Tuberculosis
Pathophysiology and Transmission

Paul K. Drain, MD, MPH, FACP
Assistant Professor
Depts. of Global Health, Medicine (Infectious Diseases), Epidemiology
University of Washington

June 16, 2016
Tuberculosis Clinical Intensive
DISCLOSURE

The following planner/speaker has reported a relevant financial relationship with a commercial interest:

- None.
Outline

• Historical Context of Tuberculosis (TB)
• *Mycobacterium* *spp.* and *M. tuberculosis*
• TB Pathophysiology
• TB Transmission
• Summary
Who identified *M. tuberculosis* as the bacterium that causes tuberculosis disease, known at the time a “Consumption”?

1. Louis Pasteur
2. Robert Koch
3. Author Conan Doyle
4. Albert Calmette and Camille Guérin
Influence of TB on Medicine

1821 – Laennec invented the stethoscope and described its utility in diagnosing TB.

1882 – Koch presented the TB bacilli as the infectious agent of TB on March 24.

1895 – Roentgen invented the chest X-ray and used it to track TB progression.

1890s – Franz Ziehl and Friedrich Neelson developed the acid-fast stain for TB.

1908 – Mantoux developed the tuberculin skin test for latent TB.

1936 – Solid culture was introduced to grow and identify TB.

Robert Koch, Nobel Prize in 1905.
In 2010, ~53% of clinics in Africa had access to Mycobacterial culture*

Kenya
TB incidence rate
1980-2007
Estimated TB incidence rates, 2014

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.


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Percentage of new TB cases with MDR-TB

Figures are based on the most recent year for which data have been reported, which varies among countries.
Current TB Epidemic

• Latent TB Infection
  – 1/3 of the world’s population

• Active TB Disease
  – 9.6 million people fell ill with TB
    • 79% in sub-Saharan Africa
    • 1.2 million (13%) in HIV-infected
    • 480,000 MDR-TB cases worldwide (among notified cases)
    • ~50,000 XDR-TB cases worldwide; reported by 105 countries
  – People co-infected with TB/HIV are 21-34 times more likely to develop active TB disease than people without HIV

• TB Mortality
  – 1.5 million annual TB deaths
    • 400,000 (31%) were HIV-infected
  – Death rate has decreased 47% from 1990 level
  – TB causes more deaths than any other infection, including HIV/AIDS

History of TB Medications

- **1943**: Streptomycin
- **1948**: PAS
- **1952**: Isoniazid
- **1952**: Pyrazinamide
- **1954**: Isoniazid
- **1955**: Clofazimine
- **1957**: Ethionamide
- **1960**: Amikacin
- **1961**: Ethambutol
- **1963**: Rifampin
- **1963**: Capreomycin
- **1976**: Ofloxacin
- **1982**: Amikacin
- **1992**: Ofloxacin
- **1998**: Gatifloxacin
- **1998**: Linezolid
- **1999**: Rifapentine
- **2000**: Moxifloxacin
- **2005**: PA-824
- **2006**: Bedaquiline
- **2010**: Delamanid

**TRENDS in Microbiology**

- **1943**: Aminoglycosides, Bacitracin (topical)
- **1945**: Tetracyclines
- **1946**: Nitrofurans
- **1947**: Polymyxins, Phenicol
- **1948**: Cephalosporins
- **1950**: Pleuromutilins
- **1952**: Macrolides
- **1953**: Glycopeptides, Nitrimidazoles, Streptogramins

- **1955**: Cycloserine, Novobiocin
- **1957**: Rifamycins
- **1961**: Trimethoprim
- **1962**: Quinolones, Lincosamides, Fusidic acid
- **1969**: Fosfomycin
- **1971**: Mupirocin
- **1976**: Carbapenems
- **1978**: Oxazolidinones
- **1979**: Monobactams
- **1987**: Lipopeptides

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DISCOVERY VOID
Outline

• Historical Context of Tuberculosis (TB)

• *Mycobacterium spp.* and *M. tuberculosis*

• TB Pathophysiology

• TB Transmission

• Summary
How many species of Mycobacterium tuberculosis complex cause disease in humans?

1. 1
2. 4
3. 7
4. 10
**Mycobacterium spp.**

- **Family:** Mycobactericciaea
- **Highly aerobic bacillus**
- **Mycolic cell wall ("waxy") with 5 layers:**
  1. Capsule
  2. Mycolic acids
  3. Lipo-arabinogalactan (LAM)
  4. Peptidoglycan
  5. Plasma membrane
- **Acid-fast Ziehl-Neelsen stain positive**
- **Non-TB Mycobacterium are ubiquitous in the environment with no person-to-person transmission, but can cause human disease**
- **M. leprae** is an exception - can be transmitted through nasal secretions; humans and armadillos are only known reservoir
Non-TB *Mycobacterium* spp.

**Classification of Non-TB *Mycobacterium* spp.**
- Group 1 (photochromogens) – *M. kansasii*, *M. marinum*
- Group 2 (scotochromogens) – *M. gordonae*, *M. scrofulaceum*
- Group 3 (non-photochromogens) – *MAC*, *M. terrae*, *M. ulcerans*, *M. xenopi*, *M. simine*, *M. malmuense*, *M. szulgai*, *M. asiaticum*
- Group 4 – Rapid Growers – *M. fortuitum*, *M. chelonae*, *M. abscessus*

**Non-TB *Mycobacterium* spp. by Organ**
- Pulmonary – *MAC* (“Lady Windemere’s Syndrome”), *M. kansasii* (most similar to TB), *M. abscessus*, *M. xenopi*, *M. bovis*
- Lymph – *MAC*, *M. scrofulaceum*, *M. bovis*
- Cutaneous – *M. marinum*, *M. fortuitum*, *M. chelonae*, *M. abscessus*, *M. haemophilum*
- Disseminated – *M. fortuitum*, *M. chelonae*, *M. abscessus*, *MAC*, *M. haemophilum*
Mycobacterium tuberculosis complex

*M. tuberculosis complex* refers to genetically related group of Mycobacterium species that can cause tuberculosis disease in humans or others

Seven species of *M. tuberculosis* complex:
1. *M. tuberculosis* (humans - global)
2. *M. canettii* (humans in horn of Africa)
3. *M. africanum* (humans in West Africa)
4. *M. bovis* (cow, antelope; humans by dairy)
5. *M. microti* (vole)
6. *M. pinnipedii* (seal)
7. *M. caprae* (goat, cattle)
**Mycobacterium tuberculosis** complex

- Aerobic, non-motile, rod shaped bacilli
- Facultative intracellular pathogen
- Slow-growing (multiplies in 18-24 hrs)
- Thick lipid cell wall
- Acid-fast bacillus (AFB); requires special stains
- Remains dormant for decades (resists dehydration, oxidative stress, low pH)
- Resistant to most common antibiotics
Latent TB Infection

- Asymptomatic people
- Mantoux PPD skin test (TST) or interferon-gamma release assay (IGRA)
- Risk factors for exposure:
  - High local TB prevalence
  - Close household contact
  - Institutional settings (hospitals, prisons, shelters)
  - Social contact (public transit)
  - Urbanization
  - Age
  - Low socioeconomic status
Active TB Disease

- Clinical Features:
  - Cough
  - Fever
  - Night sweats
  - Weight loss
  - Hemoptysis

- Diagnosed by symptoms, chest x-ray, sputum microscopy or culture

- Risk factors for active disease:
  - Proximity to contact case
  - HIV-infected
  - Immunosuppression
  - Diabetes
  - Smoking
  - Existing lung damage
  - Poor nutrition and/or low BMI
  - Host age, sex, genetics, bacterial factors
Outline

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What percentage of new TB infections lead to a primary active TB disease?

1. 5%
2. 20%
3. 40%
4. 60%
TB Pathophysiology

- Exposure
  - No infection
    - Adequate Innate immune response
  - Infection
    - Inadequate
    - Immunologic defenses
      - Inadequate Early TB Disease (5%)
      - Adequate Late TB Disease (5%)
  - Containment (95%)
    - Adequate Immunologic defenses
Spectrum of TB Infection

Bacillary Load:

(<10^4 cfu)  (<10^6 cfu)  (<10^8 cfu)
Stage 1 – TB Pathogenesis

- Stage I
  - Alveolar Macrophage
  - Ingested Tubercle Bacillus
  - Alveolar Lumen
  - Alveolar Wall
  - Capillary
Stage 2 – TB Pathogenesis
Stage 2 – TB Pathogenesis

Week 0 - 1

Week 2 - 3

Ghon’s complex

Week 4 - 5

Tuberculin reactive

Hematogenous dissemination
Stage 3 – TB Pathogenesis
Stage 4 – TB Pathogenesis

- After *M. tb* has grown to high numbers, a ‘high moi’ death rate forms central caseation and liquefies.
- This coincides with high TNF expression, inflammation, and tissue necrosis, and greater multiplication of TB.
- *M. tb* subverts the host immune system (using the inflammatory response) to complete its life cycle, by passage into airways to induce cough.
Granuloma – TB Pathogenesis

**Bacterial vs. Host Stalemate**

- **TB**
  - Uses granuloma formation to hide from host for survival/proliferation
  - Interferes with early TNF-mediated apoptosis
  - Prevents incorporation of ATP/proton pumps into the phagosome (no acidification of phagosome)

- **Host**
  - Alveolar macrophages induce phagocytosis of TB
  - Try to kill TB through CD4/CD8-mediated apoptosis
Increased Risk of TB Activation

• HIV-related impairment of CD4 lymphocyte functions (especially IFN$_{\gamma}$)

• Anti-TNF$\alpha$ therapies prescribed for rheumatologic, inflammatory bowel disease, and other conditions

• Genetic susceptibilities:
  – Animal models – variation in susceptibility/ resistance to TB
  – Twin studies – TB risk is higher among mono vs. dizygotic twins
  – Allelic variations in the NRAMP1 gene assoc. with TB susceptibility
  – Association of HLA-DR2 with vulnerability to TB
  – Familial clusters of disseminated TB infections – IFN$_{\gamma}$ receptor gene
**Innate immune phase**
- **Mtb**
- **Macrophage**

**Markers of resistance**
- Negative TST and IGRA results after repeated exposure

**Adaptive immune phase**
- Not all exposed individuals generate T cell memory

**Markers of latent infection**
- Positive TST
- Positive IFNγ and CXCL10 release assays
- B cells and Mtb-specific antibodies?

**Quiescent phase**
- MHC
- TCR
- T cell
- B cell
- Mtb-specific antibody
- Infected macrophage
- Giant foam cell

**Possibly required for protection**
- Polyfunctional T cells
- T_{H1}-type response
- Non-classical T cells
- Balanced activating and regulatory T cell responses

**Replicating phase**
- CD4⁺ T cell depletion by HIV co-infection

**Possible diagnostic markers**
- ↑ IL-1β, IL-6, IL-12, TNF
- ↑ Acute phase response
- ↑ Immune suppression including T_{Reg} cells
- Changes in memory T cell response
- Changes in T_{H1} cell balance
- Mtb-specific antibodies
Outline

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How is TB transmitted between humans?

1. Fecal-oral contamination
2. Skin-to-skin contact
3. Aerosolized droplet nuclei
4. Blood-borne exposure
M. tuberculosis

Lung

TB lesion

Cavities open into the bronchi, allowing spread of M. tuberculosis through coughing

Cavity

90–95% of infected individuals

Reactivation of TB: for example, after immunosuppression, HIV infection or smoking

Progression to cavitary TB

Haematogenous spread: M. tuberculosis DNA detected in tissues by in situ PCR

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Nature Reviews | Immunology
TB Transmission

• Patient with active, symptomatic TB disease has millions of TB bacilli

• The most important factor is droplet size
  – Intermediate-size droplets desiccate to form “droplet nuclei” (1-5 µm) to reach alveoli
  – Droplet nuclei can remain airborne indefinitely
  – *M. tuberculosis* is stable in droplet nuclei

• Coughing and sneezing projects TB
  – Cough releases 3,000 droplet nuclei
  – Sneeze release >10,000 droplet nuclei

• Average TB patient generates 75,000 infectious droplets/day before therapy
  – Decrease to 25 infectious droplets/day within 2 weeks of starting effective therapy
“Droplet Nuclei” Theory

Small droplets likely contain no TB

Intermediate droplets fall slowly, but evaporate into inhalable “droplet nuclei”

Large droplets fall to the ground quickly, before evaporating
TB Transmission

- The Baltimore VA Pilot Ward
- Effluent air passed through guinea pig cages
- Guinea pigs monitored by TST, sacrificed (and replaced) if TST+
- Time to infect one guinea pig was ~10d
- Infected animals usually had only a single lung “tubercle”

“most droplets atomized into air evaporate almost instantly, leaving disease germs drifting like cigarette smoke in the droplet nuclei”
- Wells 1948
TB Transmission

- **U.S.S. Richard E. Byrd** - 437 ft. destroyer, commissioned at Puget Sound Naval Shipyard in 1964

- Index patient: coughing with cavitary AFB smear-positive pulmonary TB

- Extensive characterization of all sailors, incl. work/sleep locations, ventilation patterns, etc.

- Overall, 139 of 308 (45%) enlisted crew converted TST; and 7 had active disease at the initial screening

- TST conversion rate was 80% in shared compartment, 53% in adjacent compartment with partially shared ventilation, and far lower elsewhere on ship

Houk et al. 1968
### TB Transmission - Droplets

<table>
<thead>
<tr>
<th>Activity</th>
<th>Particles ≤ 100 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing</td>
<td>?</td>
</tr>
<tr>
<td>Speaking</td>
<td>0 – 210</td>
</tr>
<tr>
<td>Speaking for 5 min</td>
<td>0 – 3,000</td>
</tr>
<tr>
<td>Coughing</td>
<td>0 – 3,500</td>
</tr>
<tr>
<td>Sneezing</td>
<td>4,500 – 1,000,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size</th>
<th>Time in Air</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 uM (“droplet nuclei”)</td>
<td>indefinite</td>
</tr>
<tr>
<td>10 uM</td>
<td>17 minutes</td>
</tr>
<tr>
<td>20 uM</td>
<td>4 minutes</td>
</tr>
<tr>
<td>100 uM</td>
<td>10 seconds</td>
</tr>
</tbody>
</table>

Duguid 1946; Knight, NY Academy Sci, 1980
TB Transmission – Risk Factors

CASE
- Site of TB
- Cough
- Bacillary load
  - smear+
  - cavity
- Treatment

CONTACT
- Filtration
- Ventilation
- U.V. light
- Procedures
  - sputum induction
  - bronchoscopy
  - wound irrigation
  - autopsy
- Exposure/duration of contact
- Prior TB infection
- HIV
- Immunosuppressed
- Diabetes
- Smoking
US Groups at Highest Risk for TB

- Close contact of TB case
- Foreign-born persons from high prevalence area
- Residents of long term care facilities
- Homeless
- Injection drug users
- Elderly persons
- Persons with occupational TB exposures
Isoniazid Preventive Therapy (IPT)

Vaccine
TB Transmission - Summary

• TB is spread person-to-person via aerosolized “droplet nuclei”
  – Spread by persons with active TB symptoms (cough)
  – Especially cavitary, smear positive cases
  – Droplet nuclei are inhaled by the target host

• Transmission is aided by crowding, absence of UV light, and poor ventilation

• Risk depends on concentration of droplet nuclei
  – Source case factors: Rate of cough production, TB disease
  – Environmental factors: Filtration, Ventilation, UV light
  – Contact person factors: Duration of exposure, Host resistance
TB Transmission - Airline Travel

- Limited evidence for airline transmission
- Most airlines use air filters at 3µM, which are small enough to remove droplet nuclei
- Most airplanes have 15 air-exchanges/hour
- Est. prevalence of active TB cases:
  - 0.05/100,000 (range 0 - 0.36/100,000), assuming flights to/from Africa or India

Byrne, Travel Med Infect Dis, 2007; Abubakar, Lancet ID, 2010
Outline

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Summary

• The global burden of TB is severe
  – TB causes more deaths than any other infection
• Global TB incidence/deaths is decreasing
  – But, not fast enough
• Pathogenesis of TB is complicated
• Transmission remains a major problem
Current TB Diagnostic Pipeline
## Current TB Vaccine Trials

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase IIA</th>
<th>Phase IIb</th>
<th>Phaselll</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad5 Ag85A</td>
<td>Crucell Ad35 / Aeras402</td>
<td>MVA85A /Aeras-485</td>
<td>M. Indicus pranii</td>
</tr>
<tr>
<td>McMaster University, Can Sino</td>
<td>Crucell, Aeras (formerly PhIIb)</td>
<td>UOXF, AERAS</td>
<td>IT Dpt of Biotechn (Gvt of India), Cadila</td>
</tr>
<tr>
<td>ID93 + GLA-SE</td>
<td>VPM1002</td>
<td>M72 + ASO1E</td>
<td>B</td>
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<tr>
<td>IDRI, Aeras</td>
<td>MPIIB, VPM, TBVI, SII</td>
<td>GSK, Aeras</td>
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<td>MTBVAC</td>
<td>RUTI</td>
<td>IT</td>
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<tr>
<td>UniZaragoza, Biofabri, TBVI</td>
<td>Archivel Pharma</td>
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<tr>
<td>DAR-901</td>
<td>H I + IC31</td>
<td>P priming vaccine</td>
<td></td>
</tr>
<tr>
<td>Dartmouth University, Aeras</td>
<td>SSI, TBVI, Intercell, EDCTP</td>
<td>B boosting vaccine</td>
<td></td>
</tr>
<tr>
<td>ChAdOx1.85A</td>
<td>H56 : IC31</td>
<td>IT therapeutic vaccines</td>
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<tr>
<td>UOXF</td>
<td>SSI, Intercell, Aeras</td>
<td></td>
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</tr>
<tr>
<td>Crucell Ad35 – MVA85A prime-boost</td>
<td>H4 : IC31</td>
<td></td>
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</tr>
<tr>
<td>UOXF, Aeras, Crucell</td>
<td>SSI, SP, Aeras</td>
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</tbody>
</table>

Stop TB Partnership, 2014.
Thank You!

Remember, World TB Day is March 24!

pkdrain@uw.edu