Length of exposure
  – Virulence (strength) of the tubercle bacilli

• The best way to stop transmission is to:
  – Isolate infectious persons
  – Provide effective treatment to infectious persons as soon as possible
Percentage of Secondary Cases Among Tuberculin-Positive Contacts, by Type of Source Case, Canada, 1966 - 1971

Drug-Resistant TB

- Caused by *M. tuberculosis* organisms resistant to at least one TB treatment drug
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)
- Resistant means drugs can no longer kill the bacteria
## Drug-Resistant TB

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-resistant</td>
<td>Resistant to any one TB treatment drug</td>
</tr>
<tr>
<td>Poly-resistant</td>
<td>Resistant to at least any 2 TB drugs (but not both isoniazid and rifampin)</td>
</tr>
<tr>
<td>Multidrug resistant</td>
<td>Resistant to at least isoniazid and rifampin, the 2 best first-line TB treatment drugs</td>
</tr>
<tr>
<td>Extensively drug resistant</td>
<td>Resistant to isoniazid and rifampin, PLUS resistant to any fluoroquinolone AND at least 1 of the 3 injectable second-line drugs (e.g., amikacin, kanamycin, or capreomycin)</td>
</tr>
</tbody>
</table>
TB Pathogenesis

Pathogenesis is defined as how an infection or disease develops in the body.
Sites of TB Disease

Bacilli may reach any part of the body, but common sites include:

- Brain
- Lymph node
- Pleura
- Lung
- Spine
- Kidney
- Bone
- Larynx
## Sites of TB Disease (2)

<table>
<thead>
<tr>
<th>Locations</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary TB</strong></td>
<td>Lungs</td>
</tr>
</tbody>
</table>
| **Extrapulmonary TB** | Places other than lungs such as:  
- Larynx  
- Lymph nodes  
- Pleura  
- Brain  
- Kidneys  
- Bones and joints | Found more often in:  
- HIV-infected or other immunosuppressed persons  
- Young children |
| **Miliary TB** | Carried to all parts of body, through bloodstream | Rare |
TB Pathogenesis

TB Disease

• Develops when immune system cannot keep tubercle bacilli under control

  – May develop very soon after infection or many years after infection

• About 10% of all people with normal immune systems who have LTBI will develop TB disease at some point in their lives

• People with TB disease are often infectious
TB Pathogenesis (2)
Latent TB Infection (LTBI)

• Occurs when tubercle bacilli are in the body, but the immune system is keeping them under control

• Detected by the Mantoux tuberculin skin test (TST) or by blood tests such as interferon-gamma release assays (IGRAs) which include:
  - QuantiFERON®-TB Gold test (QFT-G)
  - QuantiFERON®-TB Gold In-Tube (QFT-GIT)
  - T-Spot®.TB test (T-SPOT)

• People with LTBI are NOT infectious
## LTBI vs. TB Disease

<table>
<thead>
<tr>
<th>Latent TB Infection (LTBI)</th>
<th>TB Disease (in the lungs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inactive</strong>, contained tubercle bacilli in the body</td>
<td><strong>Active</strong>, multiplying tubercle bacilli in the body</td>
</tr>
<tr>
<td>TST or blood test results usually positive</td>
<td>TST or blood test results usually positive</td>
</tr>
<tr>
<td>Chest x-ray usually <strong>normal</strong></td>
<td>Chest x-ray usually <strong>abnormal</strong></td>
</tr>
<tr>
<td>Sputum smears and cultures negative</td>
<td>Sputum smears and cultures may be <strong>positive</strong></td>
</tr>
<tr>
<td>No symptoms</td>
<td><strong>Symptoms</strong> such as cough, fever, weight loss</td>
</tr>
<tr>
<td>Not infectious</td>
<td><strong>Often infectious</strong> before treatment</td>
</tr>
<tr>
<td>Not a case of TB</td>
<td><strong>A case</strong> of TB</td>
</tr>
</tbody>
</table>
From Infection to Disease

- Risk of developing disease
  - Multiple factors related to interaction between pathogen and human host
- Lifetime Risk:
  - About one in ten (average)
- The risk is greater initially
  - 5% within initial 2-5 years
  - 5% during the rest of lifetime
Selected Risk Factors for Tuberculosis Given that Tuberculous Infection has Occurred

- Referent: Infection >7 yr past
- Infection <1 yr past
- HIV infection
- Fibrotic lesions
- Silicosis
- Carcinoma of head or neck
- Hemophilia
- Immunosuppressive treatment
- Hemodialysis
- Underweight
- Diabetes
- Smoking, heavy
- Gastrectomy
- Jejunoileal bypass
- Infecting dose

Relative risk / odds (log scale)
Clinical Presentation
Treatment and Public Health Control Strategies
A Model for the Epidemiology of Tuberculosis

Risk factors -> Exposure
Risk factors -> Subclinical infection
Risk factors -> Infectious tuberculosis
Risk factors -> Non-infectious tuberculosis
Risk factors -> Death

Rieder HL. Infection 1995;23:1-4
Correlation Between Extent of HIV-Induced Immuno-Suppression and Clinical Manifestation of Tuberculosis

![Graph showing correlation between duration of HIV infection and median CD4 cell count.](image)

- Pulmonary tuberculosis
- Lymphatic, serous tuberculosis
- Tuberculous meningitis
- Disseminated tuberculosis

Diagnostic tools

- Traditional standard
  - Tuberculin test

- Newer interferon-
y-release test
  - T Spot-TB® (Oxford Immunotec)
  - QuantiFERON®-TB Gold (Cellestis)
STOP TB Strategy

• **GLOBAL (DOTS)**
  – MDG Targets: halt and reverse TB incidence by 2015
    • Strategy: Directly Observed Treatments Short-course (DOTS) has 5 elements: i) political commitment with increased and sustained financing ii) case detection through quality-assured bacteriology iii) standardized treatment with supervision and patient support iv) an effective drug supply and management system v) monitoring and evaluation system

• **US (Targeted testing and treating LTBI)**
  – Target TB Elimination by 2010: *1 case per million pop.*
    • 5 areas of decisive action: 1) maintain TB control, 2) accelerate decline, 3) develop new tools, 4) increase global efforts, 5) mobilize and sustain public support
      – Hopefully target can be achieved by 2035 or 2107 at the most
The result of neglecting TB

- Tuberculosis cases increased from 1988 - 1992
- Outbreaks of multidrug resistant (i.e., often incurable) tuberculosis
- This resurgence of tuberculosis cost more than $1 billion in NYC alone

US Role in Global TB Control

- Should expand and strengthen role
- Contributions include financial, technical, human resources and research
- Should be coordinated with other international agencies (e.g., Stop TB) initiative
- USAID/CDC/NIH should publish plan
• An “attenuated” strain of *Mycobacteria* that does not cause disease but can stimulate the immune response

• Newer attenuated strain vaccines and recombinant versions of BCG are now in Phase II and Phase III clinical trials