Transmission and Pathogenesis of TB Disease

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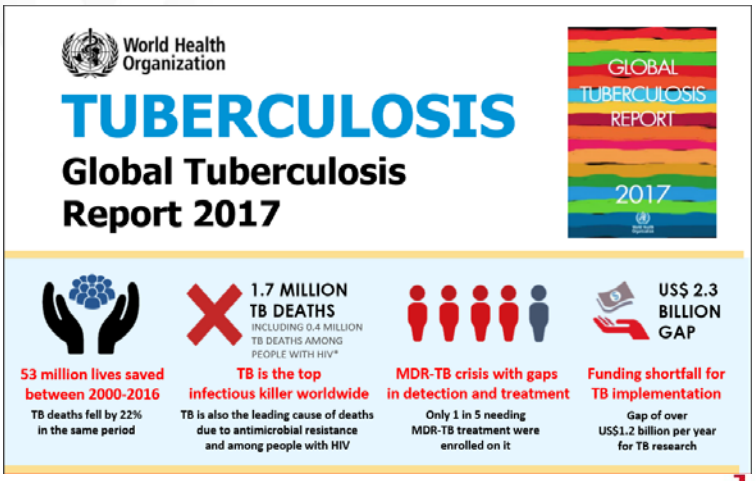
A Persistent Pathogen that has Airborne Transmission

- Worldwide TB Epidemiology
- Transmission and Pathogenesis
  - Pathogenicity factors (Many)
  - Mycolic acids = Transmission factor
- Impact of Cavitary TB Disease
- Impact of Drug-Resistant TB
- TB Classification System



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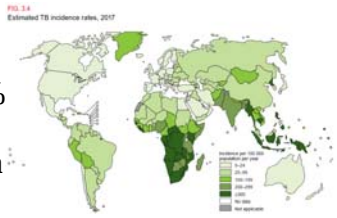
Mycobacterium tuberculosis Epidemiology

- ~23% of world (~1.7 billion people) infected
  - 10 million new cases of TB in 2017
  - Eight countries accounted for 2/3rds

  of the new cases: **India** (27%), **China** (9% **Indonesia** (8%), the **Philippines** (6%), **Pakistan** (5%), **Nigeria** (4%), **Bangladesh** (4%) and **South Africa** (3%)

  Largest case rates in sub-Saharan Africa
  - Co-infection with HIV
  - Incidence rate in South Africa ~0.8%



WHO Global TB Report 2018

http://www.who.int/tb/publications/global_report/en/

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Mycobacterium tuberculosis complex

- TB is an **airborne** disease caused by the bacteria *M. tuberculosis*
  - *M. tuberculosis* and 7 very closely related species make up MTB complex
  - In US, majority of TB cases cause by *M. tuberculosis*
- *M. tuberculosis* is carried in **airborne particles**, called **droplet nuclei**
  - Infectious droplet nuclei are generated when persons who have pulmonary or laryngeal TB cough, sneeze, shout or sing.
  - Depending on the environment, these tiny particles can remain suspended in the air for many hours.
  - MTB germs survive in droplet nuclei unless exposed to UV light, sunlight
  - Can be filtered out by a HEPA filter or diluted by special ventilation

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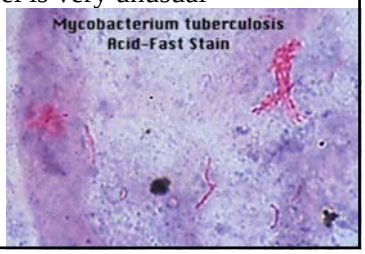
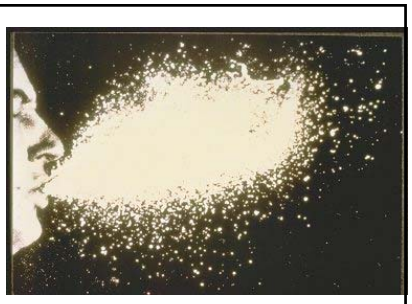
Characteristics of *Mycobacterium tuberculosis*

- Mycolic acids (lipids) in cell wall make Mycobacteria different from other bacteria
- "Acid Fast" because waxy mycolic acids hold dye and resist decolorization with acid/alcohol
- Slow-growing, multiply every 18 – 24 hours
  - Because each germ has to build a thick lipid cell wall to divide
- Can remain dormant for years
- MTB's ability to survive in a droplet nuclei is very unusual among bacteria
  - Resistant to dehydration, oxidative stress, and low pH

AKA: Red Snappers



MTB Transmission



- Inhaled **droplet nuclei** ~1 micrometer (micron) in size **which contains a tubercle bacillus** transmit and cause virtually all MTB infections
  - A particle size this small can reach alveoli when inhaled
- Infection initiated only with direct "hit" to an alveolus
  - Mucociliary blanket traps many inhaled particles
  - Trapped particles are swallowed, then inactivated by gastric acid

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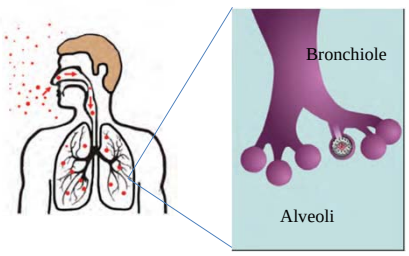
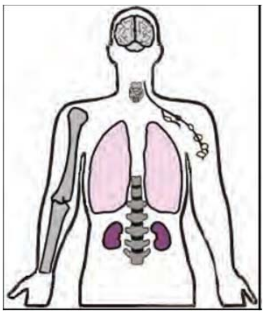
Pathogenesis of LTBI and TB Disease





Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.

Tubercle bacilli multiply in the alveoli.

A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).

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Paradigm of MTB Infection

- Inhaled airborne droplet nucleus
- Alveolar macrophage ingests (phagocytoses) MTB bacteria
  - But can't kill them, at least initially
- MTB multiplies intracellularly, then spreads regionally
- Occult preallergic lymphohematogenous dissemination

- Then, most commonly, development of effective cell-mediated immunity
  . . . and progressive infection is interrupted
  - Non-replicating persistence, instead
- Rarely see progressive primary infection, especially in a healthy host

Consequences of MTB Infection

- Latent TB Infection (LTBI) as measured by immunity:
  - TB skin test
  - IGRA for TB
- "The End" for 90% of healthy people

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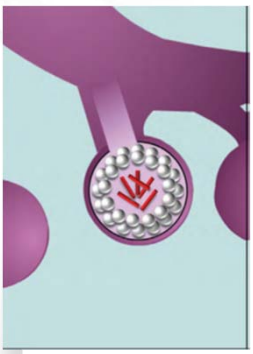
LTBI vs. TB Disease



Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control **(LTBI)**.

If the immune system **cannot** keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (**TB disease**). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone.

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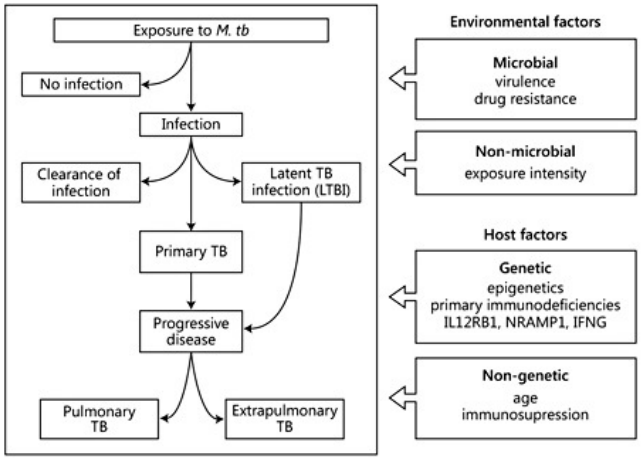

Public Health Genomics 2013;16:44–49

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Factors that Determine the Probability of Transmission of *M. tuberculosis*

Factor	Description
Susceptibility	Immune status (susceptibility) of the exposed individual
Infectiousness	Infectiousness of the 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 (Table 2.2)
Environment	Environmental factors that affect the concentration of M. tuberculosis organisms (Table 2.3)
Exposure	Proximity, frequency, and duration of exposure (Table 2.4)

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Table 2.2
Characteristics of a Patient with TB Disease that Are Associated with Infectiousness

Factor	Description
Clinical	--Presence of cough, especially lasting 3 weeks or longer --Respiratory tract disease, especially with involvement of the larynx (highly infectious) --Failure to cover the mouth and nose when coughing --Inappropriate or inadequate treatment (drugs, duration)
Procedure	--Undergoing cough-inducing or aerosol-generating procedures (e.g., bronchoscopy, sputum induction, administration of aerosolized medications)
Radiographic and Laboratory	--Cavitation on chest radiograph --Positive culture for *M. tuberculosis* --Positive AFB sputum smear result

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Table 2.3
Environmental Factors that Enhance the Probability that *M. tuberculosis* Will Be Transmitted

Factor	Description
Concentration of infectious droplet nuclei	The more droplet nuclei in the air, the more probable that *M. tuberculosis* will be transmitted
Space	Exposure in small, enclosed spaces
Ventilation	Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei
Air circulation	Recirculation of air containing infectious droplet nuclei
Specimen handling	Improper specimen handling procedures that generate infectious droplet nuclei
Air Pressure	Positive air pressure in infectious patient's room that causes *M. tuberculosis* organisms to flow to other areas

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Risk of Exposure and Transmission

- Congregate settings
  - Hospitals
  - Long-term care facilities
  - Correctional facilities
  - "Joe's Poorly Ventilated Bar and Grill"
  - Transport: Taxis, Jitneys, Airplanes, Ship
- Aerosol-Producing Procedures
  - Sputum induction
  - Bronchoscopy
  - Intubation and mechanical ventilation

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Table 2.4
Proximity and Length of Exposure Factors that Can Affect Transmission of *M. tuberculosis*

Factor	Description
Duration of exposure to a person with infectious TB	The longer the duration of exposure, the higher the risk for transmission
Frequency of exposure to infectious person	The more frequent the exposure, the higher the risk for transmission
Physical proximity to infectious person	The closer the proximity, the higher the risk for transmission

Young children with pulmonary and laryngeal TB disease are less likely than adults to be infectious. This is because children generally do **not** produce sputum when they cough. However, transmission from children can occur. Therefore, children and adolescents with TB disease should be evaluated for infectiousness using the same criteria as adults.
These criteria include:
-- presence of cough lasting 3 weeks or longer;
-- cavitation on chest radiograph; or
-- respiratory tract disease with involvement of lungs, airways, or larynx

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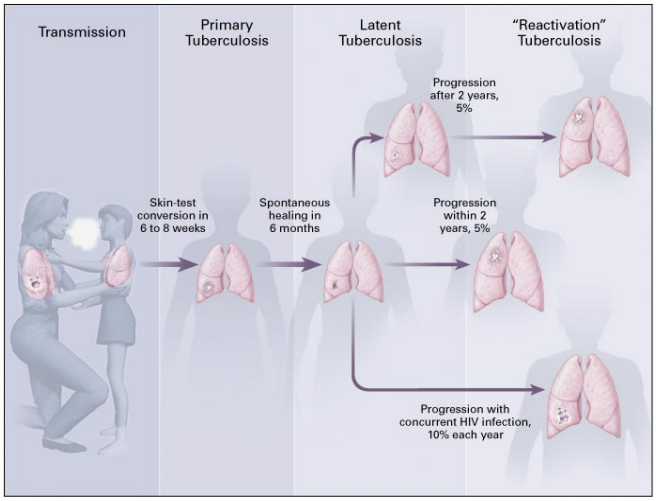

Small & Fujiwara NEJM 2001 345:192

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- After 2 years, without other risk factors, disease risk falls to <1% annually
  - But the risk doesn't go to zero
- PPD + persists ??? for life
  - William Stead's elderly NH pts in Arkansas
- Ethnic makeup affects disease rates
- Immunocompromised at risk

- **". . . The incidence of tuberculosis may decrease to the level of medical curiosities, but it is not very likely ever to become 'eradicated.'"**
  - **Grigg, "Arcana of TB," Am Rev Tuberc 1958; 78:151.**

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Which of the following environmental factors do NOT increase the probability that MTB will be transmitted?

A. Exposure in small enclosed spaces
B. Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei
C. Recirculation of air containing infectious droplet nuclei
D. Improper specimen handling procedures that generate infectious droplet nuclei
E. Negative air pressure in an infectious TB patient's room

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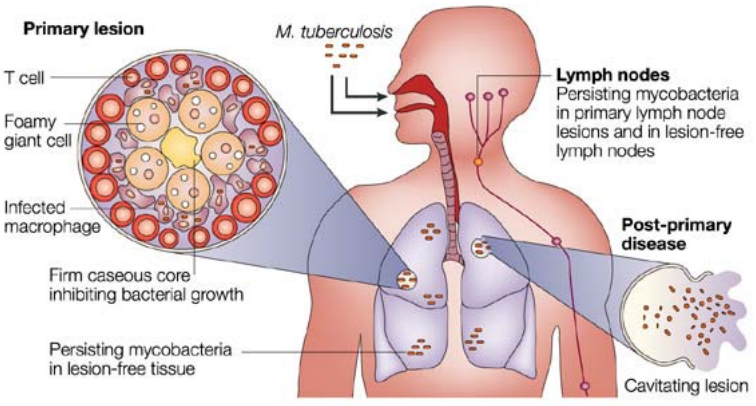

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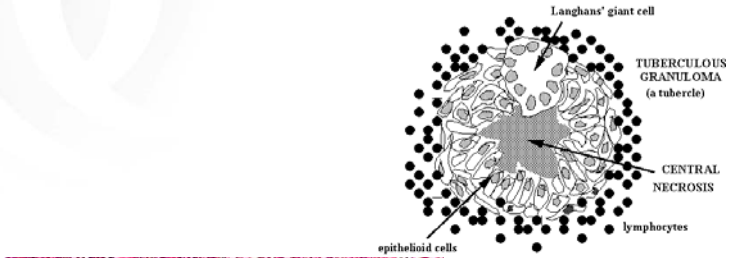

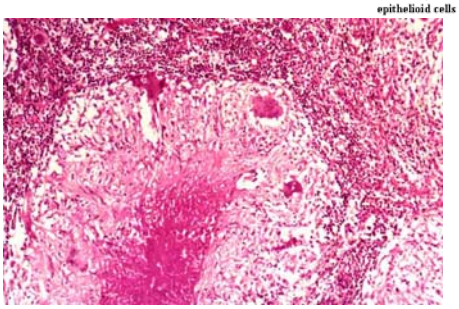

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Caseation necrosis: ". . . blocks are formed of necrotic masses; their size depends upon the initial pulmonary segment involved (several alveoli, a lobule, or a lobe). . . . The block of necrosis has now assumed an absolutely homogeneous character, becoming a solid and compact mass.

We may regard this phase of the evolution of the lesion as a kind of crossroads. The lesion may remain solid and evolve toward peripheral tubercle formation and ultimate sclerosis. This takes place in all lesions of latent infection, as well as the great majority of active tuberculous lesions. **It may on the other hand evolve towards softening of the caseum which means almost inevitably the onset of clinical tuberculosis.** Since the latent lesions in the human species are all . . . caseous at some moment of their evolution, the truly grave phenomenon in the evolution of tuberculosis is not, as is most often believed, the formation of the caseum. This is a commonplace development to which most patients adjust. The softening of the caseum is really perilous . . .

Canetti G: The tuberculosis bacillus in the pulmonary lesion of man: histobacteriology and its bearing on the therapy of pulmonary tuberculosis. 1955

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Cavitation

- Caseation tends to liquefy and drain into the bronchial tree, spreading bacillary contents by coughing
- The cavity is prevented from collapsing by the fibrous capsule and the inelasticity of the surrounding lung
  - **The pulmonary cavity favors bacillary multiplication to enormous titers, 5 to 6 logs greater than in noncavitary lesions**
- The progressive nature of pulmonary tuberculosis is due to
  (1) the tendency of apical caseous foci to liquefy,
  (2) the enormous concentrations of organisms in the resulting pulmonary cavities, and
  (3) spread of this bacilli-rich material through the bronchial tree.
- Progression from minimal infiltrate to far-advanced cavitary disease can occur within a few months

Postprimary (Adult-type) Pulmonary Tuberculosis,
Mandell, Douglas and Bennett 8th ed'n, p. 2799

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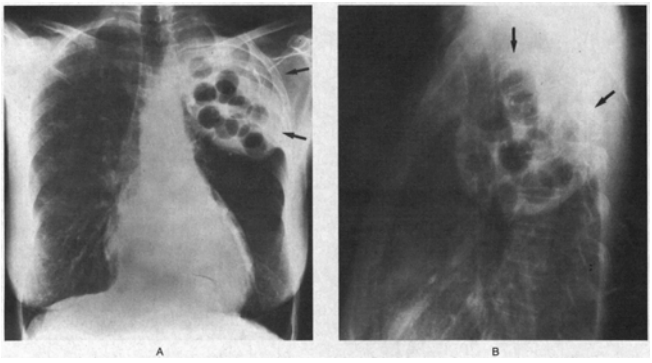
Lucite Ball Plombage, NEJM 1994



When it became clear that cavitation was the pivotal event in progressive pulmonary TB, most special therapies focused on cavity closure (in the pre-antimicrobial era)

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Indices of Source Case Infectiousness in Household Contacts Aged 14 Years or Less

Source Case Variables	Tuberculin Reactors (%)
Radiographic extent of disease	
Minimal	16.1 (5/31)
Moderately advanced	28.3 (17/60)
Far advanced	61.5 (24/39)
Bacteriologic status	
Smear neg, culture neg	14.3 (4/28)
Smear neg, culture +	21.4 (3/14)
Smear +, culture +	44.3 (39/88)

Loudon RG, *American Review of Respiratory Disease*, 1969;99:109–111

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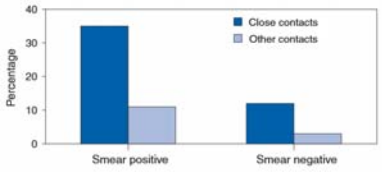
Who is more contagious?

- AFB smear + > AFB smear neg
  - But smear neg cases can still transmit
- Cavitary > non-cavitary
- Close contact > casual contact
- Prolonged > brief exposure
- HIV+ = HIV neg

Controlling Tuberculosis in the United States
Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America
MMWR 2005; 54 (No. RR-12)

FIGURE 2. Percentage of persons infected with *Mycobacterium tuberculosis*, by bacteriologic status of and proximity to the source case — British Columbia and Saskatchewan, 1966–1971



SOURCE: Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. Bull Int Union Tuberc 1975;50:90–106.

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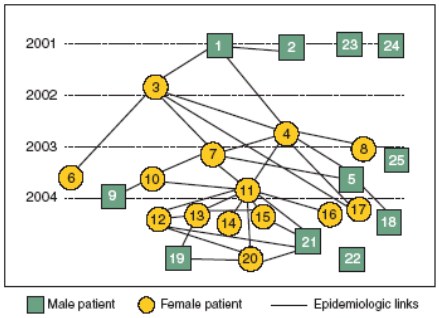
FIGURE. Year of diagnosis and epidemiologic links among tuberculosis patients* — Allen County, Indiana, 2001–2004



*Information pending on epidemiologic links for patients 22–25.

Contact investigation:
--Patients 3 and 7 were identified as contacts, started TLTBI but defaulted
--Patients 4 was an LTBI candidate who refused treatment
--All 3 progressed to TB disease

--If those 3 patients completed LTBI treatment, **16 TB cases might have been prevented.**
--Each contact who defaulted cited lack of TB knowledge as a major barrier to completing LTBI treatment.

Note: all of these MTB isolates were identical by molecular fingerprinting

www.cdc.gov/mmwr/preview/mmwrhtml/mm5348a4.htm

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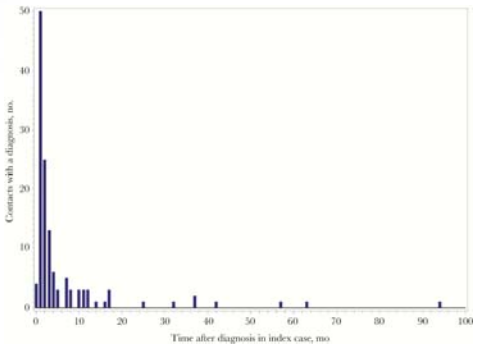
Contact Investigations are Important!

Prospective trial in NA
2002 – 2006

718 index patients

--Active TB dx'd in 158 of 4490 close contacts (4%)
--121 (77%) by CI
--37 (23%) by TB Registry cross-match



From: Risk and Timing of Tuberculosis Among Close Contacts of Persons with Infectious Tuberculosis
J Infect Dis. 2018;218(6):1000-1008. doi:10.1093/infdis/jiy265
J Infect Dis | Published by Oxford University Press for the Infectious Diseases Society of America 2018.This work is written by (a) US Government employee(s) and is in the public domain in the US.

Tuberculosis Epidemiologic Studies Consortium Task Order 2 Team

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TB Infection-to-disease Continuum?

- In some people, the tubercle bacilli overcome the immune system, resulting in progression from LTBI to TB disease
  - Whole blood transcriptional mRNA expression signature (COR) correlates with risk 6-18 months before active TB
- **The Correlate of Risk Targeted Intervention Study (CORTIS)**
  - NCT02735590 = targeted intervention study at clinicaltrials.gov
  - University of Cape Town
- Primary Aims
  - Test whether preventive therapy (3HP) reduces the rate of incident TB disease, compared to standard of care (active surveillance), in COR+ persons
  - Test whether COR status differentiates persons with cumulative prevalent or incident TB disease from persons without TB disease
- Secondary Aims
  - Estimate whether COR status differentiates persons at high risk for incident TB disease from persons at low risk for incident TB disease
  - Compare prognostic performance of the COR for incident TB disease with Interferon-gamma release assay (IGRA)

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www.clinicaltrials.gov/ct2/show/NCT02735590?term=NCT02735590&rank=1

LTBI vs. TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Has a small amount of TB bacteria in his/her body that are alive, but inactive	Has a large amount of active TB bacteria in his/her body
Cannot spread TB bacteria to others	May spread TB bacteria to others
Does **not** feel sick, but may become sick if the bacteria become active in his/her body	May feel sick and may have symptoms such as a cough, fever, and/or weight loss
Usually has a TB skin test or TB blood test reaction indicating TB infection	Usually has a TB skin test or TB blood test reaction indicating TB infection
Radiograph is typically normal	Radiograph may be abnormal
Sputum smears and cultures are negative	Sputum smears and cultures may be positive
Should consider treatment for LTBI to prevent TB disease	Needs treatment for TB disease
Does **not** require respiratory isolation	May require respiratory isolation
Not a TB case	A TB case

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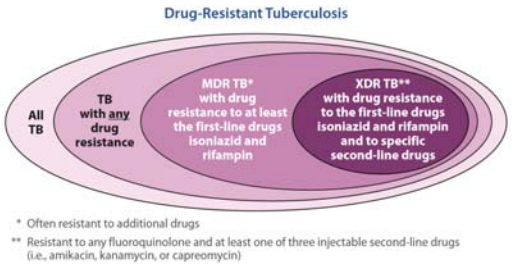
Drug-Resistant TB (MDR and XDR)

- Drug-resistant TB is caused by *M. tuberculosis* organisms that are resistant to the drugs normally used to treat the disease
- Drug-resistant TB is transmitted in the same way as drug-susceptible TB, and is no more infectious than drug-susceptible TB

However, delay in the recognition of drug resistance or prolonged periods of infectiousness may facilitate increased transmission and further development of drug resistance.



Primary and Secondary MDR TB

Primary MDR TB (Infected with Drug-Resistant Organisms)	**Secondary MDR TB** (Acquired or Developed Drug Resistance)
Caused by person-to-person transmission of drug-resistant organisms	Develops during TB treatment
• Exposure to a person who » Has known drug-resistant TB » Had prior treatment for TB (treatment failure or relapse and whose susceptibility test results are **not** known) » Is from an area in which there is a high prevalence of drug resistance » Continues to have positive smears and cultures after 2 months of combination chemotherapy • Travel in areas with a high prevalence of drug-resistant TB disease	Develops because the patient • Was **not** treated with the appropriate treatment regimen **Or** • Did **not** follow the treatment regimen as prescribed » Took the drugs incorrectly » Took the drugs irregularly • Malabsorption • Drug-drug interactions causing low serum levels

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Which of the following statements is true about drug-resistant TB disease?

A. Drug-resistant TB disease is transmitted in the same way as drug-susceptible TB disease.

B. Drug-resistant TB disease is NO more infectious than drug-susceptible TB disease.

C. Drug-resistant TB disease is easily treated with standard drug regimens.

D. A, B, and C are all correct.

E. Only A and B are correct.

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Which is MDR-TB and Which is XDR-TB?

1. Resistant to isoniazid and rifampin, plus any fluoroquinolone, and at least one of three injectable second-line drugs

2. Resistant to at least the two first-line drugs, isoniazid and rifampin

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Which is Primary Resistance and Which is Secondary Resistance?

1. Sally is diagnosed with and treated for TB by her family physician. She is not placed on directly observed therapy DOT; thus she often forgets to take her anti-TBs medicine and takes only part of her prescribed regimen. Because of inadequate treatment, she now has MDR TB

2. Li, a 13-year-old boy, immigrates from China with his family. He gets MDR TB from his older brother

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TB Classification System

Class	Type	Description
0	No TB exposure **Not** infected	- No history of TB exposure and no evidence of *M. tuberculosis* infection or disease - Negative reaction to TST or IGRA
1	TB exposure No evidence of infection	- History of exposure to *M. tuberculosis* - Negative reaction to TST or IGRA (given at least 8 to 10 weeks after exposure)
2	TB infection No TB disease	- Positive reaction to TST or IGRA - Negative bacteriologic studies (smears and cultures) - No bacteriologic or radiographic evidence of active TB disease
3	TB clinically active	- Positive culture for *M. tuberculosis* –**OR**- - Positive reaction to TST or IGRA, plus clinical, bacteriological, or radiographic evidence of current active TB
4	Previous TB disease (**not** clinically active)	- May have past medical history of TB disease - Abnormal but stable radiographic findings - Positive reaction to TST or IGRA - Negative bacteriologic smears and cultures; no clinical evidence of active TB disease
5	TB suspected	- Signs and symptoms of active TB disease, but medical evaluation **not** complete

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What is the TB Classification for Each of the Following Patients?

Patient	TB Classification
Sonya has a positive reaction to a TST. There is no bacteriologic or radiographic evidence of TB disease.	2 TB infection No TB disease
Luke has signs and symptoms of TB disease, but his medical evaluation is **not** complete.	5 TB disease suspected
Joseph has a history of exposure to *M. tuberculosis* and a negative TST result.	1 TB exposure No evidence infection
Sergei has a past medical history of TB disease. His radiographic findings are abnormal, but stable. He has a positive reaction to an IGRA. Both smear and culture results are negative and there is no clinical or radiographic evidence of current TB disease.	4 Previous TB disease (not clinically active)
Louisa has no history of TB exposure and no evidence of *M. tuberculosis* infection or disease. She has a negative IGRA result.	0 No exposure Not infected
Rosella has a positive culture for *M. tuberculosis*.	3 TB, clinically active