Tuberculosis
Organism and the host

Dr Sarabjit Chadha
The Union
• History of Tuberculosis
• Mycobacterium Tuberculosis
• Epidemiological chain of TB
  – Causal agent
  – Reservoir/Source of infection
  – Mechanism of transmission
  – Host characteristics
History of TB

- Believed to be as old as mankind
- Spinal TB has been diagnosed in Egyptian mummies dating 2400 BC
- Akhenaten and his wife Nefertiti died of Tuberculosis (1360 BC)
- In India Yakshma (resembles TB) finds a mention in scriptures dated 1500 BC
- In ancient China TB has been called xulao bing
- Hippocrates (460 BC)- described a disease of “weakness of the lung” with fever and cough- phthisis
History of TB

• 1689- Franscius Sylvius differentiated various forms of ptthisis (scrofula, Pulmonary) – *Opera Medica*

• 1720- Benjamin Marten proposed that it was caused by ‘animacula’ –

• 1768- Robert Whytt described TB meningitis

• 1779- Percivall Potte described the vertebral lesions

• 1834- Schönlein described the disease with tubercles – ‘Tuberculosis’ coined

• 1869 Jean Villemin showed TB was contagious

• 1882 Sir Robert Koch discovered MTB as cause of TB
History of TB

• 1850-1910 - in England more than 4 million people died of TB
• Called as the ‘White plague’, ‘White death’ and a ‘Romantic disease’
“If the importance of a disease for mankind is measured from the number of fatalities which are due to it, then tuberculosis must be considered much more important than those most feared infectious diseases, plague, cholera, and the like. Statistics have shown that 1/7 of all humans die of tuberculosis.”

—Die Ätiologie der Tuberculose, Robert Koch (1882)
• Earlier it was believed that human TB evolved from the bovine disease by adaptation of an animal pathogen to the human host
• *M. tuberculosis* almost exclusively a human pathogen, whereas *M. bovis* has a much broader host range
• Genome of *M. bovis* is smaller than that of *M. tuberculosis*
• The mycobacteria in the *Mycobacterium tuberculosis* complex are characterized by 99.9% similarity at the nucleotide level and identical 16S rRNA sequences
• Common progenitor

TB has co-existed with the Human Species for more than 3 Million years.

The entire population probably resulted from clonal expansion of a broader progenitor…
How did TB rise and spread?

- Out-of-and-back-to-Africa
- MTBC originated in Africa and some lineages accompanied the Out-of-Africa migrations of modern humans
• Analysis of bacterial DNA from 1,000-year-old mummies, scientists have proposed a new hypothesis for rise and spread of TB
• The disease originated less than 6,000 years ago in Africa and took a surprising route to reach the New World
• It was carried across the Atlantic by Seals
Epidemiological sequence of TB transmission

- Causal agent
- Reservoir/Source of infection
- Mechanism of transmission
- Host
Causal agent.....

- Mycobacterium tuberculosis complex
  - *Mycobacterium tuberculosis*
  - *Mycobacterium africanum*
  - *Mycobacterium bovis* (and Bacillus Calmette–Guérin strain)
  - *Mycobacterium microti*
  - *Mycobacterium canettii*
  - *Mycobacterium caprae*
  - *Mycobacterium pinnipedii*
  - *Mycobacterium mungi*
Novel
*Mycobacterium tuberculosis*
Complex Pathogen, 
*M. mungi*

Kathleen A. Alexander, Pete N. Laver, Anita L. Michel, Mark Williams, Paul D. van Helden, Robin M. Warren, and Nicolaas C. Gey van Pittius

Seven outbreaks involving increasing numbers of banded mongoose troops and high death rates have been documented. We identified a *Mycobacterium tuberculosis* complex pathogen, *M. mungi* sp. nov., as the causative agent among banded mongooses that live near humans in Chobe District, Botswana. Host spectrum and transmission dynamics remain unknown.
Various strains of *M. TB*
Global dissemination of the *Mycobacterium tuberculosis* W-Beijing family strains

Pablo J. Bifani, Barun Mathema, Natalia E. Kurepina and Barry N. Kreiswirth

*Trends Microbiol* 2002; 10: 45-52

Drug-Resistant Tuberculosis, Clinical Virulence, and the Dominance of the Beijing Strain Family in Russia

Francis Drobniewski, MD, PhD

*JAMA. 2005;293:2726-2731* drug-resistant tuberculosis is a seri


Evolutionary history and global spread of the *Mycobacterium tuberculosis* Beijing lineage.

Merker M^1, Blin C^2, Mona S^2, Duforet-Frebourg N^3, Lecher S^4, Willery E^4, Blum MG^3, Rüsch-Gerdes S^5, 


Various strains of *M. TB*

- Beijing family genotype is widespread and is a major concern
- First described in 1995, and >80% of strains from Beijing, China, were of this genotype
- Later, the Beijing genotype was detected in other parts of the world especially East Asia
Evolutionary history and global spread of the Mycobacterium tuberculosis Beijing lineage.

- Genetic analysis of 4,987 isolates from 99 countries and whole-genome sequencing of 110 representative isolates
- Lineage initially originated in the Far East, from where it radiated worldwide in several waves
- Successive increases in population size for this pathogen over the last 200 years, practically coinciding with
  - Industrial Revolution, the First World War and HIV epidemics
- Two MDR clones of this lineage started to spread throughout central Asia and Russia concomitantly with the collapse of the public health system in the former Soviet Union
Possible underlying mechanisms for successful emergence of the *Mycobacterium tuberculosis* Beijing genotype strains

Ida Parwati, Reinout van Crevel, Dick van Soolingen

The wide geographic distribution of one clade of *Mycobacterium tuberculosis*, the Beijing genotype family, and its genetic homogeneity, suggests that strains belonging to this grouping might have a selective advantage over other *M tuberculosis* strains. This hypothesis was addressed by reviewing molecular-epidemiological, experimental, and clinical studies. Beijing strains represent about 50% of strains in east Asia and at least 13% of strains worldwide. Their emergence might be linked to escape from BCG vaccination, and to multidrug resistance, which is associated with the Beijing genotype in many areas. Different animal models have shown Beijing strains to be more virulent, and to cause more histopathological changes, higher outgrowth, and increased mortality. At a molecular level, Beijing strains have specific properties in terms of protein and lipid structures and their interaction with the human immune system. Finally, the Beijing genotype has been linked to polymorphisms in immune genes, suggesting the possibility of human–mycobacterial co-evolution. The emergence of the Beijing genotype family might represent an evolutionary response of *M tuberculosis* to vaccination or antibiotic treatment, with an important negative impact on tuberculosis control. More research is needed to further unravel the mechanisms underlying the emergence of *M tuberculosis* Beijing genotype strains, and examine the implications for future control strategies.
Beijing Strain

- 50% of the Asian strains (13% in the rest of the world)
- Genetic co-evolution -
- Group with evolutive advantages
  - Escape from BCG (vaccine less protective against them)
  - Greater immunogenecity - bigger cavities, higher transmission
  - Escape from immune system (more difficult to kill):
    - More virulent (greater probability to develop disease from infection)
- MDR - TB associated in many areas
  - Greater mutation rate
  - Changes in lipid walls: drug concentrations are reduced

Implications for TB control

- Virulence and resistance
- Geographical distribution
- Vaccine development - genetic variation and vaccine escape

Parwati I. Lancet ID 2010
Causal agent.....

- MTB complex
  - Acid-alcohol resistant bacilli
  - Resistant to cold, freezing and desiccation
  - Very sensitive to heat, sunlight, and UV radiation
  - Aerobic (depends on Oxygen and pH)
  - Polyvalent behaviour, depending on medium
  - Very slow division capacity
M.TB Characteristics

- High lipid content in the cell wall
- Tint Characteristic (Acid-Alcohol Resistant Bacillus)
- Very resistant to external aggressors, even most antibiotics
M.TB Characteristics

• M *tuberculosis* complex
  – Resistant to:
    • Cold
    • Freezing
    • Desiccation
M.TB Characteristics

• Mycobacterium *tuberculosis* complex
  – Very sensitive to heat, sunlight and U.V. radiation
Does sunlight have protective effect??

- The germicidal effect is concentrated at 254nm of the UV-C radiation
- Most of the UV-C radiation is absorbed by atmosphere (Oxygen and Ozone)
M.TB Characteristics

- Mycobacterium *tuberculosis* complex

- Preferential aerobic (depends on Oxygen and pH)
Cavity

High Partial Pressure O2

Ideal Conditions for M. TB division
Polyvalent behavior depending on medium

Latent/dormant → Metabolically active

**Unfavourable conditions**
- Caseum /inside macrophages

**Favourable conditions**
- Oxygen, neutral pH
M.TB Characteristics

- Multiplies very slowly - 16-24 hrs to divide
  - Slow and insidious clinical presentation
  - Delay in seeking healthcare
  - Late diagnosis
  - Long period of transmission
Epidemiological Sequence of TB Transmission

1. Causal agent
2. Reservoir: source of infection
3. Mechanism of transmission
4. Susceptible host
Reservoir of infection

• The reservoir of infection is ‘Man’
  – Infected but not diseased
    • Of the 7 billion population nearly 2.3 billion are infected
    • Those infected with MDR TB ~50 million
  – Diseased
    • ~13 million prevalent cases
    • ~600,000 Rif res TB cases

• Animals
  – Cattle (M.Bovis)
  – Dogs, Cats, Monkeys and elephants

• Insects and inanimate objects are not reservoirs
Zoonotic TB

• Animals (Cattle) are known to suffer from M Bovis
  – Transmitted to humans through milk and meat

• Animals have been believed to contract and suffer from MTB infection
  – May be an important source of transmission
  – Those in close contact with animals are at risk (Farming community; zoo workers; Mahouts etc.)
Study conducted in organised farms in North India

- 768 samples collected from cattle suspected to have TB
  - 54 samples- culture positive 40 (\textit{M. Bovis}) 14 (\textit{M. TB})
  - 28.5% milk samples culture positive for \textit{M. TB}
  - 7.1 % of pharyngeal swabs positive for \textit{M. TB}

- Animal handlers infected by TB bacilli transmit it to cattle

Should the NTPs consider special strategies for such special populations?
The two human cases are linked to nine cases of Mycobacterium bovis infection in cats in Berkshire and Hampshire last year (6 died and 3 on treatment)
Transmission of *Mycobacterium tuberculosis* from an Asian elephant (*Elephas maximus*) to a chimpanzee (*Pan troglodytes*) and humans in an Australian zoo

- Mycobacterium tuberculosis is emerging as a significant disease of elephants in the care of humans.

- In November 2010, a clinically healthy Asian elephant in an Australian zoo was found to be shedding *M. tuberculosis*.

- In September 2011, a sick chimpanzee at the same zoo was diagnosed with TB caused by an indistinguishable strain of *M. tuberculosis*.

- 4 staff had tuberculin skin test conversions -spending at least 10 hours within elephant enclosure; none had disease

- Six chimpanzees had suspected infection
Mechanism of Transmission

- Primarily airborne transmission
TB Transmission. **Dynamics of Cough**

- **Large** Droplets (Pfluger) – fall fast!
- **Small** droplets –
  - hang around floating…
  - slowly evaporate…
  - “crystallize” creating a nucleus of infectious material inside
- 1.0 micron droplets nuclei (Wells) will eventually fall just 3 m. in 24 h.!

- **Large** droplets → Upper Airway trapping
- 1-5µ droplet nuclei reach Alveoli & cause infection
Who transmits more TB?

Speaking

Coughing

Sneezing
Who transmits more TB?

- Speaking: 0-200 bacilli
- Coughing: 0-3500 bacilli
- Sneezing: 4500-1,000,000 bacilli
Patients with TUBERCULOSIS must cover their mouth when coughing.

Surgical masks only work if used by the patient.
Greatest TB Transmitters

- People with bad coughs
- Sputum sm+ patients
- Untreated patients
- Patients who have just commenced treatment
- Cases with poor response to treatment
Mechanism of Transmission

• Primarily airborne transmission
• Uncommonly
  – Cutaneous-mucosal
  – Urogenital
  – Inoculation
  – Transplacental
A case of MDR-TB in a Peruvian infant.

His mother was diagnosed with disseminated TB, and treatment commenced 11 days postpartum.

The infant was diagnosed with TB after 40 days and died at 2 months and 2 days of age.

Congenital transmission of TB to the infant was suspected, because direct postpartum transmission was considered unlikely; also, thorough screening of contacts for TB was negative.

Spoligotyping confirmed that both mother and baby were infected with identical strains of the Beijing family (SIT1).
Epidemiological Sequence of TB Transmission

1. Causal agent
2. Reservoir: source of infection
3. Mechanism of transmission
4. Susceptible host
Susceptible Host

- Age distribution
Susceptible Host

• Gender
  – 60-70% Men; 30-40% Women

• Risk factors
  – AIDS and HIV infection
  – Recent tuberculosis infection
  – Silicosis (5-15 times)
  – Fibrotic lesions (residual TB)
  – Other Immunodeficiencies
  – Diabetes (3-5 times)
  – Smoking
Pathology and causes of death in a group of 128 predominantly HIV-positive patients in Botswana, 1997–1998


*The BOTUSA Project, Gaborone, Botswana; †Department of Histopathology, Guy’s, King’s, & St. Thomas’ School of Medicine, London, UK; ‡Department of Pathology, Nyangabgwe Hospital, Francistown, Botswana; §Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; ¶Department of Medicine, Nyangabgwe Hospital, Francistown, Botswana

BACKGROUND: Little is known about causes of death in countries of southern Africa seriously affected by the HIV/AIDS epidemic.

METHODS: After obtaining informed consent, autopsies were performed on 128 mainly hospitalised adults in Francistown, Botswana, between July 1997 and June 1998. Criteria for case selection included those who died before a diagnosis could be established, those whose condition deteriorated unexpectedly during hospitalization, and those who had respiratory disease. This represented 14% of adult medical patients who died in hospital during the study period.

RESULTS: Of the 128 patients, 104 (81%) were HIV-positive. Among HIV-positive patients, the most common pathologic findings were tuberculosis (TB) (40%), bacterial pneumonia (23%), Pneumocystis carinii pneumonia (11%), and Kaposi’s sarcoma (11%); these conditions were the cause of death in 38%, 14%, 11%, and 6%, respectively. Of the 40 pulmonary TB cases, 90% also had disseminated extra-pulmonary TB. Chest radiology could not reliably distinguish the pathologies pre-mortem.

CONCLUSIONS: TB was the leading cause of death in our series of HIV-positive adults in Botswana, selected towards those with chest disease; in most, it was widely disseminated. Bacterial pneumonia also played an important role in mortality. Pneumocystis carinii pneumonia was present, but relatively uncommon.

KEY WORDS: HIV/AIDS; pathology; mortality; tuberculosis, Pneumocystis carinii; Africa; Botswana
Natural history of TB

Risk factor → Exposure → Infection → Infectious TB (Sm+) → Death
Risk factor → Exposure → Infection → Non-inf. TB (Sm-) → Disease

Don’t confuse: risk of Exposure-Infection with risk of Disease
Natural history of TB

Don’t confuse: risk of Exposure-Infection with risk of Disease
Thank You