Tuberculosis

Caused by strains of closely related bacteria known as the Mycobacterium tuberculosis complex
- 30% world population infected
- 2012:
  - 1.3 million deaths
  - 8.6 million developed active TB
  - Each will infect 10-12 more/yr
  - 80% of these in 22 “high burden” countries
  - 1.1 million of these coinfected with HIV—most in Africa
- TB Leading cause of death in HIV+
  - 320,000 in 2012

Impact of TB
- 90% illness & death occurs in developing countries (focus of control)
- 75% disease & death occurs in 15-54 yr age group, having a large impact on income & productivity
  - Average patient loses 3-4 months of work due to illness & income drops 30-100%
  - Mean household spending on TB is 8-20% of income, varies by region
  - Thousands of children must leave school due to sick parents
- Drug resistance is a global threat: 20% new cases developed MDR-TB and 3.6% developed XDR-TB in 2012


History
- Evidence of disseminated disease (long bones, spine)
  - 6000 BC prehistoric stone age skeletons, Europe
  - 5000 y.o. Egyptian mummies
  - TB in spine in Egyptian paintings
  - M. tb DNA found in PreColumbian Peruvian mummies date to AD 800-1000
  - New evidence in 2008 shows human (not bovine) Mtb DNA in bones from human remains dating 9000 bc in Israel
**TB Origins: Anthropologist’s view**
- Domestication of cattle (8000-6000 BC) led to TB due to consumption of M.bovis from ingestion of milk
- Thought to spread along migration routes by milk-drinking Indo-Europeans
- After 1000 BC widespread pulmonary TB emerges “crowd disease.”
- M.bovis “evolved” into M. tuberculosis of humans

**TB origins. A molecular view**
- M. tuberculosis genome sequenced in 1998
- 2004 comparisons to M. bovis vaccine strain shows M. tb did not evolve from bovis.
- 2005 Pasteur Institute report rare strains of human TB from East Africa
  - Genetic analysis showed that these strains were the progenitors of M.tb & they may be 3 million years old
  - Disease affected early hominids
- 2008 Genetic evidence indicates
  - Most common ancestor of Mtb complex emerged 40,000 years ago, coinciding with Human migration out of East Africa
  - 10-20,000 yrs later one clade spread from humans to animals

**TB has had many names**
- Phthisis (greek: wasting)
- Scrofula (swollen lymph nodes)
- Kings evil (medieval europe)
- Lupus vulgaris (skin, werewolf legend?)
- Pot’s disease/Gibbus (TB of spine)
- Vampire’s Disease
- Consumption (fever/wasting)

**Key Events in TB Control**
- Seraksham movement
- 1904 National TB association
- Social reform
- Pasteurization of milk against M. tubercle
- BCG vaccine (after 1924)
- Skin testing X ray development
- Surgical pneumothorax
- Streptomycin (1944) & other antibiotics
- Directly Observed Therapy (DOT)

**Resurgence of TB: factors**
- Dismantling of TB programs, 70’s/80’s
- Social poverty/crowding:
  - Prisons
  - Homelessness
  - Drug users
- HIV pandemic
- Migration
  - 40% of TB in USA in foreign born persons from endemic areas (S. E. Asia)

**Microbiology**
- Slender, clumped bacilli
- Waxy cell walls
- Slow-growing
- Aerobes
M. tuberculosis

- 1882: Robert Koch reports isolation of bacteria from "tubercles"
- Develops tuberculin
  - Used for skin test
- 1905: Nobel Prize

TB transmission

- Spread through aerosolized droplets
  - From infectious person coughing, sneezing or talking
  - Close contacts of infectious person at highest risk
  - Sputum smear + case most contagious

TB INFECTION
- AFB in body
- Skin test often +
- Normal Chest X ray
- Sputum/culture -
- No symptoms
- NOT infectious
- NOT a case of TB

TB DISEASE
- AFB in body
- Skin test often +
- Abnormal chest X ray
- Sputum/culture +
- Symptoms: Cough, fever, weight loss
- Infectious w/o Rx
- Case of TB

Who gets active TB?

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>How many times higher is risk of disease?</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>170</td>
</tr>
<tr>
<td>HIV</td>
<td>113</td>
</tr>
<tr>
<td>Recent (&lt;2yr) infection</td>
<td>13</td>
</tr>
<tr>
<td>Immune suppression, cancer, diabetes</td>
<td>3-16</td>
</tr>
</tbody>
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Detecting infection/latent TB

- Tuberculin skin test (ppd)
  - Read swelling at 48-72 hr. If >10 mm = +
  - > 5mm = + in immune suppressed & close contacts of active cases
- Memory T cell response
- Vaccines may test +
  - A separate blood test distinguishes true positives

People with TB infection
- No risk factors
  - 90% no disease
  - 10% risk of disease Over lifetime

People with TB infection
- HIV coinfection
  - 10% risk of disease/year

People with TB infection
- HIV coinfection
  - 10% risk of disease/year
Detecting disease
- Chest xray
- Stain sputum smear
- Culture bacteria
- Test all cultures for drug resistance

Disseminated “miliary” TB

Immune response to TB

TB drugs
- Isoniazid (INH) for prevention & Rx
- Streptomycin
- Rifampin
- Pyrazinamide
- Ethambutol
- Combinations must be used
- DOT very effective for cure
  - Global Fund treated an additional 5.4 million cases in 140 countries as of July 2009

Treating TB
- CDC recommends supervised DOT for first 2 months for all HIV+ & high risk persons
  - Includes 4 drugs
- Continuation phase
  - 2 drugs for 4 months
- Drug resistant TB
  - 5% of 8 million new cases =MDR
  - Resist first line drugs (INH, Rif)
  - Need 2nd line drugs up to 2 years
  - More costly & more side effects

DOTS Strategy
- Cure rates >95% including poor countries
- Prevents TB spread by curing infectious patients
- Prevents rise of drug resistance by ensuring compliance
- Costs $10 US for 6-8 months
- World Bank ranks as a highly effective prevention measure

Source: Global Fund Disease Report 2009
TB vaccine

- "Bacillus of Calmette & Guerin". BCG
  - Consists of live, attenuated M. bovis strain
  - Only protects against more severe childhood forms
  - Given to children in endemic countries to protect against miliary TB
  - Not routinely used in US as it eliminates utility of skin testing (causes false + reactions)
  - Can cause disease in immune suppressed
- 2012-2013, ten vaccines in trials, none better than BCG yet