TUBERCULOSIS

EPIDEMIOLOGY, BACTERIOLOGY and TRANSMISSION

+++COUGHING
± Singing
± Sneezing
± Speaking
+ Forced breathing

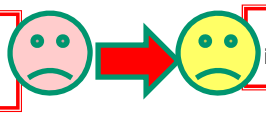
A droplet of	Will fall in
100 µm	10 seconds
40 µm	1 minute
20 µm	4 minutes
10 µm	20 minutes
5-10 µm	30-45 minutes
≤5 µm Droplet Nuclei	Remains suspended in the air for hours May travel long distances

40 µm = Diameter of a hair

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.

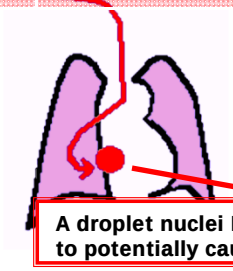
Minimum infectious dose
1 bacillus probably



10 to 20 infections

Cough
1 good cough produces 465 droplet nuclei
After 30 minutes the amount left in the air: 228 (49%)

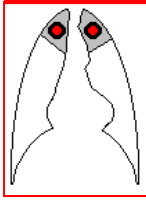
Speech:
Counting from 1 to 100 ➔ 1764 droplet nuclei
After 30 minutes there are: 106 (6%) left in the air



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

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…

Source of Infection



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

• Positive sputum in µscopy:	1 to 10 million Bacilli /mL
• Negative sputum:	< 1,000 /mL
• Contacts positive sputum:	30% to 50% infected
• Contacts of negative sputum:	1% to 5% infected
• Ctc of pos sputum >48 coughs/night:	44% infected
• Ctc of pos sputum <12 coughs/night:	27% infected

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

Identify Suspects / Think TB

- **Identify suspects**
- **Confirm with sputum examination**
- Xrays are not as useful as sputums because they do not identify who is infectious
- Annual chest Xrays not for infectious TB screening
- TB diagnosis is sometimes missed among patients with other chronic pulmonary conditions such as COPD

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

LENGTH OF ISOLATION

- 2 OR 3 weeks after treatment started
- Ideally after 2 to 3 negative sputum examination
- Waiting for a negative culture would take too long and prevent good compliance

- **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

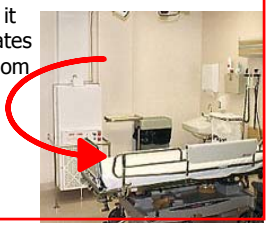
PREVENTION: Always use AIRBORNE precautions
- **Avoid high risk procedures whenever possible**: Nebulization, bronchoscopy, procedures close to the face: eye examination, dental exam…

AIR-BORNE 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

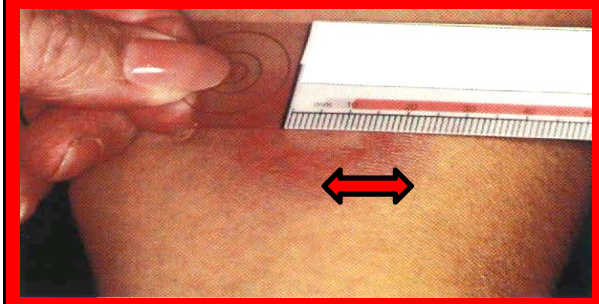
Special airborne isolation room
-Negative pressure: Air flow from the corridor into the room,
-Air flow goes through ceiling,
-After being filtered \through HEPA filter
-Sent back to corridor
-Expensive ($5,000 to $10,000)
-Difficult to maintain
-Requires continuous monitoring
-Required to keep air conditioning

Plain Room with Ventilation /Filtration Unit
The VFU draws in the air from the room, filters it and recirculates it into the room



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

TST mm	Risk group
By definition	**Converters**
Any	**HIV** + recent exposure, HIV+old TB, HIV Infection
≥ 5mm	HIV infection
≥ 5mm	**Immuno-Suppressed**
≥ 5mm	**Close contacts** to infectious case
≥ 5mm	**Old TB** / TB not properly treated
≥ 10mm	Children < 4 years age
	Injectable drug user (IDU), crack coke (ccu)
	High risk medical condition
	Foreign born, in US ≤5yrs
	LTCF resident
	Mycobacteriology lab
	HCW low, intermediate, high risk
≥ 15mm	Routine reactor, no risk factors,
	HCW minimal, very low

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 M.tb disease or infection (LTBI)

T-Spot

-2008, T-Spot approved by FDA

-Peripheral blood mononuclear cells (PBMCs) incubated with control materials and 2 mixtures of peptides, one ESAT-6 and CFP-10.

-Test uses an enzyme-linked immunospot assay (ELISpot) to detect increases in the number of cells that secrete IFN-γ

-Use of a borderline category address test variation and uncertainty for results near dichotomous cut point

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
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
Infected, Chest Xray normal	0.1 %
lesion 1-2 cm2	0.2 %
lesion 2-7 cm2	0.4 %
lesion >7cm2	0.8 %

Medical Risk Factors

Malnutrition	x 3
Gastric Resection	x 4
Diabetes	x 4
Silicoseis	x 5
Steroids	x 10
HIV infection 7% /year	7 % per yr

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 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)**
5-After many years, TB Bacilli start to multiply again and invade the body: **Reactivation TB**

There are NO symptoms specific of TB

GENERIC SYMPTOMS
Not specific
Fatigue,
Loss of weight,
Loss of appetite,
Irritability

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

CHRONIC INFECTION SYMPTOMS
Persistant low fever, Night sweats, Headache
Inluenza-like illness

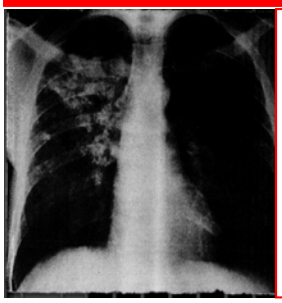
Improvement of symptoms after anti-TB treatment proves nothing

PULMONARY PHTYSIS 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).

	Infection	Disease
Acid Fast Bacilli	Dormant	Active
Mantoux	Positive	Positive (1/7 Neg)
Sputum Smear	Negative	50%positive
Sputum Culture	Positive	85% positive
Chest XRay	Normal	Abnormal
Symptoms	None	Cough, Fever…
Contagious	No	Yes
Active TB	No	Yes

Chest Xrays only show shadows that may or may not be typical of lesions produced by TB



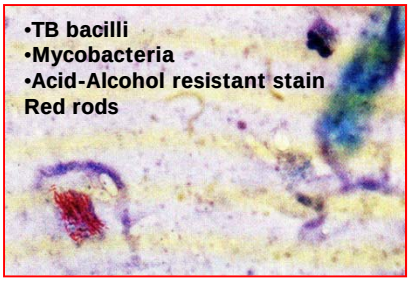
-Chest Xrays cannot confirm TB

-Chest does not show if the case is contagious or not

-Chest Xrays are subjective. Interpretation may vary according to radiologists

-Chest Xrays SHOULD NOT be used to evaluate response to treatment since response is very slow to show on chest Xrays.

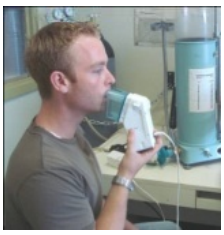
Laboratory Confirmation

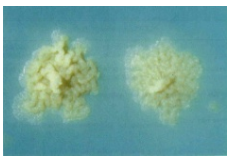


Culture provides the definitive diagnosis
•Laboratory must be very performing
•Slow, 8 weeks
•Differentiate TB bacilli from other mycobacteria
•Allow testing of resistance to anti TB drugs
•Faster methods are available, more expensive
•Genetic diagnosis possible : PCR

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





Treatment

Anti-TB Drugs

INH	**H**	Isoniazid	Bactericidal	Most important anti-TB drug - Early bacterial kill
RIF	**R**	Rifampin	Bactericidal	Key drug for short course Tx- Active on dormant bacilli or persisters – without R, treatment lasts 9-18 months
PZA	**Z**	Pyrazinamide	Bactriostatic	Active on Mtb (bacilli at acid pH) – important for early sterilization – Not useful after 2 months (in standard rx)
EMB	**E**	Ethambutol	Bactriostatic	Weak, bacteriostatic, only useful to cover possible resistance. If HR are effective, E not useful

Population of TB Bacilli

1-TB Bacilli extra-cellular Multiplying rapidly Rapdly killed by INH	**2-TB Bacilli intra-cellular or in caseum** Multiply slowly Inactivated by PZA
3-TB Bacilli dormant Slow metabolism Killed by Rifampin only	**4-TB Bacilli dormant,** In bad shape Will die rapidly

Number of TB Bacilli

Cavity	1,000,000,000	10^7 - 10^9
Caseous mass	100 to 100,000	10^2 - 10^5
Bone TB	1,000	10^3
Renal TB	100	105
Spontaneous resistance to INH	1 / 100,000	10^{-5}
Spontaneous resistance to Streptomycin	1/miilion	10^{-6}
Probability of being resistant to 2 drugs	1/ 100 billion	10^{-11}

Directly Observed Therapy is 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 2weeks daily then daily or twice weekly (2/w)
E* stop EMB if *Mtb* sensitive to HRZ
Adult, Xpm: same regimen, extend only if poor clinical response
Adult, Pulm Sputum neg: HRZ daily or 2/w ⇨ Total 4m
Pregnancy: HR E* No Z, No S ⇨ Total 9m
Children, Pm & X pm: HRZE* 2m + HRE 4m ⇨ Total 6m
Children, CSF, Bone Jnt, miliary: same but ⇨ Total 12m
HIV Positive no difference w HIV neg except poor response ⇨ 9m
HIV+Xpm: tuberculoma, Bone Jnt: 12 m; **HIV+Pregnancy**:PZA ok
Regimen with Rifabutin: E part of induction for **entire** 2m

Monitoring First Line Drugs

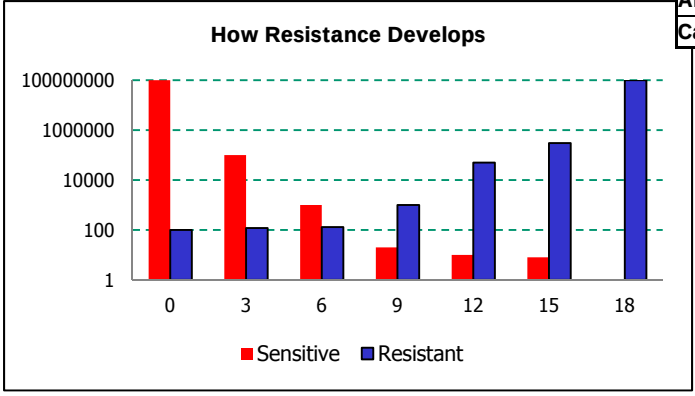
Baseline for HRZE:

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;

Any Symptoms
Stop treatment
Request Lab tests
Consult



NEVER ADD A SINGLE DRUG TO A FAILING REGIMEN

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
Chest Xrays are too slow at showing worsening
Extrapulmonary: clinical and functional evaluation

DOT required:

2/w reg, age<15, resistance, HIV, senile, Homeless,
Sub abuse, Relapse, Non-adherence; 2/w= Mon&Thu, Mon&Fri, Tue&Fri

DOSES	Daily mg/kg	Daily Max mg	3 / week mg/kg	3 / week Max
INH (H)	5 (4-6)	300	10 (8-12)	900
Rifampin (R)	10 (8-12)	600	10 (8-12)	600
Pyrazinamide (Z)	25 (20-30)	-	35 (30-40)	-
Ethambutol (E)	15 (15-20)	-	30 (25-35)	-
Streptomycine (S)	15 (12-18)	-	15 (12-18)	1

Other anti-TB Drugs

Drug			Daily max	mg /kg	$/ m	Formul mg	Level
Ethionamide	THA		500-1,000	15-20	110	Tab 250	1-5
Cycloserine	CYS	**Y**	500-1,000	15-20	260	Cap 250	20-35
PAS	PAS	**A**	8-12,000	150		Tab500	20-60
Clofazimine	CFZ	**Cl**	100-300	1.5-5			0.5-2
Ciprofloxacin	CIP	**C**	1-1,500	15-20	190	250,500,750	4-6
Ofloxacin	OFL	**O**	600-800	15-Oct	220	200,300,400	8-12
Levofloxacin	LEV	**L**	500-1,000	15-20	450	250,500	35-45
Kanamycin	KAN	**K**	1,000	15-Oct	300	injectable	35-45
Amikacin	AMI	**Am**	1,000	15	3,000	injectable	35-45
Capreomycin	CAP	**Cp**	1,000	15	600	injectable	35-45