

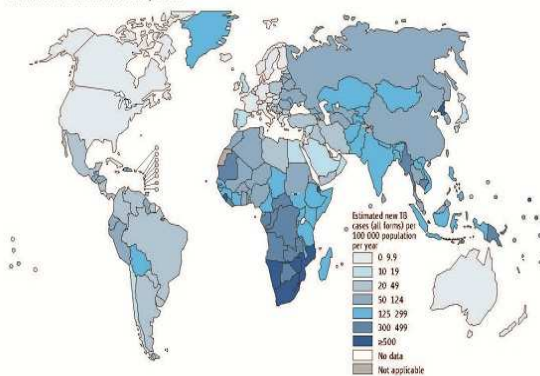
Tuberculosis



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
 - 1.1million of these coinfectd with HIV –most in Africa
- TB Leading cause of death in HIV+
 - 320,000 in 2012

FIGURE 2.5
Estimated TB incidence rates, 2012

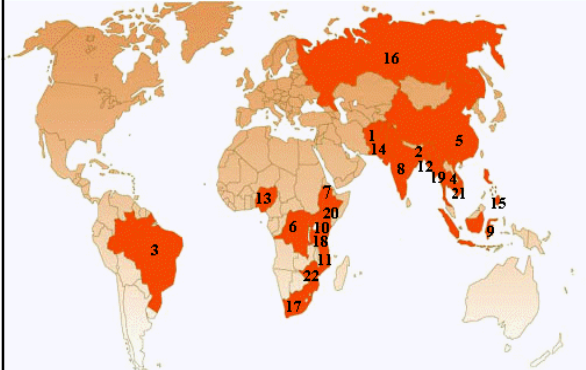


Impact of TB

- 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

Source: WHO Global TB Report, 2013

22 High Burden Countries Responsible for 80% TB in 2012

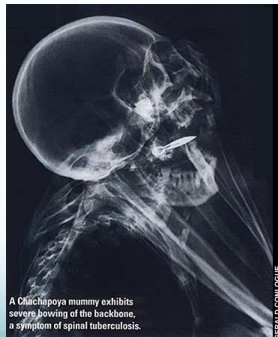


History

- 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 (8000-4000 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?)
- Pott's disease/Gibbus (TB of spine)
- Vampire's Disease
- Consumption (fever/wasting)



Key Events in TB Control

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

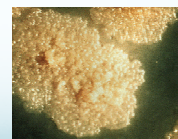
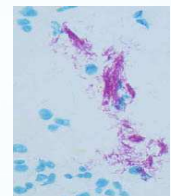


Resurgence of TB: factors

- Dismantling of TB programs, 70's/80's
- Social poverty/crowding:
 - Prisons
 - Homelessness
 - Drug users
- HIV pandemic
- Migration
 - 40% of TB in USA is in foreign born persons from endemic areas (S.E. Asia)
- Rise in drug resistance: MDR-TB, XDR-TB, TDR-TB

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 | • TB DISEASE |
| • AFB in body | • AFB in body |
| • Skin test often + | • Skin test often + |
| • Normal Chest X ray | • Abnormal chest X ray |
| • Sputum/culture - | • Sputum/culture + |
| • No symptoms | • Symptoms: Cough, fever, weight loss |
| • NOT infectious | • Infectious w/o Rx |
| • NOT a case of TB | • Case of TB |

Who gets active TB?

Risk Factor	How many times higher is risk of disease?
AIDS	170
HIV	113
Recent (<2yr) infection	13
Immune suppression, cancer, diabetes	3-16

People with TB infection
No risk factors



90% no disease

People with TB infection
HIV coinfection



10% risk of disease/year

10% risk of disease
Over lifetime

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
- Vaccinees may test +
 - A separate blood test distinguishes true positives

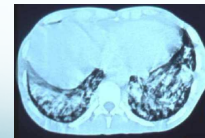
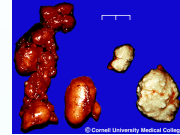


Detecting disease

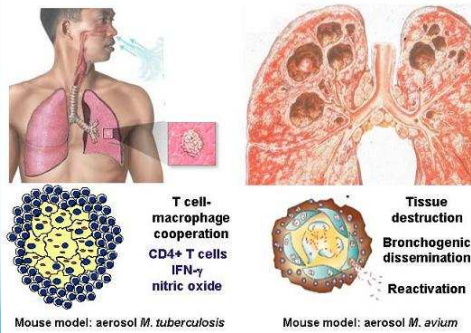
- Chest xray
- Stain sputum smear
- Culture bacteria
- Test all cultures for drug resistance



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 & Guérin”. BCG
 - Consists of live, attenuated *M. bovis* strain
 - Only protects against more severe childhood forms
 - Given to children in endemic countries to protect against military 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