Coughing

1. For a negative culture would take too long and may not be practical.
2. If inhaled, they get stuck on the upper respiratory tract, trachea and bronchi. They will then be swept up by ciliary cells and will never make it to the alveoli. Eventually they will be swallowed and will not cause an infection.
3. Natural cough produces droplet nuclei of lesser quality than artificial aerosols.

Droplets

- The droplets greater than 5 µ fall rapidly.
- If inhaled, they get stuck on the upper respiratory tract, trachea and bronchi. They will then be swept up by ciliary cells and will never make it to the alveoli. Eventually they will be swallowed and will not cause an infection.

Source of Infection

- Pulmonary or laryngeal TB
- Severe cough
- Cavitary pulmonary disease
- Positive sputum in microscopy
- Positive TB culture
- Average infects 10-20 persons

PREVENTION OF TRANSMISSION

Preventing at the source

- Cover your cough: sleeve, tissue or mask
- Simple surgical mask is sufficient, can be worn for long periods of time
- Triage anyone coughing and hand out simple mask
- Cover cough of anyone suspect of TB with simple mask
- Isolate patient in special negative pressure room
- No transportation outside the room without simple mask

Prevention for persons exposed: N95 Masks

- Wear a mask that prevents droplet nuclei from passing through. Surgical masks do not block droplet nuclei, N95s do.
- Make sure there are no gaps between face and mask

Preventive: Artificial aerosols differ from those generated by cough, speech...:

- Artificial aerosols are ≤5-6 µ, with less than 10% > 8 µ
- Natural cough produces droplet nuclei of lesser quality than artificial aerosols

Minimum infectious dose

1 bacillus probably infects 10-20 persons

10 to 20 infections

Other transmission modes are very rare: Drinking large quantities of infected milk, aerosol of TB pus, when opening a TB abscess or a cavity at autopsy.

TB is NOT transmitted by contact, by inhaling dust.

A droplet nuceli MUST REACH THE ALVEOLI to potentially cause an infection

AERIAL PRECAUTIONS

1. N95 masks
2. Negative pressure
3. Recirculation of air flow
   - after filtration or
   - air exhaust to the outside
4. Six (6) to twelve (12) air exchange /hour

Special airborne isolation room

- Negative pressure: Air flow from the corridor into the room,
- Air flow goes through ceiling,
- After being filtered through HEPA filter
- Sent back to corridor
- Requires continuous monitoring
- Required to keep air conditioning

Plain Room with Ventilation / Filtration Unit

The VFU draws the air from the room, filters it and recirculates it into the room.

A droplet of Will fall in

- 100 µm = 10 seconds
- 40 µm = 1 minute
- 20 µm = 4 minutes
- 10 µm = 20 minutes
- 5-10 µm = 30-45 minutes
- ≤5 µm Droplet Nuclei

Remains suspended in the air for hours

May travel long distances

Other transmission modes are very rare: Drinking large quantities of infected milk, aerosol of TB pus, when opening a TB abscess or a cavity at autopsy. TB is NOT transmitted by contact, by inhaling dust.
Latent TB Infection

**Mantoux**

- Measure induration, NOT redness
- 5-9mm = Infected if contact, HIV, other high risk
- >10mm = Infected

**LTBI as defined by Mantoux Test**

<table>
<thead>
<tr>
<th>TST mm</th>
<th>Risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5mm</td>
<td>Any</td>
</tr>
<tr>
<td>≥ 5mm</td>
<td>HIV + recent exposure, HIV+old TB, HIV Infection</td>
</tr>
<tr>
<td>≥ 5mm</td>
<td>Immuno-Suppressed</td>
</tr>
<tr>
<td>≥ 10mm</td>
<td>Close contacts to infectious case</td>
</tr>
<tr>
<td>≥ 15mm</td>
<td>Routine reactor, no risk factors,</td>
</tr>
<tr>
<td></td>
<td>HCW low, intermediate, high risk</td>
</tr>
</tbody>
</table>

**Interferon-Gamma Release Assays (IGRA)**

**Interferon-gamma release assays (IGRA):**
- In patients infected with TB (LTBI): WBCs recognize MtB simulated antigens and release interferon-gamma (IFN-γ); results are based on the amount of IFN-γ released.
- Count of number of anti-mycobacterial effector T cells, WBC producing interferon-gamma, in a sample of blood
- Overall measurement of the host immune response against MtB disease or infection (LTBI)

**Contact Investigation**

**How to carry out a contact investigation**

1. Consider settings:
   - Home: Infectiousness of source
   - Work: Air space shared: enclosed, open
   - Leisure: Time air shared

2. Establish before testing, the risk circles base on settings
   - Highest risk circle: Household
   - Level 2: Coworker, friends >4hrs/day, enclosed space
   - Level 3: 2 hrs/day enclosed space, open air contact
   - Lowest risk: Casual contact < 30mn/day

3. Start testing the highest risk circle
4. Use TST or IGRA tests
5. Calculate the % positive. STOP when the % positive = 5%

**Priorities for contact investigation**

1. Contacts of infectious TB pulmonary, smear+ culture+
2. Contacts of non-infectious TB cases
3. Look for a source case for new pos TST in <15 years old
4. Look for a source case for new positive pregnant woman
5. If resources are scarce, DO PRIORITY # 1 ONLY

**Interpretation of TST**
- Positive close contact = 5mm; Treat all
- Negative close contact: repeat TST @3 month;
- Prev Tx for high risk: children ≤5, anyone in group highly positive

**Risk of Disease**

**Risk of developing disease**
- First year after infection: 3%
- Following 2 years: 1% per year
- From then on: 0.1% = 100/100,000 per year
- Overall life time risk: 5%-10%
- HIV untreated: 7%-10% per year

**Medical Risk Factors**

<table>
<thead>
<tr>
<th>Medical Risk Factors</th>
<th>x 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition</td>
<td></td>
</tr>
<tr>
<td>Gastric Resection</td>
<td>x 4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>x 4</td>
</tr>
<tr>
<td>Silicosis</td>
<td>x 5</td>
</tr>
<tr>
<td>Steroids</td>
<td>x 10</td>
</tr>
<tr>
<td>HIV infection</td>
<td>7 % /year</td>
</tr>
</tbody>
</table>
**Clinical**

### Classification
0- No exposure
1- Exposed, no infection
2- Infection occurred, No disease: Tuberculin Skin Test positive (see interpretation) or GRA positive = LTBI or Latent TB Infection
3- Active Tuberculosis disease: Pulmonary or Extra-pulmonary, smear or culture positive
4- Tuberculosis, inactive disease; history of past disease, chest Xray showing old lesions

### Steps
- The TB must reach the aveoli
- A macrophage gets activated and engulfs the TB bacilli then:
  - 1-TB bacilli multiply → Tuberculosis Infection
  - 2-TB bacilli invade the body → Primary TB disease
  - 3-TB bacilli are held in check → Latent TB Infection (LTBI)
  - 4-TB bacilli are destroyed or,
    - 2-TB bacilli multiply → Tuberculosis Infection
  - 3-TB bacilli invade the body → Primary TB disease
  - 4-TB bacilli are held in check → Latent TB Infection (LTBI)
- After many years, TB Bacilli start to multiply again and invade the body:
  - Reactivation TB

### PULMONARY SYMPTOMS
- Cough
- Sputum: increases, then becomes purulent, then bloody
- Chest pain rare except if pleurisy

### CHRONIC INFECTION SYMPTOMS
- Persistent low fever
- Night sweats
- Headache
- Influenza-like illness

### GENERIC SYMPTOMS
- Not specific
- Fatigue, Loss of weight, Loss of appetite

### Improvement of symptoms after anti-TB treatment proves nothing

### PULMONARY PTYSIS or Acute Pulmonary TB
- Acute Pulmonary TB is the main DRIVER of TB SPREAD
  - Extensive cavities
  - Positive sputum
  - Numerous TB Bacilli > 10 / high power field (x1,000). > 500,000/m
  - High mortality without treatment (75%)
  - Very transmissible: 50% of close contacts are infected
  - RAPID evolution

### Active TB is NOT A SILENT DISEASE
- 95% of patients with positive sputum on microscopy have one or more symptoms suggestive of TB
- 70% have COUGH as a major symptom, 20% have fever or an influenza-like illness (Toman WHO 1979)

### Laboratory Confirmation

The diagnosis of active pulmonary TB is made on sputum NOT on chest Xrays

### Source of sputum
- Must come from the LUNGS, not saliva, not nasal nor pharyngeal discharges
- If no spontaneous sputums, take 3 deep breaths and try coughing
- If this fails: SPUTUM INDUCTION
- Other sources: Gastric aspirate, tracheal suction, bronchoscopic lavage

### Culture provides the definitive diagnosis
- Laboratory must be very performing
- Slow, 8 weeks
- Differentiate TB bacilli from other mycobacteria
- Allow testing of resistance to anti TB drugs
- Faster methods are available, more expensive
- Genetic diagnosis possible: PCR

### Improvement of symptoms after anti-TB treatment proves nothing
**Treatment**

### Anti-TB Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Activity</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (H)</td>
<td></td>
<td>Bactericidal</td>
<td>Most important anti-TB drug - Early bacterial kill</td>
</tr>
<tr>
<td>Rifampin (R)</td>
<td></td>
<td>Bactericidal</td>
<td>Key drug for short course Tx; Active on dormant bacilli or persisters – without R, treatment lasts 9-18 months</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td></td>
<td>Bacteriostatic</td>
<td>Active on Mtb (bacilli at acid pH) – important for early sterilization – Not useful after 2 months (in standard rx)</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td></td>
<td>Bacteriostatic</td>
<td>Weak, bacteriostatic, only useful to cover possible resistance. If HR are effective, E not useful</td>
</tr>
</tbody>
</table>

### Population of TB Bacilli

<table>
<thead>
<tr>
<th>Bacilli Type</th>
<th>Characteristics</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-TB Bacilli extra-cellular</td>
<td>Multiplying rapidly</td>
<td>Inactivated by INH</td>
</tr>
<tr>
<td>2-TB Bacilli intra-cellular in caseum</td>
<td>Multiply slowly</td>
<td>Inactivated by PZA</td>
</tr>
<tr>
<td>3-TB Bacilli dormant</td>
<td>Slow metabolism</td>
<td>Killed by Rifampin only</td>
</tr>
<tr>
<td>4-TB Bacilli dormant, in bad shape</td>
<td>Will die rapidly</td>
<td></td>
</tr>
</tbody>
</table>

### Number of TB Bacilli

<table>
<thead>
<tr>
<th>Organ</th>
<th>Number of Bacilli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavity</td>
<td>1,000,000,000</td>
</tr>
<tr>
<td>Caseous mass</td>
<td>100 to 100,000</td>
</tr>
<tr>
<td>Bone TB</td>
<td>1,000</td>
</tr>
<tr>
<td>Renal TB</td>
<td>100</td>
</tr>
<tr>
<td>Spontaneous resistance to INH</td>
<td>1 / 100,000</td>
</tr>
<tr>
<td>Spontaneous resistance to Streptomycin</td>
<td>1 / million</td>
</tr>
<tr>
<td>Probability of being resistant to 2 drugs</td>
<td>1 / 100 billion</td>
</tr>
</tbody>
</table>

### Directly Observed Therapy

- The best approach to ensure compliance and prevent development of resistance.

### Patient & Regimen

**Adult, Pulm Sputum pos:** HRZ E* 2m + HR E* 4m =Total 6m

- DOT: first 2 weeks daily then daily or twice weekly (2/w)
- E* stop EMB if Mtb sensitive to HRZ

**Response to Treatment**

- **Pulmonary:** Monitor sputum monthly until negative, Continue monitoring if resistance develops
- **Chest X-rays are not reliable** to evaluate activity of pulm lesion
- **Extrapulmonary:** clinical and functional evaluation

### Monitoring First Line Drugs

**Baseline for HRZE:**
- Med Hx (EPI) record; Signed contract; Sputum (3); TST; HIV;
- Blood (Age <15) AST, Bili, CBC, W platelet, Uric

**E only:** Visual acuity & color vision;

**Monitoring for HRZE:** monthly
- Nausea, vomiting, anorexia, dark urine, Jaundice,
- Fever unexplained for 3 days
- Rash, pruritus (hepatotox or other)
- Paresthesia hands, feet
- Bruising, abnormal bleeding
- Flu-like sx

**E only:** Visual acuity & color vision;

### Never Add a Single Drug to a Failing Regimen

- **Caveats:**
  - Pulmonary: Monitor sputum monthly until negative, Continue monitoring if resistance develops
  - **Chest X-rays are not reliable** to evaluate activity of pulm lesion
  - **Extrapulmonary:** clinical and functional evaluation

### DOSES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily max</th>
<th>Daily Max mg</th>
<th>3 / week mg/kg</th>
<th>3 / week Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (H)</td>
<td>5 (4-6)</td>
<td>300</td>
<td>10 (8-12)</td>
<td>900</td>
</tr>
<tr>
<td>Rifampin (R)</td>
<td>10 (8-12)</td>
<td>600</td>
<td>10 (8-12)</td>
<td>600</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>25 (20-30)</td>
<td>-</td>
<td>35 (30-35)</td>
<td>-</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>15 (15-20)</td>
<td>-</td>
<td>30 (25-35)</td>
<td>-</td>
</tr>
<tr>
<td>Streptomycin (S)</td>
<td>15 (12-18)</td>
<td>-</td>
<td>15 (12-18)</td>
<td>1</td>
</tr>
</tbody>
</table>

### Other anti-TB Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily max</th>
<th>mg/kg</th>
<th>$/mL</th>
<th>Formul mg</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethionamide</td>
<td>THA</td>
<td>500-1,000</td>
<td>15-20</td>
<td>110</td>
<td>Tab 250</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>CY</td>
<td>500-1,000</td>
<td>15-20</td>
<td>260</td>
<td>Cap 250</td>
</tr>
<tr>
<td>PAS</td>
<td>PAS</td>
<td>8-12,000</td>
<td>150</td>
<td>Tab500</td>
<td>20-60</td>
</tr>
<tr>
<td>Clofazidine</td>
<td>CFZ</td>
<td>100-300</td>
<td>1.5-5</td>
<td>0.5-2</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>CIP</td>
<td>1-1,500</td>
<td>15-20</td>
<td>190</td>
<td>250,500,750</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>OFL</td>
<td>600-800</td>
<td>15-Oct</td>
<td>220</td>
<td>200,300,400</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>LEV</td>
<td>500-1,000</td>
<td>15-20</td>
<td>450</td>
<td>250,500</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>KAN</td>
<td>1,000</td>
<td>15-Oct</td>
<td>300</td>
<td>Injectable</td>
</tr>
<tr>
<td>Amikacin</td>
<td>AMI</td>
<td>1,000</td>
<td>15 / 3,000</td>
<td>Injectable</td>
<td>35-45</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>CAP</td>
<td>1,000</td>
<td>15</td>
<td>600</td>
<td>Injectable</td>
</tr>
</tbody>
</table>

### How Resistance Develops

- Sensitive
- Resistant

**How Resistance Develops**

- **Directly Observed Therapy** is the best approach to ensure compliance and prevent development of resistance.

- **Monitoring First Line Drugs**

- **Response to Treatment**

- **Never Add a Single Drug to a Failing Regimen**

- **Monitoring for HRZE:** monthly

- **Other anti-TB Drugs**

- **DOSES**