Transmission & Pathogenesis of Tuberculosis

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April-December, 2011: TB cases reported by the media in US

TB found at Seaside High School – 124 exposures (The Oregonian)

TB Reported at San Marino High School – 374 possible exposures (KNBC News LA)

Exposure to TB at Daycare Center -100 children, 10 elderly and 20 staff members exposed to MDR-TB (YNN News Rochester)

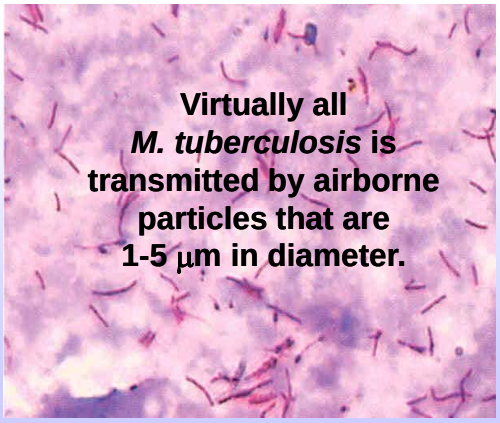
Elephants Blamed For TB Outbreak at Tennessee Sanctuary - 6 workers affected (CBS News)

Panic at Saint Louis Zoo: An elephant tested positive for MDR-TB - 238 people **exposed** (KMOV-TV Saint Louis)

Immigration fuels increase in TB rates with 124 cases of MDR/XDR TB **during this year** (Honolulu Star-Bulletin)

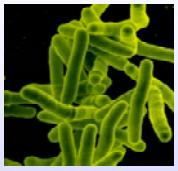
High-school 127 students tested positive for *M.tb* **exposure** (Ennin News, Texas)

Slide courtesy of Jordi Torrelles, PhD



NEJM 345:189, 2001

Mycobacterium tuberculosis & TB disease

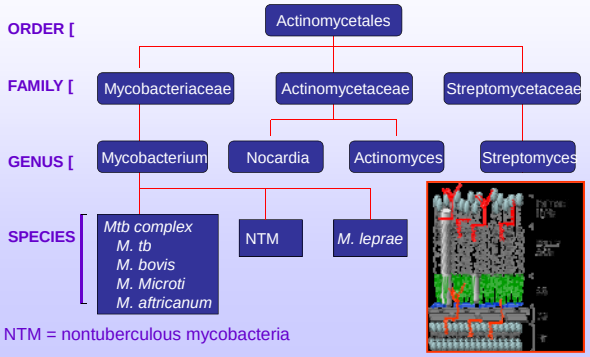


- Acid fast bacillus
- Slow growing
- Intracellular pathogen
- Thick waxy cell wall
- Non-replicating persistence

- Productive cough
- Dramatic weight loss
- Night sweats
- General malaise
- Pulmonary or extra-pulmonary

Slide courtesy of Joanne Turner, PhD

The Taxonomic Tree for Selected Mycobacteria and Related Species



NTM = nontuberculous mycobacteria

Overview of inhaled mycobacterial diseases

(prototype: *M. tb, other major NTM: M. aviumintracellulare Complex and M. kansaii)*

The Paradigm: Latent Infection vs. Active Disease

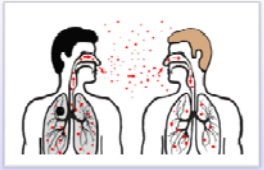
Inhaled airborne droplet nuclei
↓
Phagocytosis by alveolar macrophages
↓
Regional spread
↓
Dissemination

Resolution-common development of effective cell-mediated immune response
↓
Reactivation disease

Primary active disease (uncommon in healthy host)

Transmission of *M. tuberculosis*

- ***M. tb*** **spread via airborne particles called droplet nuclei**
- **Expelled when person with infectious TB coughs, sneezes, shouts, or sings**
- **Transmission occurs when droplet nuclei inhaled and reach the alveoli of the lungs, via nasal passages, respiratory tract, and bronchi**



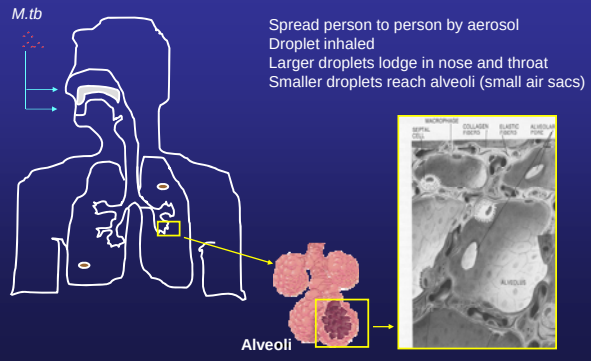
Pathogenesis

- **Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli**

- **Tubercle bacilli multiply in the alveoli**

M. tb infection Pathway

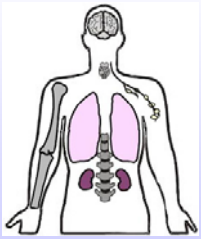
Stage 1



Spread person to person by aerosol
Droplet inhaled
Larger droplets lodge in nose and throat
Smaller droplets reach alveoli (small air sacs)

Slide courtesy of Jordi Torrelles, PhD

Pathogenesis



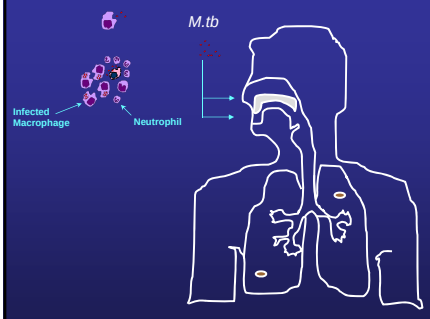
- **A small number of tubercle bacilli enter the bloodstream and spread throughout the body**
- **Tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop**
  - Brain, larynx, lymph node, lung, spine, bone, or kidney

Pathogenesis

- **Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli**
- **The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control (LTBI)**

- **If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease)**
- **This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone**

M. tb infection Pathway and Granuloma formation



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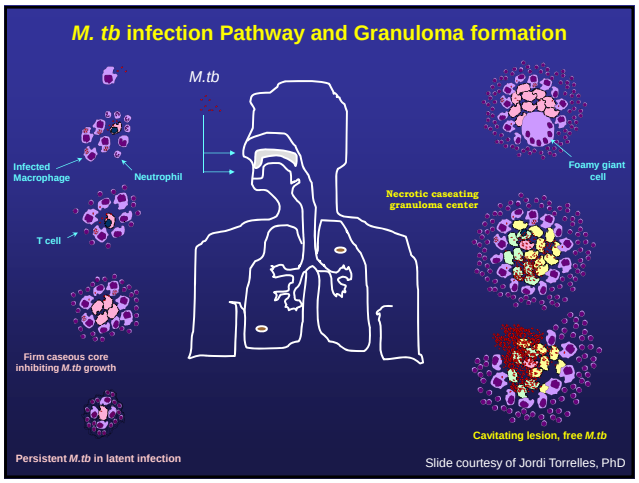
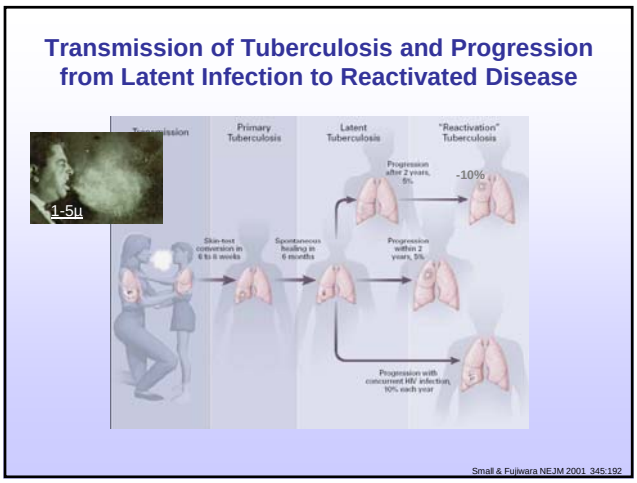
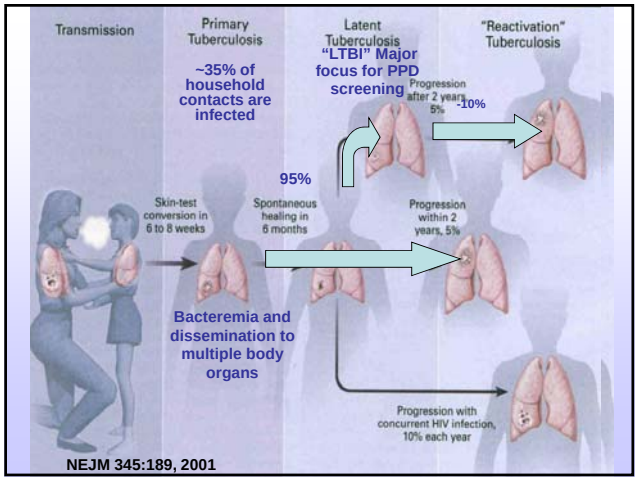


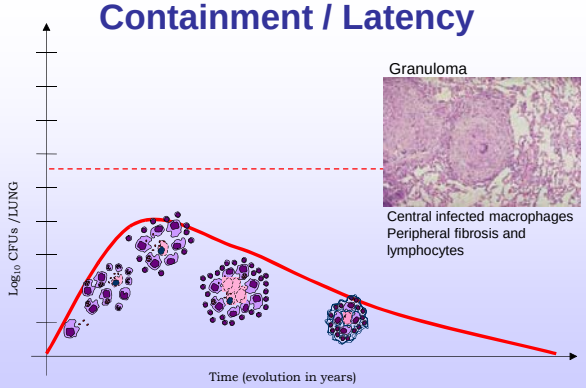




Latent TB Infection (LTBI)

- Granulomas may persist (LTBI), or may break down to produce TB disease
- 2 to 8 weeks after infection, LTBI can be detected via tuberculin skin test (TST) or interferon gamma release assay (IGRA)
- Immune system is usually able to stop the multiplication of bacilli
- Persons with LTBI are not infectious and do not spread organisms to others

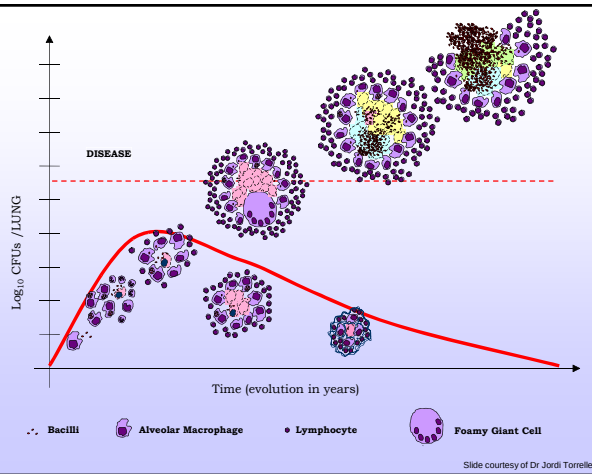
Containment / Latency



Slide courtesy of Joanne Turner PhD, and Jordi Torrelles, PhD

TB Disease

- In some, the granulomas break down, bacilli escape and multiply, resulting in TB disease
- Can occur soon after infection, or years later
- Persons with TB disease are usually infectious and can spread bacteria to others
- Positive *M.tb* culture confirms TB diagnosis



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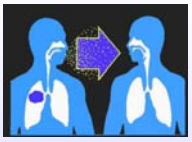
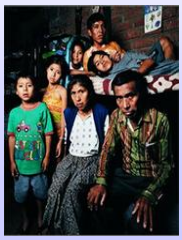
Transmission of *M. tb*

- Transmission is airborne from patients with active pulmonary TB
- **Vehicle**: droplet nuclei (1-5 µm)
- **Quantity** of organism high with cavitary disease
- **Environment**: spread is enhanced by crowded, poorly ventilated spaces
- **Bottom line: duration of exposure and concentration of organisms in the air**
- *Host susceptibility increases risk of infection and disease progression*





Risk of Exposure/ Transmission

- Congregate settings
  - Hospitals, autopsy suites, long term care facilities
  - Correctional facilities
  - Bars
  - Choirs
  - Airplanes, ships
- Aerosol producing procedures: intubation, bronchoscopy, sputum induction

Who is Infectious?

- Smear + > smear* –
- Cavitary > non-cavitary
- Close contact > casual contact
- Prolonged > brief exposure
- Men > women
- Young > old
- HIV + = HIV –

Smear negative cases can still transmit

Drug Resistant TB

- Transmitted same way as drug-susceptible TB
- MDR-TB and XDR-TB are not more infectious
- Unsuspected or delayed detection of drug resistance may delay start of therapy and prolong period of infectiousness

Sites of Disease

- Lungs (pulmonary): most common site, usually infectious
- Miliary: hematogenous dissemination; rare, but fatal if untreated
- Central nervous system: usually occurs as meningitis, but can occur in brain or spine

Sites of Disease

- Outside the lungs (extra-pulmonary): usually not infectious unless person has;
  - Concomitant pulmonary disease
  - Extrapulmonary disease in the oral cavity or larynx, or
  - Extrapulmonary disease with open site, especially with aerosolized fluid

LTBI	Active TB Disease
No symptoms or physical findings suggestive of TB	Symptoms *may* include fever, cough, weight loss, night sweats, fatigue
TST or IGRA usually positive	TST or IGRA usually positive
Radiograph is typically normal	Radiograph may be abnormal
Sputum smears & cultures are negative	Sputum smears & cultures may be positive
Cannot spread to others	May spread TB bacteria to others
Treat for LTBI to prevent TB disease	Needs treatment for TB disease

Classification System for TB

- Based on TB pathogenesis (stage of disease)
- Helps clinician track the development of TB in patients
- Persons with class 3 or 5 TB should be reported to health department
- Patients should not be classified as class 5 for more than 3 months

TB Classification System

Class	Stage of Disease
0	No exposure, no infection
1	Exposure, no evidence of infection
2	TB infection, no disease
3	TB, clinically active
4	TB, not clinically active
5	TB suspect

Questions?