Lecture 9: Tuberculosis
Tuberculosis is highly contagious and spreads through the air from coughing.

If not treated, a person with TB infects an average of 10 to 15 new people each year.

Once thought to be under control, tuberculosis still kills well over 1.5 million people each year, a figure that is now increasing slightly each year.

Source: WHO
88 Volumes (1/year), around 6 issues/year
History and TB

- In the entire history of humankind, it is believed that tuberculosis has killed more people than any other disease (in shorter periods of time, the epidemics of the Black Death and AIDS have killed more).

- Tuberculosis dates back to at least 4000 BC and was present in ancient Egypt, Greece, Rome, and India.

- Known as consumption, it was responsible for one in five deaths in 17th century London.

Source: WHO
Famous people who died of TB

Doc Holliday, 1851-1887
Shooter with Wyatt Earp
Dentist, gambler, gun fighter
at the OK Corral
His mom also died of TB
c. 1342-1324 BC, King
Tutankhamen, died at aged 18,
Probably of TB – but an X-ray in
1969 showed a bone chip in his skull

Frederic Chopin, 1810-1849
Virtuoso pianist and composer
of the Romantic period
Famous people who died of TB

Cardinal Richelieu, 1581-1642
Spinoza, 1632-1677
Simon Bolivar, 1783-1830
John Keats, 1795-1821
Elizabeth Barett Browning, 1806-1861
Edgar Allen Poe, 1809-1849
Emily Bronte, 1818-1848
R.L. Stevenson, 1850-1894
Anton Chekov, 1860-1904
Eleanor Roosevelt, 1884-1962
D.H. Lawrence, 1885-1930
George Orwell, 1903-1950
Vivien Leigh, 1913-1967
Famous people who had/have TB

Jean Moliere, 1622-1673
Francois Voltaire, 1694-1778
Johann Goethe, 1749-1832
Sir Walter Scott, 1771-1832
Niccolo Paganini, 1782-1840
Ralph Waldo Emerson, 1803-1882
Fyodor Dostoyevski, 1821-1881 (lung hemorrhage associated with emphysema and an epileptic seizure)
Paul Gaugin, 1848-1903 (died of Syphillis instead)
Franz Kafka, 1883-1924 (died from not being able to eat with TB)
Adolf Hitler, 1889-1945 (died of suicide)
Nelson Mandela, 1918- [Hardloop Madiba!!]
Famous people who had/have TB

- Honore de Balzac, Gorky, Heinlein, Alexander Pope, Jean-Jacques Rousseau, John Ruskin, Dylan Thomas, Thoreau, Modigliani, Boccherini, Purcell, John Calvin, Alexis de Tocqueville, Ulysses S. Grant, Louis XII and XVII, Napoleon II, Rawlins, Alexander Graham Bell, Sarah Bernhardt, Louis Braille, W.C. Fields, Tom Jones, Kant, Florence Nightingale, Schrodinger, Ho Chi Minh, Camus (died in a car accident)

- Charles Bukowski (1920-1994), American author and poet, contracted TB in 1988; he recovered, losing 60 lbs.

- Rene Laennec, French physician; inventor of the stethoscope

- Takasugi Shinsaku (1839-1867), samurai
"The Next to Go: Fight Tuberculosis."
[American Red Cross], 1919. Poster
**Mycobacterium tuberculosis**

In 1882, the microbiologist Robert Koch discovered the tubercle bacillus, at a time when one of every seven deaths in Europe was caused by TB.

Robert Koch (Heinrich Hermann Robert Koch) was born on December 11, 1843 in Clausthal, Germany and died on May 27, 1910.

A physician, he isolated *Bacillus anthracis*, the tuberculosis bacillus AND the cholera vibrio. Nobel Prize for Physiology and Medicine in 1905.
**TB Symptoms**

TB has two "stages":

1. **TB infection or latent TB**
2. **Active TB or TB disease**

TB infection (latent TB) is characterized by the following:

- The TB germ is present in the body
- There are no symptoms
- The person is not infectious (contagious)
- Sometimes, antibiotics will be used at this stage to keep the TB infection from becoming disease.
**TB Symptoms**

- During *Active TB* symptoms of TB are present, which can include:
  - coughing
  - weight loss
  - loss of appetite
  - night sweats
  - fever
  - chest pain

- Active TB is infectious and can be spread by coughing, sneezing, laughing, singing, or just talking

*Insets: Nicole Kidman playing “Satine” in the movie Moulin Rouge – coughing up bloody sputum isn’t as romantic as it looks*
The agent: Mycobacteria sp.

- Actinobacteria (Phylum), family Mycobacteriaceae
- Genus *Mycobacteria*
- Species are described in several major groups for purpose of diagnosis and treatment:
  - *M. tuberculosis* complex which can cause tuberculosis: *M. tuberculosis*, *M. bovis*, *M. africanum*, and *M. microti*;
  - *M. leprae* which causes Hansen’s disease or leprosy;
  - Nontuberculous mycobacteria (NTM) are all the other mycobacteria which can cause pulmonary disease resembling tuberculosis, lymphadenitis, skin disease, or disseminated disease.
## The agent: Mycobacteria sp. – 137 species

1. *M. abscessus*
2. *M. africanum*
3. *M. agri*
4. *M. aichense*
5. *M. alvei*
6. *M. arupense*
7. *M. asiaticum*
8. *M. aubagnense*
9. *M. aurum*
10. *M. austroafricanum*
11. *Mycobacterium avium* complex (MAC), is a group of species which are significant cause of death in AIDS patients. Species in this complex include:
   - 12. *M. avium*
   - 13. *M. avium paratuberculosis*, which has been implicated in Crohn’s disease in humans and Johne’s disease in sheep
   - 14. *M. avium silvaticum*
   - 15. *M. avium “hominissuis”*
   - 16. *M. boenicei*
17. *M. bohemicum*
18. *M. bolletii*
19. *M. bovinense*
20. *M. bovis*
21. *M. branderi*
22. *M. brisbanense*
23. *M. brumae*
24. *M. canariasense*
25. *M. caprae*
26. *M. celatum*
27. *M. chelonaee,*
28. *M. chimaera*
29. *M. chitae*
30. *M. chlorophenolicum*
31. *M. chubuense*
32. *M. colombiense*
33. *M. conceptionense*
34. *M. confluentis*
35. *M. conspicuum*
36. *M. cookii*
37. *M. diernhoferi*
38. *M. doricum*
39. *M. cosmeticum*
40. *M. duvalii*
41. *M. elephantis*
42. *M. falax*
43. *M. farrinogenes*
44. *M. flavescens*
45. *M. florentinum*
46. *M. fluoroanthrenivorans*
47. *M. fortuitum*
48. *M. fortuitum subsp. acetamidolyticum*
49. *M. frederiksborgense*
50. *M. gaudi*
51. *M. gastri*
52. *M. genavense*
53. *M. gilvum*
54. *M. goodii*
55. *M. gordonae*
56. *M. haemophilum*
57. *M. hassiacum*
58. *M. heckeshornense*
59. *M. heidelbergense*
60. *M. hibernae*
61. *M. hodleri*
62. *M. holsticum*
63. *M. houstonense*
64. *M. immunogenum*
65. *M. interjectum*
66. *M. intermediate*
67. *M. intracellulare*
68. *M. kansasii*
69. *M. komossense*
70. *M. kubicae*
71. *M. kumamotonense*
72. *M. lacus*
73. *M. lentiflavum*
74. *M. leprae, which causes leprosy*
75. *M. lepraemurium*
76. *M. madagascariense*
77. *M. mageritense*
78. *M. malmoense*
79. *M. marinum*
80. *M. massiliense*
81. *M. microti*
82. *M. monacense*
83. *M. montefiorensense*
84. *M. moriokaense*
85. *M. mucogenicum*
86. *M. murale*
87. *M. nebraskense*
88. *M. neoaureum*
89. *M. neworleansense*
90. *M. nonchromogenicum*
91. *M. novocastrense*
92. *M. obuense*
93. *M. palustre*
94. *M. parafortuitum*
95. *M. parascrofulaceum*
96. *M. paratuberculosis*
97. *M. pergerinum*
98. *M. phlei*
99. *M. phocaicum*
100. *M. pinnipedi*
101. *M. porcinum*
102. *M. poriferae*
103. *M. pseudohotshottii*
104. *M. pulveris*
105. *M. psychrotolerans*
106. *M. pyrenivorans*
107. *M. rhodesiae*
108. *M. saskatchewanense*
109. *M. scrofulaceum*
110. *M. senegalense*
111. *M. seoulense*
112. *M. septicum*
113. *M. shimoidei*
114. *M. shottii*
115. *M. simiae*
116. *M. smegmatis*
117. *M. sphagni*
118. *M. szulgai*
119. *M. terrae*
120. *M. thermoresistibile*
121. *M. tokaiense*
122. *M. triplex*
123. *M. triviale*
124. *Mycobacterium tuberculosis* complex (MTBC); members are causative agents of human and animal tuberculosis. Species in this complex include:
   - 125. *M. tuberculosis, the major cause of human tuberculosis*
   - 126. *M. bovis*
   - 127. *M. bovis BCG*
   - 128. *M. africanum*
   - 129. *M. canetti*
   - 130. *M. caprae*
   - 131. *M. pinnipedi*
   - 132. *M. tusciae*
   - 133. *M. ulcers, which causes the “Buruli”, or “Bairnsdale, ulcer”*
   - 134. *M. vaccae*
   - 135. *M. vanbaalenii*
   - 136. *M. wolinskyi*
   - 137. *M. xenopi*
M. avium complex (MAC)

*Mycobacterium avium complex* (MAC), is a group of species which are a significant cause of death in AIDS patients.

Thought to be acquired environmentally, they cause disease in birds primarily, ungulates and swine also

- *M. avium avium*
- *M. avium paratuberculosis*, which has been implicated in Crohn's disease in humans and Johne's disease in sheep
- *M. avium silvaticum*
- *M. avium "hominissuis"
- *M. avium intercellulare*
**M. avium complex (MAC)**

- MAC can spread through the bloodstream to infect lymph nodes, bone marrow, liver, spleen, spinal fluid, lungs and intestinal tract. Typical symptoms of MAC include night sweats, weight loss, fever, fatigue, diarrhea and enlarged spleen.

- MAC is usually found in people with CD4 counts below 100.

- **Lady Windemere’s Syndrome** is caused by *M. avium* – named after the Oscar Wilde character in *Lady Windemere’s Fan* who seemed to have characteristic symptoms:

  "How do you do, Lord Darlington. No, I can't shake hands with you. My hands are all wet with the roses."
**M. tuberculosis complex (MTBC)**

Causative agents of human and animal tuberculosis. Species in this complex include:

- *M. tuberculosis*, the major cause of human tuberculosis
- *M. bovis*
- *M. bovis BCG*
- *M. africanum*
- *M. canetti*
- *M. caprae*
- *M. pinnipedii'* (pinnipeds – poor seals!)
M. Tuberculosis – ‘human TB’

22 countries have 80% of TB cases today (tbalert.com)
M. Tuberculosis – ‘human TB’

- How many people have tuberculosis today?
- Reporting to the WHO is a hassle if you have civil war
- Getting tested, staying on meds, filling out paperwork is complicated if you’re lacking clinics
- 2004, mortality and morbidity statistics included 14.6 million chronic active TB cases, 8.9 million new cases, and 1.6 million deaths,
- 2000 to 2004, 20% of TB cases were resistant to standard treatments and 2% resistant to second-line drugs
- MDR and XDR TB are the bane of modern existence
M. Tuberculosis – ‘human TB’

- Tuberculosis is more common in elderly persons.
- More than one-fourth of the nearly 23,000 cases of TB reported in the United States in 1995 developed in people above age 65.
- Many elderly patients developed the infection some years ago when the disease was more widespread.
- Those living in nursing homes and similar facilities are in close contact with others who may be infected. The aging process itself may weaken the body's immune system, which is then less able to ward off the tubercle bacillus. Finally, bacteria that have lain dormant for some time in elderly persons may be reactivated and cause illness.
M. Tuberculosis – ‘human TB’

- TB also is more common in blacks, who are more likely to live under conditions that promote infection.
- As the end of the century approaches, two-thirds of all cases of TB in the United States affect African Americans, Hispanics, Asians, and persons from the Pacific Islands.
- Another one-fourth of cases affect persons born outside the United States. As of 1992, the risk of TB was still increasing in all these groups.
M. Tuberculosis – ‘human TB’

- Lifestyle factors promoting risk
- The high risk of TB in AIDS patients extends to those infected by HIV who have not yet developed clinical signs of AIDS.
- Alcoholics and intravenous drug abusers are also at increased risk of contracting tuberculosis.
- Economic and social factors – until these are remedied, there is no real possibility of completely eliminating the disease.
**M. Tuberculosis – ‘human TB’**

- **TB test is the Mantoux skin test (PPD)**
  - a small amount of fluid (called tuberculin) is injected into the forearm just under the skin.
  - A health professional should read the test 48 to 72 hours after it is administered to check for a reaction.
  - If there is a reaction (swelling), more testing is done.
  - The Tine test (which uses a 4-pronged device) is no longer recommended because it is not as effective in delivering the proper amount of tuberculin under the skin.

- **TST and the QuantiFERON®-TB Gold test (QFT-G) are not contraindicated for persons who have been vaccinated with BCG.**
  - Um, okay. (CDC)
M. Tuberculosis – ‘human TB’

- A positive test generally means that a person is infected with TB
- Only 10% of people who test positive for TB infection ever develop active disease
  - For HIV positive people the risk is much higher.
  - HIV can also produce a false negative reading on the Mantoux skin test

- After a positive test, an X-ray or sputum (coughed up phlegm) sample is needed to confirm active disease.

- MSF (Medecins Sans Frontiers) complaint that the microscope method is old (120 years ago), and can only detect 45-65% of cases
  - TB is out of control (DoctorsWithoutBorders.org)
    - “Today, Tuberculosis will kill 5,000 people. Why?”
The standard four medications (yes, all at once) for starting treatment for TB in the US are:

- Isoniazid (called INH)
- Rifampicin
- Pyrazinamide (PZA)
- Ethambutol

- Ok, so you take your pills
  - For 6-8 months
<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Reactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Hepatitis, drug interactions, numbness, tingling, pain in extremities, fatigue</td>
<td>Raises Dilantin and INH blood serum levels if taken together; this may lead to toxicity</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Stomach upset, Symptoms of Flu, Bleeding, Rashes, Hepatitis</td>
<td>If you are taking other drugs (such as birth control pills) consult your doctor. Rifampin can turn body fluids orange but this is temporary.</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Joint aches, Hepatitis, Rashes, Stomach upset, Gout (rarely)</td>
<td>Avoid in pregnancy</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Visual Problems</td>
<td>Should not be used in young children whose vision can't be tested unless there is drug resistant TB</td>
</tr>
</tbody>
</table>

And no drinking while taking the meds

*and they might not work*

This table was compiled from the CORE CURRICULUM ON TUBERCULOSIS - What the clinician should know 3rd edition, 1994. Published by the U.S. Department of Health and Human Services. Source: http://medicine.emory.edu/id/ATPC/tbinfo.html
Antibiotics used to treat “TBs” of all kinds

• Rifampicin
• Rifabutin
• Ciprofloxacin
• Amikacin
• Ethambutol
• Streptomycin
• Clarithromycin
• Azithromycin
The Romance of Consumption: The rise of the sanitorium

• In Victorian times, because antibiotics were unknown, the only means of controlling the spread of infection was to isolate patients in private sanitoria or hospitals limited to patients with TB—a practice that continues to this day in many countries.

• The net effect of this pattern of treatment was to separate the study of tuberculosis from mainstream medicine.

• Entire organizations were set up to study not only the disease as it affected individual patients, but its impact on the society as a whole.
Save the people with tuberculosis – romanticizing ‘consumption’

Association d'Hygiène Sociale et de Préservation Antituberculeuse du 1st Arr..ont.,
*Sauvons les Tuberculeux*, color trade card, Paris, c. 1929,
In the U.S.

- At the turn of the twentieth century more than 80% of the population in the United States were infected before age 20, and tuberculosis was the single most common cause of death.

- By 1938 there were more than 700 TB hospitals in this country.
Arkansas Sanitorium, Booneville

- By the late 1800's and early 1900's, tuberculosis was taking over the population of not only Arkansas, but also the United States. Highly contagious, poorly understood and almost impossible to cure, the mortality rate was very high (80.2%).
- Urged by Judge Joseph Hill, who was diagnosed with Tuberculosis in the fall of 1905, the Arkansas Legislature passed Act 378 in March of 1909 to construct the Arkansas Tuberculosis Sanatorium.
- First Patient Admitted - August 1910
- 1910 Patient Population - 64
- 1959 Patient Population - 1,017
- Last Patient Discharged - February 1973
- Act 320 of 1973 Authorized Closing the State Sanatorium

http://www.booneville.com/C-TB.htm
Arkansas Sanitorium, Booneville

The three purposes of the Sanatorium, according to the 1909 Act, were to:

1. To search for the tuberculosis people among the Arkansas population and see to their supervision and treatment

2. To search for the people who had been exposed to the infection and give them repeated examinations

3. To weed out tuberculosis among people who appeared to be well, even those who had no known contact with the disease

http://www.booneville.com/C-TB.htm
"The Board has decided that the Sanatorium should be located south of the mountains and will need a large tract of land, at least 1000 acres. The site should be a section free of malaria, where the drainage is good and the streams fresh and wholesome; the soil should be sandy or rocky in order for there to be as little dampness as possible. Pine lands where the timber has been cut off is preferable, and it must be where the transportation facilities are adequate for patients to come from all parts of the state . . ."
The Romance of Consumption: The fall of the sanitorium

- When streptomycin, the first antibiotic effective against *M. tuberculosis*, was discovered in the early 1940s, the infection began to come under control.

- Although other more effective anti-tuberculosis drugs were developed in the following decades, the number of cases of TB in the United States began to rise again in the mid-1980s.

- This upsurge was in part again a result of overcrowding and unsanitary conditions in the poor areas of large cities, prisons, and homeless shelters.

- Infected visitors and immigrants to the United States also contributed to the resurgence of TB.
**M. bovis – ‘cow TB’**

*Badgers, Buffalo and Elephants*

- 1st half of 20th century, estimated that more farm animals died of *M. bovis* than all other infectious diseases combined

- 1930s UK, 40% of cattle were infected with *M. bovis* leading to 50,000 cases of human *M. bovis* a year

- 2004, UK, 5.6% of herds had any bTB infection, since 1990, one human case of *M. bovis*

- Destructive method w/ random testing

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M. bovis – ‘cow TB’

- Pasteurization reduced human transmission – mostly caught from infected milk
  - Still happens in parts of the world where milk is just milk
  - Can also be caught from aerosol droplets from cattle or other bovids

- Internationally regulated for beef cattle trade
  - Countries gain TB-free status via veterinary checks and reporting
  - Clearly involves some issues
M. bovis – ‘cow TB’

- Around 30 years ago, in the UK, badgers (Meles meles) were found to carry bTB
- Famous report in 1997 (Krebs et al.) showed that badgers were a major vector for TB in cattle herds
- Conservationists versus Farmers
- The Randomised Badger Culling Trial
  - Proactive and reactive local culling of badgers
  - Badger behavior makes this a bad idea – lots of papers studying this
- Badgers really are quite big in the UK – icon of the countryside and also a suburban fixture

Badgers in a suburban garden (from the failblog.wordpress.com)
**M. bovis – ‘cow TB’**

- Test and cull methods – most of Europe is TB-free
- Some of the Caribbean (including Cuba) are mostly free
- Australia is mostly free – except remaining possible reservoir in wild, introduced Asian water buffalo (*Bubalus bubalis*)
- Brush-tailed possums in New Zealand
- White tailed deer in Michigan
- Elk in Manitoba, Canada
Treat yourself to real mozzarella di bufala

Fresh from our farm in northern California, delivered to your door.

http://www.realmozzarella.com/
**M. bovis – ‘cow TB’**

- Kruger National Park, South Africa
- Epidemic front is moving northward from its point of introduction from cattle in the south, sometime around the 1960s (estimate).
- Buffalo are a reservoir host, maintaining the disease at high prevalence (~60%)
- Predators such as lions and leopards appear to be spill-over hosts.
- As an exotic disease, managers would like to control or eradicate this disease via culling, vaccination, or a combination of the two.
Kruger National Park, around 19,000 km² (Israel, Scotland, New Jersey)
One herd of African buffalo (around 450) at a waterhole, Klaserie
Bovine TB

August 10th, 2001, KNP
M. bovis – ‘cow TB’ in KNP

- At prevalence upward of 60% in the major reservoir (30k+ buffalo), culling is not a good strategy
- Lions and other predators need buffalo
- Spillover hosts make managing it hard
  - Kudu shed it through their ears onto the shrubs!
- LARGE park
- Not a lot of economic resources
- Inefficient vaccines
- People living around the park are refugees
  - Often with HIV
  - Subsistence living
  - Displaced by the park
  - Cattle farmers with, yes, cows and no pasteurization
Spillback issues

• Elephants and rhinos in zoos can get TB, both kinds
  – Who is going to test them? (unfinished work with the AAZV/Audubon society)
  – Quarantine for CITES species – big skin test
    • Active or latent – will you send the ellie back?
    • Did it get it in the zoo or in the wild?

• Baboons in the Serengeti
  – (Sapolsky, A Primate’s Memoir)
    • TB positive meat in the dump, raided by Baboons
  – Baboons in KNP had the same problem – different dead animal
TB Management?

- Identification of TB is hard
- Treatment is long and expensive
- Complications of zoonotic TBs
- Complications with HIV
- Rising MDR and XDR strains (readings)
- Socioeconomic risk factors and crowding will increase
Silver lining?

- In 1995 the World Health Organization launched a multi-pronged tuberculosis program called DOTS (Directly Observed Therapy – Short course).
- Since then it has successfully treated more than 22 million tuberculosis patients.
- Funding is needed so that this effective program can expand to reach all the people who need it.

Sources: WHO, Stop-TB Partnership
HOW TO PREVENT CONSUMPTION (TUBERCULOSIS) AND OTHER GERM DISEASES
For School Children to Take Home and to Read Every Day.
DON'T FORGET THESE FACTS.

Germs are very small microscopic plants. Germs are found in all Dust and Dirt. Some germs are harmless, others cause disease. Germs cause Consumption. Avoid germs and Prevent Consumption.

TRY TO

TRY to breathe through the nose rather than through the mouth.
TRY to fill the lungs with pure air, free from dust.
TRY to turn the head away from a person when coughing or sneezing, or hold a handkerchief or your hand over your mouth.
TRY to spit out material coughed up from the lungs.
TRY to spit into a piece of paper or cloth and burn as soon as possible.
TRY to gargle your throat with salt water or some other mild mouth wash after being exposed to any contagious disease.
TRY to clean the nose with a handkerchief.
TRY to keep the hands clean.
TRY to keep your finger nails cut short.
TRY to brush your teeth night and morning.
TRY to eat clean food and drink pure water.
TRY to eat slowly and chew your food well.
TRY to keep moving about when heated from play.
TRY to keep your feet dry.
TRY to sleep in a room with partly-opened windows.
TRY to live in the sunshine.
TRY to be out of doors as much as possible.

TRY NOT TO

Try NOT to take a full breath in a cloud of dust.
Try NOT to cough or sneeze in another’s face.
Try NOT to swallow what you raise in coughing.
Try NOT to spit upon the floor or sidewalk.
Try NOT to cough long without seeing a physician.
Try NOT to kiss a sick friend.
Try NOT to pick your nose with your fingers.
Try NOT to eat with dirty hands.
Try NOT to eat things made dirty by the handling of other persons.
Try NOT to eat a piece of candy or apple picked up from the sidewalk or street.
Try NOT to have long and dirty finger nails.
Try NOT to go about with unclean teeth.
Try NOT to drink out of a cup that has been used unless you wash it first.
Try NOT to eat when heated or tired.
Try NOT to eat fast.
Try NOT, when heated, to sit down where it is cold.
Try NOT to play in wet shoes and stockings.
Try NOT to sleep in a warm or hot room.
Try NOT to shut out the sunshine.
Try NOT to form the habit of living around a stove.

Gardner Association for the Prevention and Relief of Tuberculosis.
NEXT WEEK

Guest Lecture:
Dr. Maria Sanchez, UC Berkeley

*Ongoing TB and HIV research*