What is TB?

- Tuberculosis is an infectious disease caused by bacteria (mycobacterium tuberculosis)
- The TB bacteria usually attack the lungs but it can also attack the kidneys, spine & brain. It is fatal if untreated
Tuberculosis – Old Disease

- TB present in human population since 2400 BCE
- Egyptian mummies shown signs of tubercular decay in spine and skull
460 BCE Greece Hippocrates called disease Phthisis
Wide spread always fatal
17th century to the next 200 years epidemic in Europe called “Great White Plague”
TB was in America before Columbus
History Cont’d

- 17th century Franciscus Sylvius de la Boe of Amsterdam first to identify tubercles as a characteristic consistent with TB infection
- English physician Richard Morton confirmed tubercles always present in the lungs of TB infection
- Gaspard Laurent Bayle (1774-1816) proved tubercles were not products of TB, but the cause.
- TB appeared in the medical language in connection with Bayle’s theory
- 1720 English physician Benjamin Marten said “TB could be caused by wonderfully minute living creatures ….”
- He stated lying in bed, eating, drinking, talking or breathing could spread disease
March 1882, in Berlin, Robert Koch proved to German doctors that bacilli caused TB

He became known as The Father of Bacteriology

Receive the Nobel Prize in Physiology in 1905
Mortality from tuberculosis in developed countries

Mortality rate per 100,000

Tb evidenced in 4,000 BC
Mortality from tuberculosis in developed countries

Mortality rate per 100,000

1804 Laennec associates lesions, describes “phthisis”

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- 1882, Koch discovers mycobacterium tuberculosis
- 1946, Streptomycin used as antibiotic
- 1917 Flu pandemic
Famous victims of TB

• Anton Chekov
• Branwell Bronté
• Emily Bronté
• Frédéric Chopin
• John Keats
• D.H. Lawrence
• Vivien Leigh
• George Orwell
• Paganini
• Edgar Allan Poe
• Jean J. Rousseau
• Sir Walter Scott
• P.B. Shelly
• R.L. Stevenson
• Simonetta Vespucci  girl friend of Guiliano de‘ Medici

He asks Sandro Botticelli to create a painting of her...
Tuberculosis

Sandro Botticelli, Die Geburt der Venus (1485/86), Uffizien, Florenz
Global Importance
Tuberculosis – The facts!

- TB is curable but kills 5000 people every day or 2 million per year.
- 2 billion people (1/3 of world’s population) are infected with the microbes that cause TB.
- 1 in 10 people infected with TB microbes will become sick with active TB in their lifetime.
- TB is contagious & spreads through the air: if not treated each person with active TB infects 10-15 people every year (approx).
- Almost 9 million new cases occurred in 2010.
Global importance

- Most prevalent infections of Human beings
- The World Health Organization (WHO) estimates that 1/3 of the world's population is infected with TB
- 7 to 8 million new cases occur each year
- The WHO estimates that between the year 2000 and 2020 one billion new people will be infected, 200 million will get sick, and 35 million will die
## The global burden of TB - 2012

<table>
<thead>
<tr>
<th>Estimated number of cases</th>
<th>Estimated number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All forms of TB</strong></td>
<td></td>
</tr>
<tr>
<td>8.6 million</td>
<td>1.3 million*</td>
</tr>
<tr>
<td>• 0.5 m in children</td>
<td>• 74,000 in children</td>
</tr>
<tr>
<td>• 2.9 m in women</td>
<td>• 410,000 in women</td>
</tr>
<tr>
<td><strong>HIV-associated TB</strong></td>
<td></td>
</tr>
<tr>
<td>1.1 million (13%)</td>
<td>320,000</td>
</tr>
<tr>
<td><strong>Multidrug-resistant TB</strong></td>
<td></td>
</tr>
<tr>
<td>450,000</td>
<td>170,000</td>
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</tbody>
</table>

* Including deaths attributed to HIV/TB

Source: WHO Global Tuberculosis Report 2013
At the 65th World Health Assembly in May 2012, Member States called upon WHO to develop a new post-2015 TB strategy and targets, and present this to Member States at the 67th World Health Assembly in 2014.
Estimated **absolute numbers** of reported cases with MDR-TB*

*among reported pulmonary TB patients*
Countries that had reported at least one XDR-TB case by Oct 2011
TB Incidence and TB Mortality, R. Moldova, 1991 - 2013

TB incidence, abs
Tb Mortality, abs
TB incidence - Rate/100000
TB Mortality - Rate/100000

DOTS
DOTS Plus

100% DOTS

Shortages in public health financing, including TB service

National health insurance

NTP 2001 - 2005
NTP 2006 - 2010
NTP 2011–2015
MDR TB, new cases and retreatment, Republic of Moldova, 2003 – 2013, %

- %MDR TB Primary
- %MDR TB Secondary

<table>
<thead>
<tr>
<th>Year</th>
<th>%MDR TB Primary</th>
<th>%MDR TB Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>6%</td>
<td>38%</td>
</tr>
<tr>
<td>2004</td>
<td>10%</td>
<td>39%</td>
</tr>
<tr>
<td>2005</td>
<td>13%</td>
<td>50%</td>
</tr>
<tr>
<td>2006</td>
<td>19%</td>
<td>51%</td>
</tr>
<tr>
<td>2007</td>
<td>18%</td>
<td>52%</td>
</tr>
<tr>
<td>2008</td>
<td>24%</td>
<td>59%</td>
</tr>
<tr>
<td>2009</td>
<td>22%</td>
<td>68%</td>
</tr>
<tr>
<td>2010</td>
<td>25%</td>
<td>65%</td>
</tr>
<tr>
<td>2011</td>
<td>26%</td>
<td>64%</td>
</tr>
<tr>
<td>2012</td>
<td>24%</td>
<td>64%</td>
</tr>
<tr>
<td>2013</td>
<td>25%</td>
<td>61%</td>
</tr>
</tbody>
</table>
Why the global increase of TB?

- Population growth
- Urbanisation
- Increasing poverty
- Rates of HIV infection – this weakens the immune system. If HIV + 100x more likely to develop TB
- Drug resistant TB (costs for LEDCs?)
- Young adults & women aged 15-44, most at risk
- Poorly managed TB programmes – especially in LEDCs (Africa & SE Asia)
The Problem Gets Worse

- Multi-Drug Resistance TB (MDR-TB)-strain of TB resistant to front line anti-biotic treatment
- Extensively Drug Resistance TB (XDR-TB)-strain of TB resistant to first and second line antibiotic treatment
- Confirmed cases in 45 countries
- Requires lengthier and more costly treatments
MDR TB is a manmade problem.....It is costly, deadly, debilitating, and the biggest threat to our current TB control strategies.
MDR-TB
SPREADING THROUGH
ALL HUMANITY
Causes of TB epidemic in Moldova

1. Socio-economical crisis
2. Massive migration of population
3. Unemployment;
4. Shortages in public health financing, including TB service:
   a) deficiency of the cooperation between the TB service and both, Primary Health Care and Public Health Centers;
   b) insufficient support of implementation and inadequate financing of the programme;
   c) lack of antituberculosis drug supply during 1996-2001
5. Tuberculosis in prisons
6. High levels of MDR-TB
Reasons of TB Resistance in Moldova

1. Poor infection control in TB hospitals
2. Low compliance of treatment (massive migration of population, patient knowledge, health system)
3. The lack in surveillance of the treatment (~ 60% of DOT)
4. Very low treatment success rate of new and re-treatment TB (62.2%)
5. Increasing of number of patients with TB/HIV co-infection
Control and Prevention
DOTS (Directly Observed Treatment Short Course)

- Currently the most effective method of treating TB
- 6 to 8 months of drug treatment including direct supervision by health care providers
- Treatment requires months and is labor intensive
“If the Global Plan to Stop TB 2006-2015 is fully funded and implemented, 14 million lives will be saved and 50 million people treated.”

World Health Organization
Mycobacterium tuberculosis
Overview Mycobacteria

• There are >70 species of mycobacteria

• Of these, two are major pathogens:
  1. Mycobacterium tuberculosis (Koch, 1882)
  2. Mycobacterium leprae (Hansen, 1874)

• The remaining mycobacteria are environmental organisms—collectively known as MOTTS (Mycobacteria Other Than Tuberculosis)

• MOTT organisms are responsible for opportunistic infections, especially in people with AIDS
Classification

Mycobacteria belong to the

• Order: ACTINOMYCETALES
• Family: MYCOBACTERIACEAE
• Genus: MYCOBACTERIUM

All mycobacteria are:
1. ACID FAST - i.e. they do not destain with acid and alcohol once stained with arylmethane dyes
2. AEROBIC
3. CONTAIN MYCOLIC ACIDS
4. THEIR GENOMES HAVE A 59-66% GC CONTENT
5. Resistant to drying and chemical disinfectants
6. Sensitive to heat (Pasteurization) and UV light
**Mycobacterium tuberculosis**

- Member of the *Mycobacterium tuberculosis* complex which includes *M. tuberculosis*, *M. bovis*, *M. africanum*
- An obligate aerobe
- Non-spore forming, Non-motile
- Cell wall lipid rich (25-60% dry weight of the organism), mycolic acid – retains acid fast stain
- Virulence factors---Cord factor, sulfatides
- Growth - doubling time of 15-20 hrs
Lipid-Rich Cell Wall of Mycobacterium

Mycolic acids
- D-arabinose and D-galactose
- N-acetylglucosamine and N-acetylmuramic acid
- D-glutamic acid, m-diaminopimelic acid, L- and D-alanine

CMN Group:
Unusual cell wall lipids (mycolic acids, etc.)

(Purified Protein Derivative)
Mycobacterial cell wall

- Proteins
- Man-capped lipoarabinomannan
- Mycolic acid
- Glycolipids
- Arabinogalactan
- Peptidoglycan
Sources of infection

- the patient with pulmonary tuberculosis
- cattle are the principal reservoir for M. bovis
Pathways of infection penetration in the body

- TB is spread **through the air** in droplet nuclei 1-5 microns in size containing tubercle bacilli
- Transmitted by coughing, sneezing, singing, talking, breathing infected air
- Ease of transmission depends on duration and proximity of contact as well as the number of bacteria excreted
- Infection can result from only 1-5 bacteria entering a terminal alveolus
- Only those with active pulmonary TB are infectious
Transmission

- **Digestive route** - transmitted through cow’s milk before pasteurization

- **Mucocutaneous route**

- **Placental transmission**
Pathogenesis of TB

Infection - Immunity
Pathogenesis of tuberculosis

- Infection versus disease
  - Host factors
  - Pathogen factors
Pathogenesis

- Host factors include
  - Social e.g.
    - Poverty
    - Alcoholism
  - Age e.g.
    - Baby
    - Teenage girl
    - Old age
  - Immunity e.g.
    - HIV
    - Gamma interferon
Pathogenesis

- Organism factors e.g.
  - Virulence factors
  - Drug resistance
Medical conditions that increase risk for active TB

- HIV positive
- Substance abuse
- Diabetes Mellitus
- Silicosis
- Cancer of the head or neck
- Leukemia or Hodgkin’s disease
- Severe Kidney Disease
- Low body weight > 10% of ideal body weight
- Certain Medical Treatments (corticosteroid treatment or organ transplant)
- Specialized treatment for rheumatoid arthritis or Crohn’s disease
TB Transmission: from Infection to TB disease

- From person (TB patients) to person
- Via airborne transmission (cough, sneeze etc)

- Non infected person
- Infected person (healthy)
- TB patient (active TB)

10% life time risk to develop TB
HIV+: 10% annual risk of TB
Figure 2. A model for tuberculosis epidemiology, following the pathogenesis of tuberculosis. Figure reproduced with the permission of Urban & Vogel from [2].
Human tuberculosis: Natural History

- Infection
- Initial containment – 95%
- Early Progression - 5%
  “Fast TB”
Tuberculosis: Transmission and Natural History

Initial containment – 95%

Infection

Self-Cure – 90%

Initial containment – 95%

Early Progression - 5%
“Fast TB”

Late Progression - 5%
“Reactivation TB”
Natural History of TB Infection

Exposure to TB

No infection (70-90%)

Infection (10-30%)

Latent TB (90%)

Never develop Active disease

Active TB (10%)

Untreated

Die within 2 years

Survive

Treated

Die

Cured

4/22/2013

Dr. T. V. Rao MD
Overview of TB pathogenesis

Primary infection (tuberculin positive) →

\[
\begin{align*}
\text{90\% no sequellae} \\
\text{5\% primary TB (within 2 years)} \\
\text{5\% reactivation (later in life)}
\end{align*}
\]

GET IN

STAY IN

GET OUT

WHY?
Pathogenesis of infection with *Mycobacterium tuberculosis*

- mycobacteria-containing droplets
- primary infection
- primary lesion
- Ghon complex = granuloma + draining lymph node
Pathogenesis of infection with Mycobacterium tuberculosis

- Mycobacteria-containing droplets
- Primary infection
- Primary lesion
- Ghon complex = granuloma + draining lymph node
- Abortive infection (?)
- Containment of infection
- Uncontrolled spread in immunocompromised patients
Pathogenesis of infection with Mycobacterium tuberculosis

- **Latent**: strong cellular immunity, containment to granuloma
- **Active**: weak cellular immunity, exacerbation, spread

Immunosuppression (malnutrition, HIV, aging, immunosuppressive drugs etc.)

Exogenous reinfection
Progression of TB

1. Tubercle bacilli that reach the alveoli of the lung (Figure 24.2) are ingested by macrophages, but some often survive. Infection is present, but no symptoms of disease.

2. Tubercle bacilli multiplying in macrophages cause a chemotactic response that brings additional macrophages and other defensive cells to the area. These form a surrounding layer and, in turn, an early tubercle. Most of the surrounding macrophages are not successful in destroying bacteria but release enzymes and cytokines that cause a lung-damaging inflammation.
Progression of TB

After a few weeks, disease symptoms appear as many of the macrophages die, releasing tubercle bacilli and forming a caseous center in the tubercle. The aerobic tubercle bacilli do not grow well in this location. However, many remain dormant (latent TB) and serve as a basis for later reactivation of the disease. The disease may be arrested at this stage, and the lesions become calcified.
Progression of TB

4 In some individuals, disease symptoms appear, as a mature tubercle is formed. The disease progresses as the caseous center enlarges in the process termed liquefaction. The caseous center now enlarges and forms an air-filled tuberculous cavity in which the aerobic bacilli multiply outside macrophages.

5 Liquefaction continues until the tubercle ruptures, allowing bacilli to spill into a bronchiole (see Figure 24.2) and thus be disseminated throughout the lungs and then to the circulatory and lymphatic systems.
Pathogenesis of Tuberculosis

- Inhalation of small (1-5 μm) droplet nuclei containing M. tuberculosis expelled by coughing, sneezing, or talking of another individual with cavitary tuberculosis.
Pathogenesis

- Inhalation -> phagocytosis by alveolar macrophages
- Bacterial multiplication occurs intracellularly
- Lymphatic spread to regional lymph nodes or hematogenous dissemination
- Immune response results in granuloma formation (containment of infection)
- Cell death in the granuloma results in caseous necrosis
- Bacteria can remain dormant in the granuloma
Pathogenesis

- Inhaled aerosols
  - Engulfed by alveolar macrophages
    - Bacilli replicate
    - Macrophages die

- Infected macrophages migrate to local lymph nodes
  - Develop Ghon’s focus
  - Primary complex

- Cell mediated immune response stops cycle of destruction and spread

- Viable but non replicating bacilli present in macrophages

Evidence of infection with M Tuberculosis:
- Chest x-ray / positive skin test
Pathogenesis of Tuberculosis

- Dissemination of infected macrophages through the draining lymphatics into the circulation
- Development within 3-8 weeks of a CD4+ T cell dependent cell-mediated immune response with granuloma formation and macrophage activation at sites of infection
Immunity in Tuberculosis

- Antigen-specific activation of CD4+ T lymphocytes with secretion of IL-2, increased expression of IL-2 receptors, and secretion of IF-γ
- Antigen-driven clonal expansion of CD4+ T lymphocytes by IL-2 acting via autocrine and paracrine mechanisms
- Activation by IF-γ of Mycobacterium tuberculosis killing by macrophages
The human tuberculous granuloma
Pathogenesis of Tuberculosis

- Active infection usually transformed into latent infection (exceptions: infants, AIDS)
- With decrement in T-cell dependent cell mediated immunity (years later) infection reactivated with development of tuberculosis (HIV infection, diabetes mellitus, renal disease, cancer, advanced age)
Pathogenesis of Tuberculosis

- Reactivation of M. tuberculosis infection with partial immunity produces high tissue concentrations of mycobacterial antigens that provoke an intense mononuclear cell response (type 4 hypersensitivity reaction)
Pathogenesis of Tuberculosis

- Dense mononuclear cell infiltrates damage tissue due to release of active oxygen radicals and lysosomal neutral proteases
- Tissue damage occurs as caseation necrosis that progresses to liquefaction necrosis in the absence of tuberculosis drug treatment
TB Pathogenesis

- Bacterial entry
- T Lymphocytes
- Macrophages
- Epitheloid cells
- Proliferation
- Central Necrosis
- Giant cell formation
- Fibrosis
Histopathological Features of TB

- **Granulomas**: Focal tissue aggregates of epithelioid cells (activated macrophages), Langhans’ giant cells, lymphocytes, and granulation tissue (tubercles)

- Langhans’ giant cells reflect the most successful host tissue response in tuberculosis, absent in fulminant tuberculosis (especially AIDS patients)
Diagram of a Granuloma

NOTE: ultimately a fibrin layer develops around granuloma (fibrosis), further “walling off” the lesion.

Typical progression in pulmonary TB involves caseation, calcification and cavity formation.
Tuberculous Granulomas
Caseation Necrosis
Epitheloid cells in Granuloma
Cells in Granuloma
Symptoms of Infections

- Initially the symptoms are mild and may be mistaken for a cold or the flu
- TB grows most successfully in environments with high O2 content ex. Lungs and blood
- If infection persists or goes untreated, it can develop into progressive pulmonary TB which forms cavities in the lungs, hemoptysis fibrosis, and chest pain.