Tuberculosis

2017

Lea Pehme, PhD
Senior Lung Physician
Lung Clinic
Tuberculosis (TB) is a disease caused by bacteria that are spread through the air from person to person. If not treated properly, TB disease can be fatal. People infected with TB bacteria who are not sick may still need treatment to prevent TB disease from developing in the future. Learn to recognize the symptoms of TB disease and find out if you are at risk.

**TB Case**

- Symptoms 6 months
- Shortness of breath on physical exercise
- Night sweats and cough with sputum.
- General condition is satisfactory levels
- Worked in agriculture
- Smear positive 3+

Female, 62 years
Topics

- Epidemiology of TB
- Transmission of TB
- TB Pathogenesis
- Risk factors for TB
- Diagnosis
  - Latent TB
    - Mantoux test
    - IGRA test
  - Active TB
    - General symptoms, pulmonary symptoms
    - Radiology
    - Mycobacteriology
- TB Treatment. Sensitive and multiresistant cases.
  - Outcomes of TB
- Tuberculosis and immunosupression
  - Anti TNF alpha treatment
  - HIV
  - ESRD
  - Transplant recipients/drug-mediated immunosuppression
- TB prophylaxis. BCG-Vaccination
- Summary. TB policy in the near future
• Prevalence of infectious cases
• Duration of illness
• Intensity, frequency and duration of contact

Largely exogenous
• Particles/volume x exposure time
• Production of infectious droplets
• Clearance of air
• Extent of exposure

Largely endogenous
• Innate resistance
• Performance of cell-mediated immunity
• Strain virulence

• Form and site of TB
• Age
• Patient’s susceptibility
• Delay in diagnosis

TB epidemiological model
Transmission of TB
Latent TB.
• **Exposure** is defined as occurring in a person who breathes in an environment that contains tubercle bacilli.
• A pragmatic definition thus might be contact with a person at a distance that allows talking when outdoors.
• Indoors, it might be defined as a room in which a tuberculosis patient has been within the past few hours.
Tuberculosis (TB) is caused by a bacterium called *Mycobacterium tuberculosis*. The bacteria usually attack the lungs, but TB bacteria can attack any part of the body such as the kidney, spine, and brain. 

WHO, Mar 20, 2016

- TB can affect all organs and tissues
- The localization of TB depends
  - Age
  - Gender
  - Race
  - Immune status (HIV, anti-TNF alpha treatment)

- EPTB in HIV negative patients 10–50%, in HIV positive patients 30–75%

From a clinical and public health perspective, patients with TB are pragmatically classified as having

- **latent TB infection** (LTBI), which is an asymptomatic and non-transmissible state,
- **active TB disease**, which is transmissible (in active pulmonary TB) and for which culture-based or molecular diagnostics can be used.
The number of bacilli influenced by

- a form of the disease (cavitary pulmonary)
- events promoted aerolization of respiratory secretions

Potential Transmitters of *M. tuberculosis*

- Persons who cough
- Persons with sputum positive for acid-fast bacilli
- Persons not on chemotherapy
- Persons with a poor response to chemotherapy
Transmission of *M. tuberculosis*

- *M. tuberculosis* is spread from person to person through the air
- It is spread primarily by droplet nuclei expelled by a person who has infectious TB disease.
- When a person with pulmonary or laryngeal TB coughs, sneezes, speaks, or sings, droplet nuclei containing *tubercle bacilli* are expelled into the air.

Spread in droplet nuclei (1-5 µm) produced by sneezing, coughing and talking

Transmission *M. bovis* takes place in endemic areas via unpasteurized milk products.
Smaller droplets dry in air and form droplet nuclei

Dry in air

Droplets below <140 µm evaporate in 2 sec – forming droplet nuclei (1-5 µm)

Droplet nuclei can contain bacilli (2-3 M. tub) Small particles float in air

Very small droplets take a long time to reach the ground while large ones reach it very fast

All but very small droplets would fall to the ground from a height of two meters in less than 10 seconds

Droplet nuclei can penetrate a normal surgical mask
- Sediment – 1 cm/min if no air currents
The large droplets and the mucoid matter rapidly fell to the ground, forming large complex structures with dust.

The time such larger droplets spend in the air is too short for them to be inhaled by a susceptible person.

These particles, even if made airborne again, were highly unlikely to traverse the airways when inhaled.

Very small droplets take a long time to reach the ground from 2 meters above ground, while large ones reach it very fast.

All but very small droplets would fall to the ground from a height of two meters in less than 10 seconds.

Very small droplets containing particles (*M. tuberculosis*) will evaporate until only *M. tuberculosis* (one to a few bacilli) remain. These are then called **infectious droplet nuclei**.

Infectious droplet nuclei are the principal source of transmission of *M. tuberculosis*.

Small enough to reach alveolus in the periphery of the lung.
Coughing produces by far the largest number of droplets.

**Larger particles**
- drop rapidly to the ground and reach the ground without appreciable loss by evaporation
- if inhaled, trapped in the mucociliary system of the tracheobronchial tree, swept up and rendered harmless through swallowing
- these particles, even if made airborne again - were highly unlikely to traverse the airways when inhaled

**Very small droplets**
- settle slowly and evaporate almost immediately
- droplet nuclei settle at a rate of 0.2 mm per second, they stay airborne for long periods
- depending on the environment, these tiny particles can remain suspended in the air for prolonged periods

Transmission of TB via routes other than aerosols – theoretical
• Transmitted in the same way as drug-susceptible TB

• Drug-resistant TB is no more infectious

• Delay in the recognition of drug resistance and resultant prolonged periods of infectiousness, may facilitate increased transmission.
Transmission of tuberculosis via routes other than aerosols

- Direct transfer in bronchoscopy: Possible
- Gastrointestinal tract: Minimal risk
  - 10,000 x higher infective dose compared to inhalation
- Books: No
- Bed clothing
- Cups, spoons
- Floors, table surfaces
- Infection via skin: Minimal risk

TB is not transmitted normally on hand welcoming, the same dishes or toilet
Transmission of TB, Contributing Factors

TB patient must be able to produce airborne infectious droplets (TB of the respiratory tract)

When a susceptible person inhales droplet nuclei containing the tubercle bacilli, TB transmission may occur.

The probability that TB will be transmitted depends on the

1. Infectiousness of the person with TB disease (smear results, cough)
2. Contact factors Duration of exposure
3. Environmental conditions
4. M. tuberculosis factors enhancing transmission
1. Infectiousness of the person with TB disease

Potential Transmitters of *M. tuberculosis*

- Disease in the lungs or larynx, presence of cavities
- Persons who cough (purulent cough)
- Persons with sputum positive for acid-fast bacilli
- Persons not on chemotherapy
- Persons with a poor response to chemotherapy
- Failure of the patient to cover the mouth and nose when coughing and sneezing
1. Infectiousness of the person with TB disease

- The infectiousness of a person with TB disease is directly related to the number of tubercle bacilli that he or she expels into the air. Persons who expel many tubercle bacilli are more infectious than patients who expel few or no bacilli.

- Patients with sputum smear-positive TB of the respiratory tract are more infectious than smear-negative (but culture-positive) patients (Shaw, Wynn-Williams, 1954; Grzybowski et al, 1975; van Geuns et al, 1975)

2. Contact factors

- Close contacts are at the highest risk of becoming infected with \textit{M. tuberculosis}
  Household contacts, contacts in similar age and social group (family members, roommates, friends, coworkers)

- Repeted expousures

- > 8 hours critical in well ventilated environments (airplanes)

- In the pre-chemotherapy era one infetious source infected about 20 persons during the 2-year period the case remined infectious before death or spontaneous bacteriologic conversion (Styblo, 1991)
3. Environmental factors
Risk of exposure in the society may vary

- **TB incidence**
  At the same level of incidence, risk of exposure may vary greatly

- **Population density**
  Urban, rural area, different areas of the country

- **Duration of infectiousness**
  Crucial importance for the risk of the general population, delayed diagnosis and treatment

- **Family size, social arrangements in the family**
  The degree of social interactions differs by gender in different societies

- **Different climatic conditions**
  Indoor, outdoor contacts, outdoor social activities, opened windows, sunlight
3. Environmental factors

- Expansion of infectious airspace
  Air containing infectious droplet nuclei flows from room to room

- Concentration of life bacilli in the air
  - Number of infectious patients in the space
  - Degree of infectiousness among them (AFB+, +++)
  - Number of recipients in the space
  - Size of space
  - Ventilation
  - Air cleaners

Ventilation and removal of bacilli affect the concentration of bacilli in the air. Ventilation dilutes the concentration of infectious droplet nuclei. 
OPEN WINDOWS!
COUGH-INDUCING PROCEDURES, HOSPITAL WARDS
Extrapulmonary TB is rarely contagious (except for laryngeal TB)
Transmission from extrapulmonary sites has been reported to occur during aerosol-producing procedures

* Cutaneous and soft tissues TB
  Abscessus of the soft tissues of the left hip. Surgery, dressing changes.

* Autopsy

* Laboratory of bacteriology

* Fiberopitic bronchoscope

Routine dressing care created highly transmissible particles
The pattern of dilution of infectious particles
Take a message

Concentration of life bacilli in the air is the most important factor in getting infected

- Cumulative percentage of small droplets, expelled during coughing is higher than in expelled during singing and talking, is higher

- Close contacts are at the highest risk of becoming infected with *M. tuberculosis*

- Patients with sputum smear-positive TB of the respiratory tract are more infectious than smear-negative

- Drug-resistant TB is no more infectious

- To reduce the probability of transmission prevention source cases from producing infectious droplets
  - Covering the mouth and nose during coughing
  - Covering the mouth and nose during coughing

The most effective – treatment of diagnosed TB cases
**Mycobacterium tuberculosis** infection

Infection begins when *Mycobacterium tuberculosis* enters the lungs via inhalation, reaches the alveolar space and encounters the resident alveolar macrophages.

If this first line of defence fails to eliminate the bacteria, *M. tuberculosis* invades the lung interstitial tissue,

- either by the bacteria directly infecting the alveolar epithelium
- or the infected alveolar macrophages migrating to the lung parenchyma.

Subsequently, either dendritic cells or inflammatory monocytes transport *M. tuberculosis* to pulmonary lymph nodes for T cell priming. This event leads to the recruitment of immune cells, including T cells and B cells, **to the lung parenchyma to form a granuloma.**
Latent *M. tuberculosis* Infection Pathogenesis

- The immune response kills most of the bacilli, leading to Formation of a granuloma.

- At this point latent TB infection (LTBI) has been established, detected by the Mantoux tuberculin test or the Quantiferon-TB test.

- Immune responses soon develop to thwart the bacilli. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression.
Definitions of LTBI

Latent Tuberculosis Infection
mycobacteria are surviving in the organism, and may start developing again if the immune defense mechanisms fail (is probably true in some 10% of infected contacts)
or

Lasting Tuberculosis Immune response:
mycobacteria were eliminated but the T-cells have retained the memory of the contact and react to the stimulation by specific antigens (TST or IGRAs) (may be true in some infected contacts, who will never develop the disease)

**b Mycobacterium tuberculosis infection**

The bacteria replicate within the growing granuloma. If the bacterial load becomes too great, the granuloma will fail to contain the infection and bacteria will disseminate eventually to other organs, including the brain. At this phase, the bacteria can enter the bloodstream or re-enter the respiratory tract to be released — the infected host is now infectious, symptomatic and is said to have active TB disease.
The spectrum of TB — from *Mycobacterium tuberculosis* infection to active (pulmonary) TB disease

<table>
<thead>
<tr>
<th></th>
<th>Infection eliminated</th>
<th>Latent TB infection</th>
<th>Subclinical TB disease</th>
<th>Active TB disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With innate immune response*</td>
<td>or</td>
<td>With acquired immune response</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Mycobacterium tuberculosis</td>
<td>Granuloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>TST</th>
<th>IGRA</th>
<th>Culture</th>
<th>Sputum smear</th>
<th>Infectious</th>
<th>Symptoms</th>
<th>Preferred treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>No</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
<td>None</td>
<td>Preventive therapy</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Positive</td>
<td>Intermittently positive</td>
<td>Positive</td>
<td>Sporadically</td>
<td>Mild or none</td>
<td>Multidrug therapy</td>
</tr>
<tr>
<td></td>
<td>Usually positive</td>
<td>Usually positive</td>
<td></td>
<td></td>
<td>Yes</td>
<td>Mild to severe</td>
<td>Multidrug therapy</td>
</tr>
</tbody>
</table>

---

Pai, M. et al. (2016) Tuberculosis
*Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.76

*Nature Reviews | Disease Primers*
Active *M. tuberculosis* Infection. Pathogenesis

- Latent *M. tuberculosis* progresses to active disease in
  - A very small number of persons soon after infection (Primary progression)
  - About 5% of infected persons within first 2 years of infection
  - About 5% of infected persons at sometime in later life

- Risk greater if cell-mediated immunity impaired

- The risk of developing TB is 10% over a lifetime for persons infected only with *M. tuberculosis*

- The risk may be approximately 3 times greater (diabetes)
  100 times greater (HIV infection)
Latent TB Infection (LTBI) Diagnosis

Latent infection

- *M. tuberculosis* cannot be cultured from latently infected individuals:

Two tests are available for the identification of LTBI:

1) **TST** = Mantoux test
2) **IGRA, Interferon-Gamma Release Assay**
   - T-SPOT *TB*
   - QuantiFERON-TB Gold

- TST and the IGRA are acceptable but imperfect tests for LTBI.
- They have reduced sensitivity in immunocompromised patients
- Neither test is able to accurately differentiate between LTBI and active TB disease
- Neither test is able to distinguish between new infections and re-infection events, a distinction that could be relevant in settings in which individuals who had previously received preventive therapy are at risk of becoming re-infected.
Tuberculin skin test = TST= Mantoux test

Performed using the Mantoux technique

- intradermal injection of 5 tuberculin units (5 TU) of purified protein derivative (PPD) S or 2 TU of PPD RT23.
- In a person who has cell-mediated immunity to these antigens, a delayed-type hypersensitivity reaction will occur within 48–72 hours.
- Interpretation of the TST takes into account the size of induration
- Reproducibility in giving the test
- Subjectivity in reading the test
- Repeat visit needed
- 3 days before result
- Positive reaction after 6-8 weeks after infection

0 - 4 mm negat
≥ 5 mm posit
≥ 10 infected

0 - 4 mm negat
≥ 5 mm posit
≥ 10 infected
**Tuberculin skin test (TST)**

TST does not distinguish among all these different clinical situations

<table>
<thead>
<tr>
<th>Positive TST</th>
<th>Active TB disease</th>
<th>Latent TB infection</th>
<th>Exposure to environmental mycobacteria</th>
<th>BCG-vaccination</th>
<th>BCG-vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. tuberculosis</em></td>
<td></td>
<td></td>
<td>Positive result 2-20 years after BCG vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG-vaccination</td>
<td></td>
<td></td>
<td>Positive result 2-20 years after BCG vaccination</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**False-Positive Reactions**

Two major limitations.

1) its specificity is compromised by late (that is, post-infancy) or repeated BCG vaccination (booster vaccinations) and, to a limited extent, by exposure to non-tuberculous mycobacteria.
## False-Positive and False-Negative Reactions to the Tuberculin Skin Test

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Possible Cause</th>
<th>People at Risk</th>
<th>Action to Take</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>False-positive</strong></td>
<td>• Nontuberculous Mycobacteria</td>
<td>People infected with NTM</td>
<td>Evaluate for TB disease if person has TB symptoms</td>
</tr>
<tr>
<td></td>
<td>• BCG vaccination</td>
<td>People vaccinated with BCG</td>
<td>Assess likelihood of true TB infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive result 2-20 years after BCG vaccination</td>
<td></td>
</tr>
<tr>
<td><strong>False-negative</strong></td>
<td>• Anergy</td>
<td>HIV-infected people, other people with weakened immune systems</td>
<td>Retest 10 weeks after exposure to TB ended</td>
</tr>
<tr>
<td></td>
<td>• Recent TB infection</td>
<td>People infected with M. tuberculosis within the past 10 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Very young age</td>
<td>Children younger than 6 months old</td>
<td>Retest when child is 6 months old and 10 weeks after exposure to TB ended</td>
</tr>
</tbody>
</table>
IGRA
RD1-based assays:
T-SPOT TB
QuantiFERON-TB Gold

IGRAs are *in vitro* blood tests of cell-mediated immune response: they measure T cell release of IFNγ following stimulation by RD1-encoded antigens.

RD1 antigens are more specific for *M. tuberculosis* than PPD antigens, they are not encoded in the genome of any BCG vaccine strains or of most species of non-tuberculous mycobacteria (exceptions are *M. marinum*, *M. kansasii*, *Mycobacterium szulgai* and *Mycobacterium flavescens*).

- **Negative control**
- **TB antigen**
  Antigens, TB proteins (ESAT-6, CFP-10 ja TB7.7)
- **Positive control**
  Mitogen, stimulates INF-γ production by lymphocytes
IGRA and TST perform suboptimal in patients with immunosuppression.
Progression to active TB disease
Risk factors for developing TB disease.

1. HIV/AIDS

2. Immunocompromised individuals (other than HIV/AIDS)
   - Solid organ and stem cell transplants
   - Tumor-necrosis factor (TNF-α) blocking medication
   - Renal failure
   - Corticosteroid medication
   - Neoplasia / malignancy
   - Diabetes
   - Silicosis
   - Gastro-intestinal surgery
   - Aging
   - Inborn errors in immunity
## TB risks factors: population attributable fraction

<table>
<thead>
<tr>
<th>TB risk factor</th>
<th>Relative risk for active TB disease</th>
<th>Weighted prevalence (22 HBCs)</th>
<th>Population Attributable Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>8.3</td>
<td>1.1%</td>
<td>7%</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>3.0</td>
<td>17.2%</td>
<td>25%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.0</td>
<td>3.4%</td>
<td>6%</td>
</tr>
<tr>
<td>Alcohol use (&gt;40g / d)</td>
<td>2.9</td>
<td>7.9%</td>
<td>13%</td>
</tr>
<tr>
<td>Active smoking</td>
<td>2.6</td>
<td>18.2%</td>
<td>23%</td>
</tr>
<tr>
<td>Indoor air pollution</td>
<td>1.5</td>
<td>71.1%</td>
<td>26%</td>
</tr>
</tbody>
</table>

HBC = 22 high-burden countries with >80% of the global new TB cases

\[
PAF = \frac{P \times (RR - 1)}{P \times (RR - 1) + 1}
\]