UNIVERSITÀ
DEGLI STUDI DI BARI
ALDO MORO

HYGIENE COURSE

Scuola
di
Medicina

Tuberculosis

Silvio Tafuri

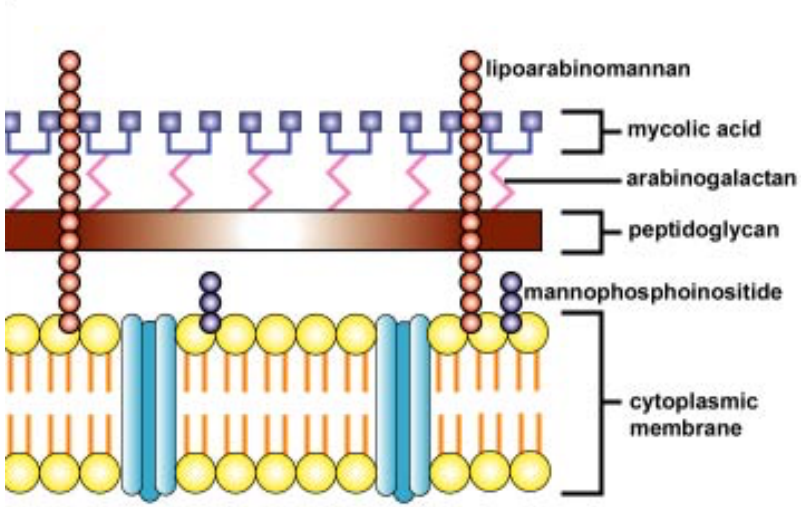
Etiology

Mycobacterium tubercolosis

- first discovered in 1882 by R. Koch
- small bacillus
- gram positive, non motile, non sporulating, obligate aerobe

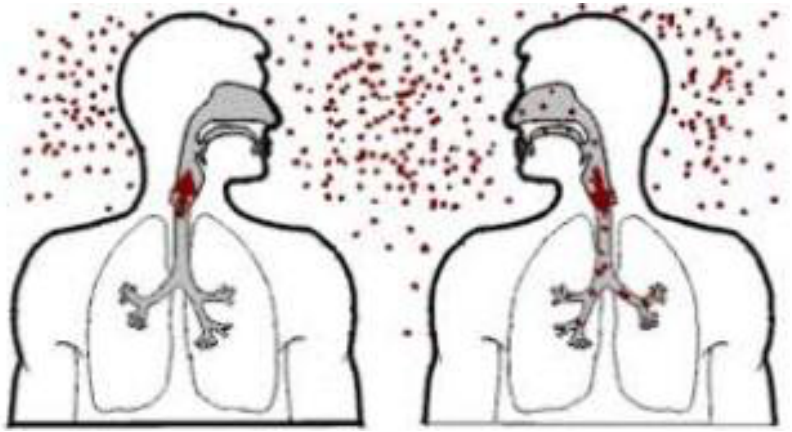
Etiology

- Cell wall structure
  - 15% proteins
  - 60% lipids (micolic acids, micolenici e cere)



How TB spread

- person to person
- through the air
- TB **is NOT spread** by
  - ✓ shaking someone's hand
  - ✓ sharing food or drink
  - ✓ touching bed linens or toilet seats
  - ✓ sharing toothbrushes
  - ✓ kissing

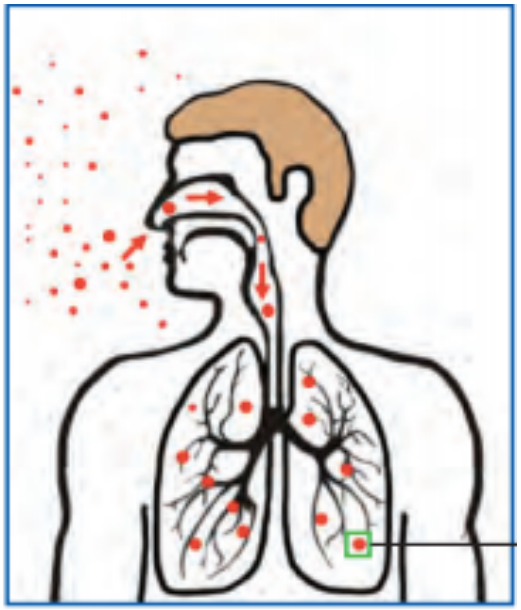


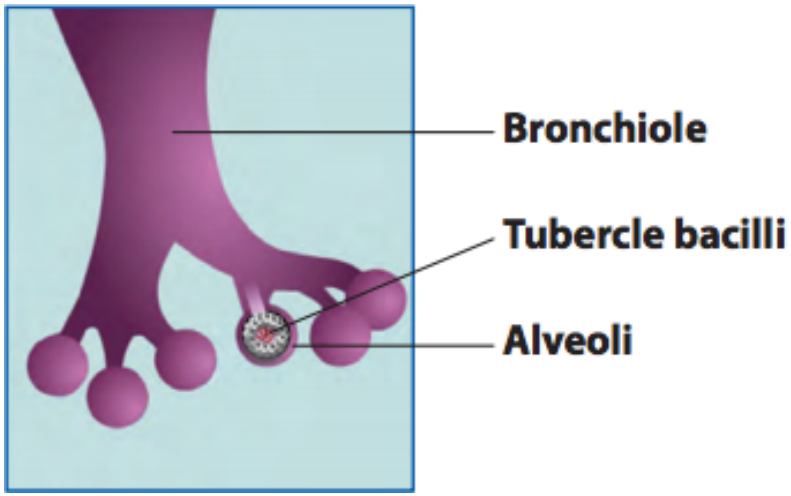
Factors that Determine the Probability of M. tuberculosis Transmission

Factor	Description
Susceptibility	Susceptibility (immune status) 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
Environment	Environmental factors that affect the concentration of M. tuberculosis organisms
Exposure	Proximity, frequency, and duration of exposure

Pathogenesis

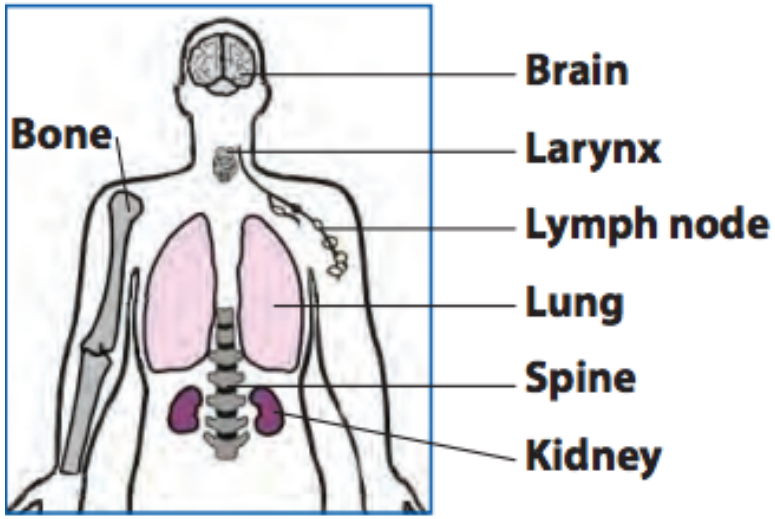
- Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.





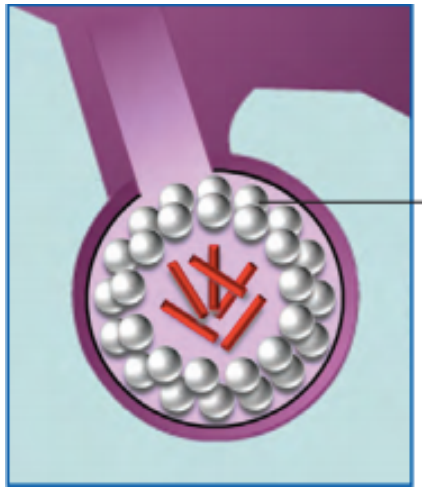
- Tubercle bacilli multiply in the alveoli.

Pathogenesis



- 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).

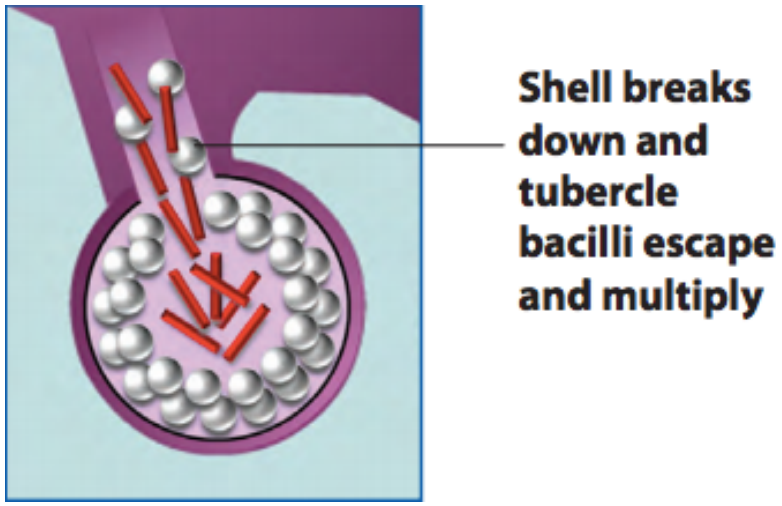
Pathogenesis



Special immune cells form a barrier shell (in this example, bacilli are in the lungs)

- 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).

Pathogenesis



- 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

Latent TB Infection (LTBI)

- Granuloma may persisist (LTBI), or may break down to produce TB disease
- 2 to 8 weeks after infection, LTBI can be detected via TST or IGRA
- the immune system is usually able to stop the moltiplication of bacilli
- persons with LTBI are not infectious and do not spread organisms to others

TB disease

- Granuloma break down, bacilli escape and multiply, resulting in TB disease
- Can occur soon after infection or years later
- Persons with TB disease are usually infectious and can spread bacteria to others
- Positive M.tb culture confirms TB diagnosis

Site of Disease

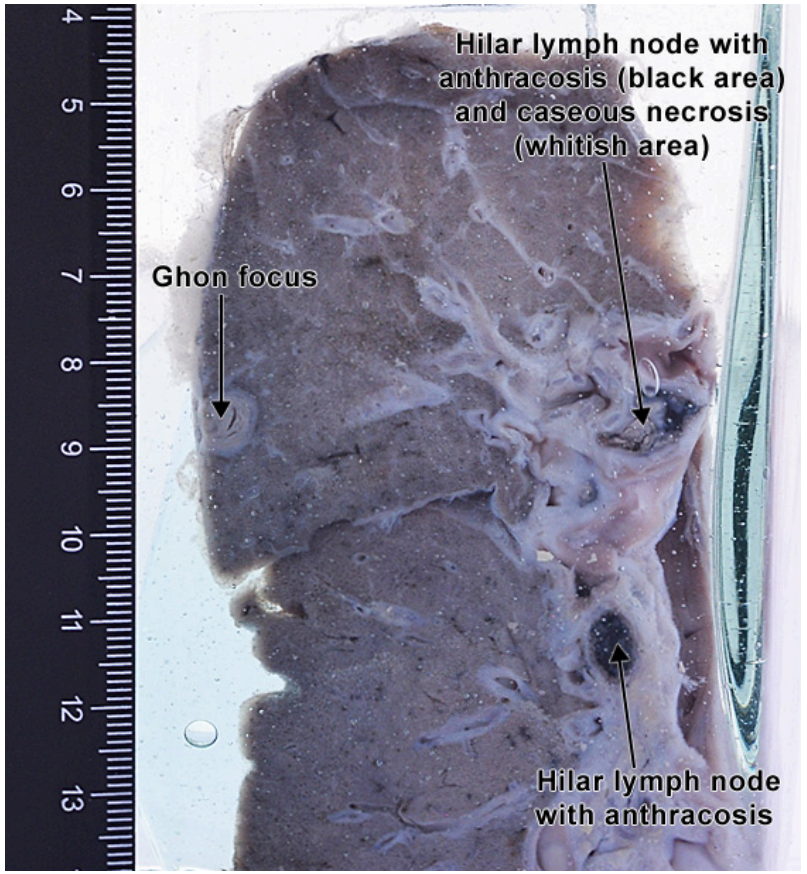
- **LUNG** (pulmonary): most common site, usually infectious
- **MILIARY**: occurs when bacilli spread to all parts of the body; rare, but fatal if untreated
- **Central Nervous System**: usually occurs as meningitis, but can occur in brain or spine
- **Outside the lungs** (extrapolmonary): larynx, lymph nodes, pleura, brain, kidneys, bones and joints. Usually not infectious

Primary Tuberculosis

Ghon complex:

1. Ghon focus
2. Lymphadenitis
3. Lynphangitis

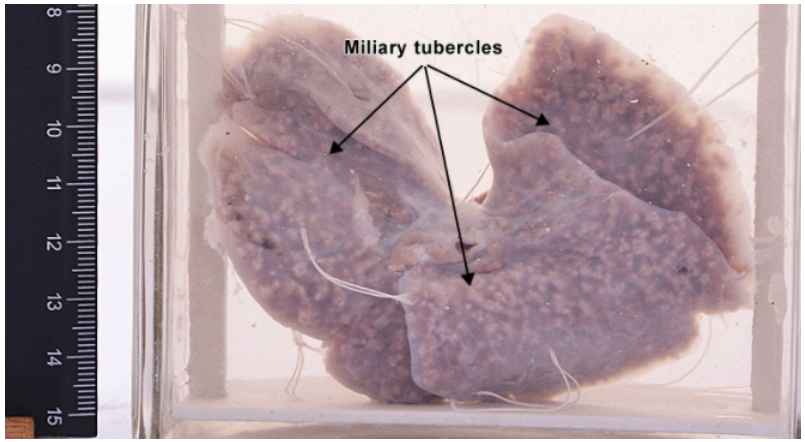
Primary pulmonary tuberculosis has a favorable evolution, with healing by fibrosis and/or calcification, in 95 % of cases



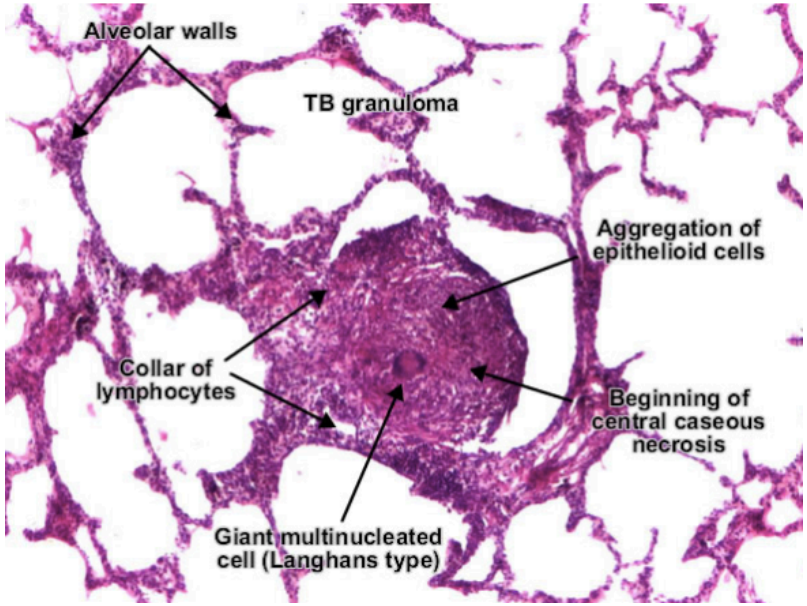
Secondary Tuberculosis

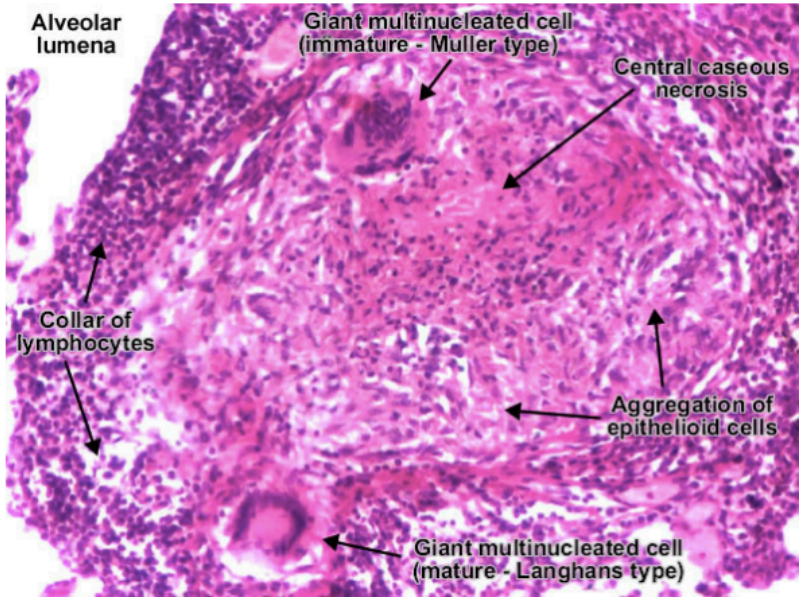
Otherwise, it evolves into **progressive primary tuberculosis**, which includes the following entities :

- **Primary caseous pneumonia**
- **Tuberculous bronchopneumonia**
- **Miliary tuberculosis**



Tuberculous Granuloma



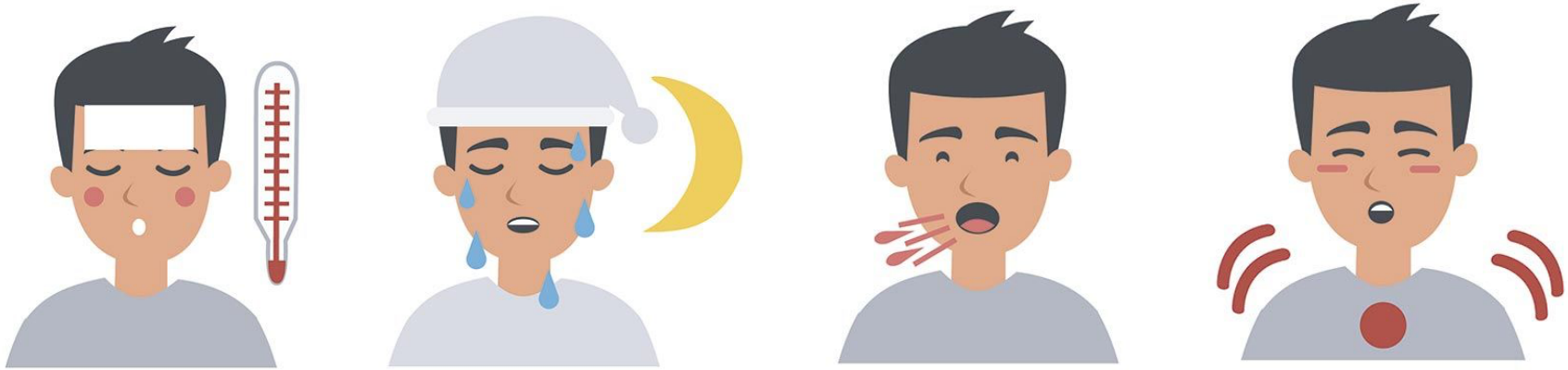


Persons at Increased Risk for TB Disease

Persons at Increased Risk
• Persons infected with HIV;
• Children younger than 5 years of age;
• Persons who were recently infected with *M. tuberculosis* (within the past 2 years);
• Persons with a history of untreated or inadequately treated TB disease, including persons with fibrotic changes on chest radiograph consistent with prior TB disease;
• Persons who are receiving immunosuppressive therapy such as tumor necrosis factor-alpha (TNF) antagonists, systemic corticosteroids equivalent to/greater than 15 mg of prednisone per day, or immunosuppressive drug therapy following organ transplantation;
• Persons with silicosis, diabetes mellitus, chronic renal failure, leukemia, or cancer of the head, neck, or lung;
• Persons who have had a gastrectomy or jejunoileal bypass;
• Persons who weigh less than 90% of their ideal body weight;
• Cigarette smokers and persons who abuse drugs and/or alcohol; and
• Populations defined locally as having an increased incidence of disease due to *M. tuberculosis*, including medically underserved, low-income populations.

Symptoms

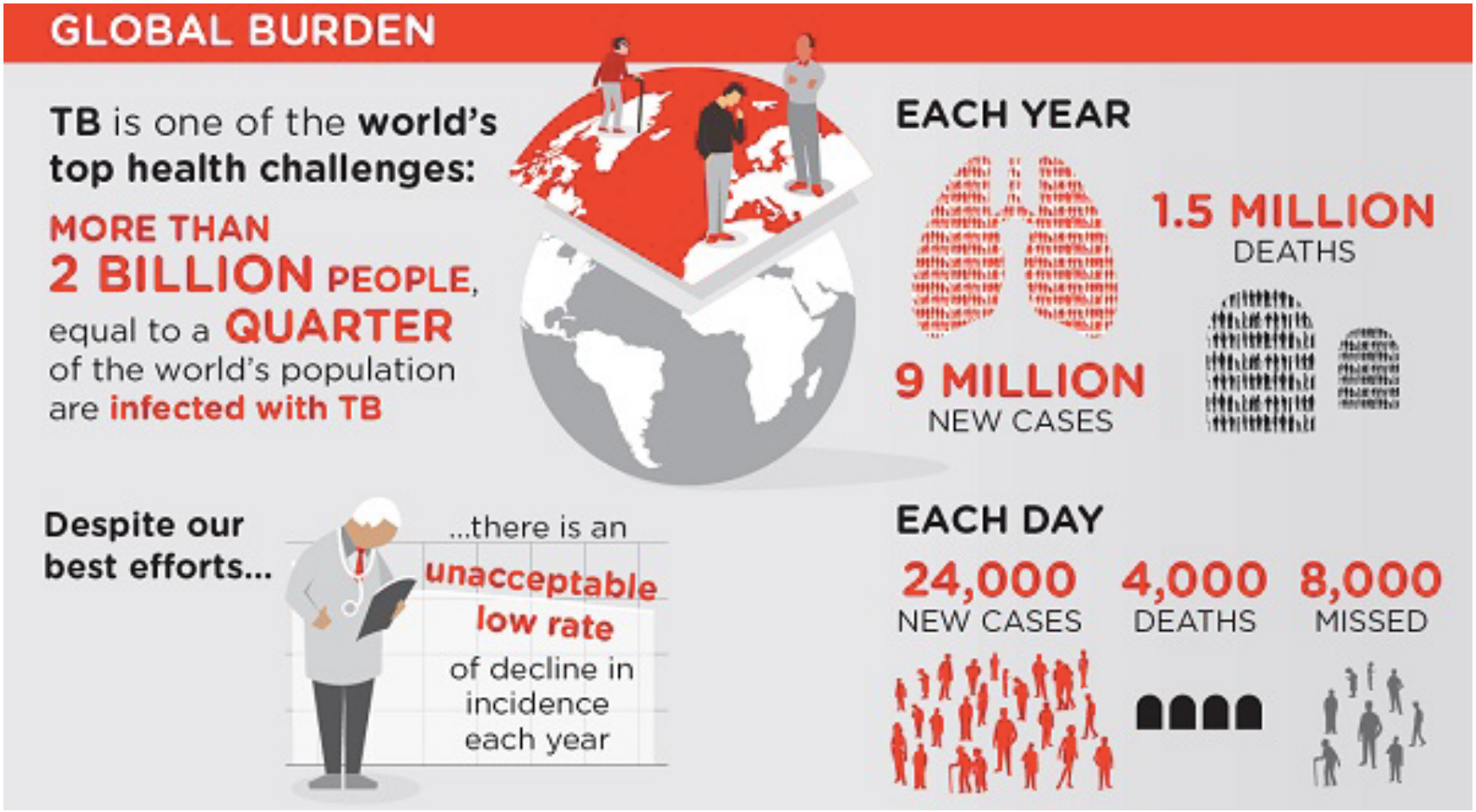
- ✓ Fever (low)
- ✓ Night sweats
- ✓ Loss of appetite, weight loss
- ✓ Fatigue
- ✓ Cough (especially if lasting for 3 weeks or longer)
- ✓ Haemoptysis
- ✓ Chest pain
- ✓ Dispnea



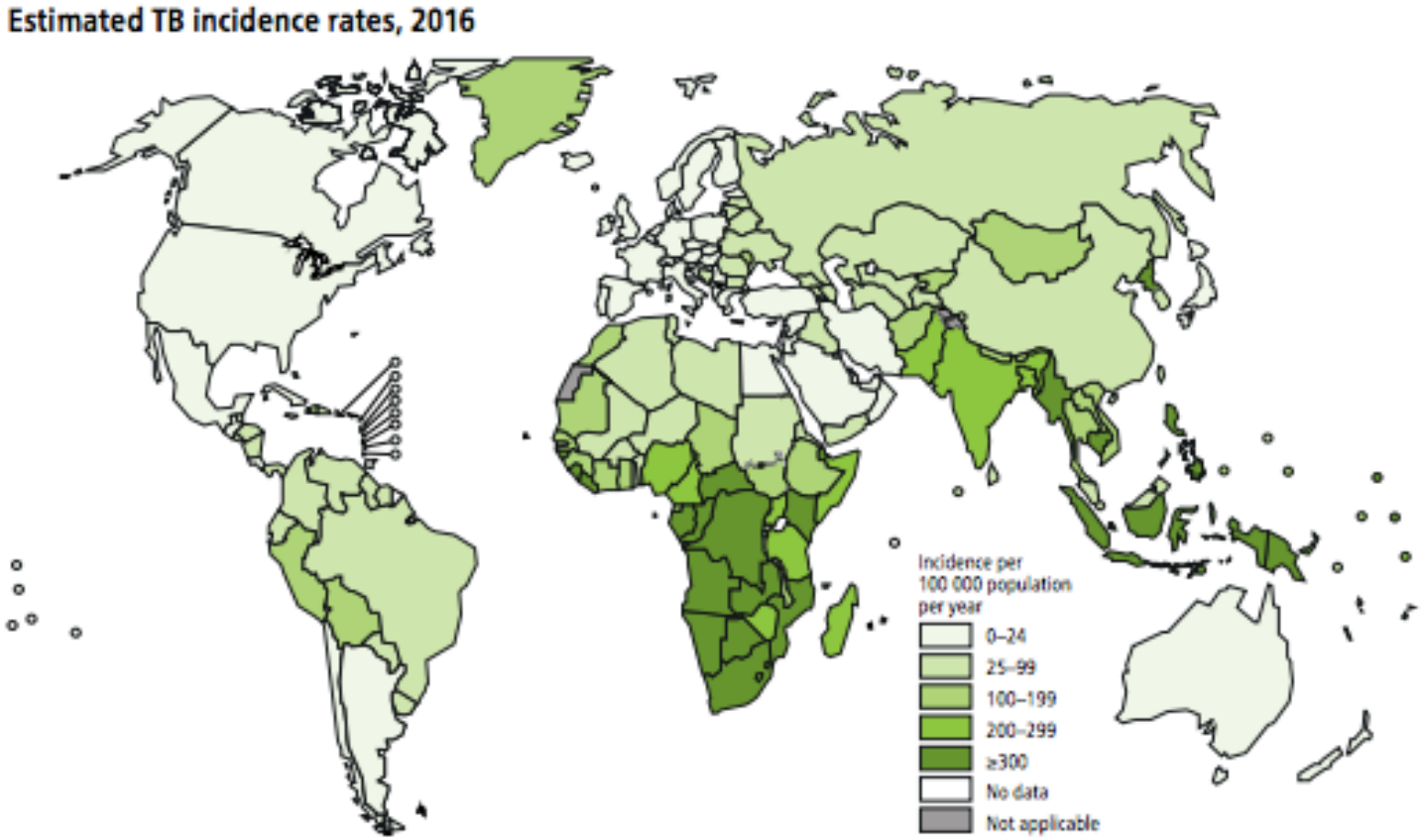
Complications

- Collapse/consolidation
- Bronchiectasis
- Fibrosis/emphysema
- Obstructive airways disease
- Pleurisy
- Pneumothorax
- Meningitis

Epidemiology - World



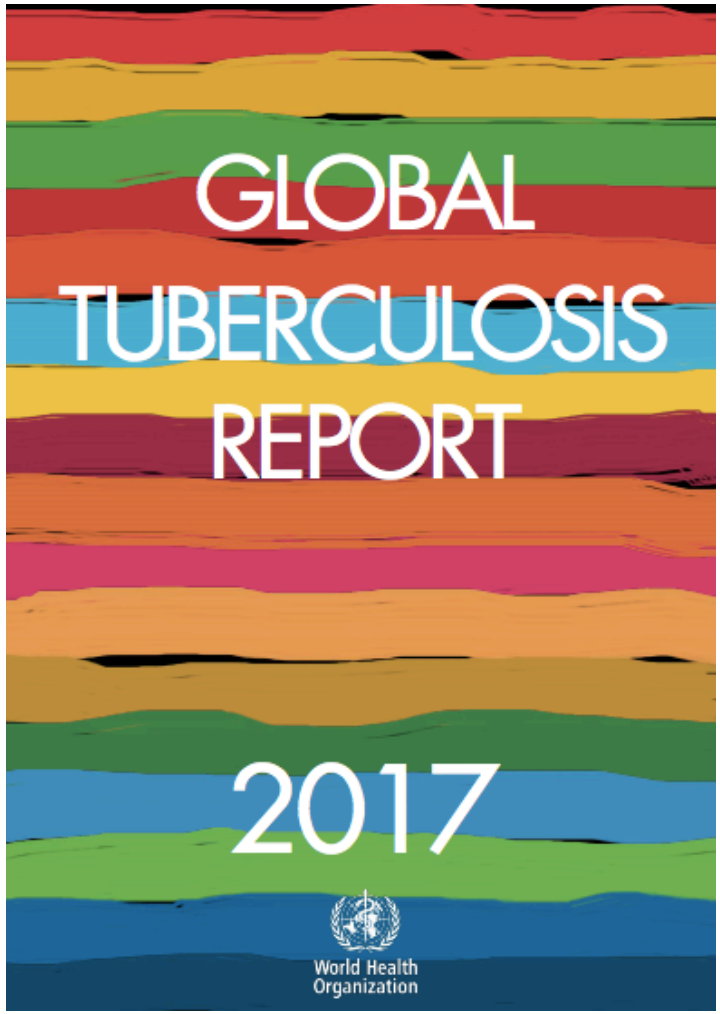
Epidemiology - World



OMS, "Global tubercolosis report 2016

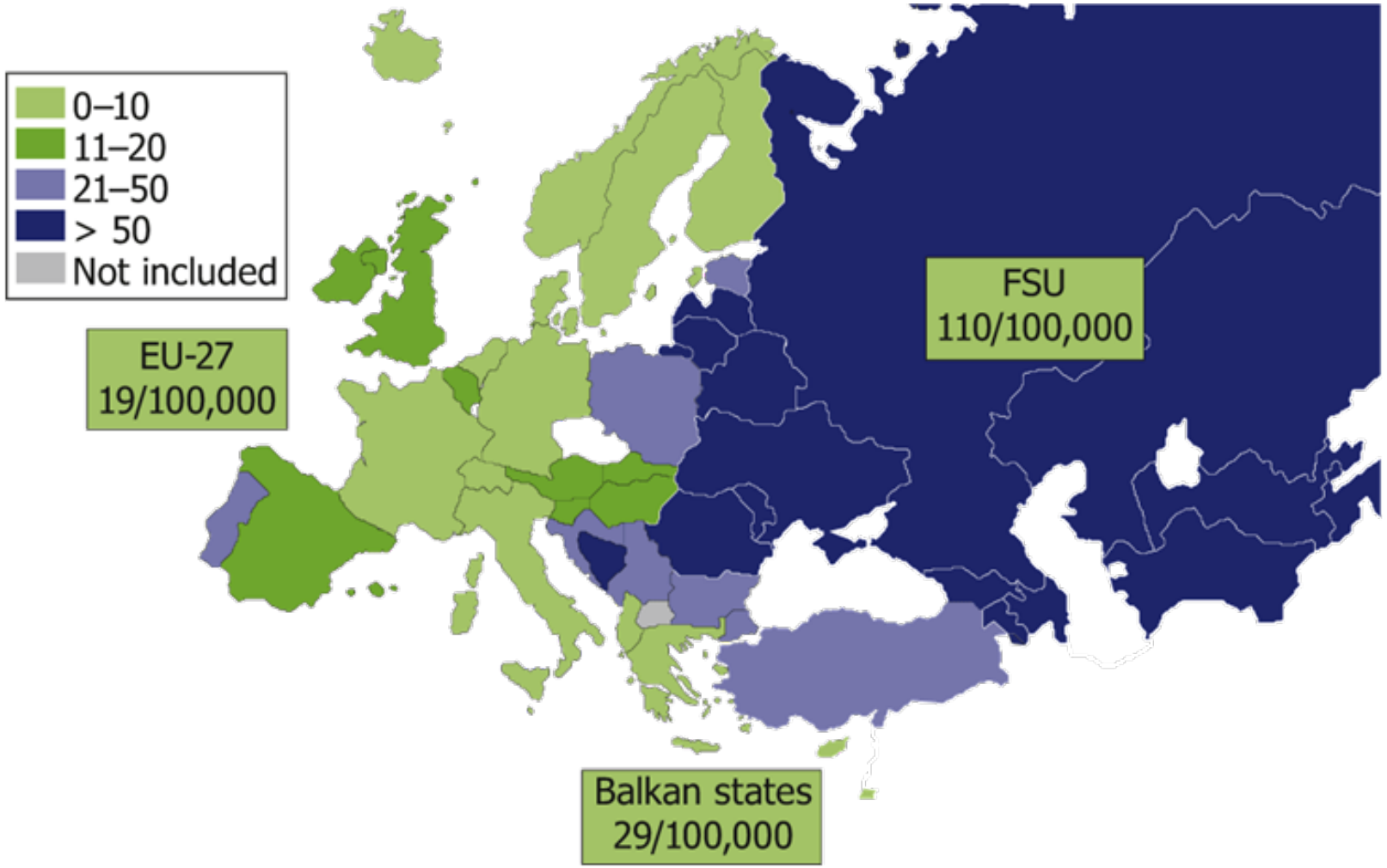
Epidemiology – World - 2016

- Incidence: 10,4 mln
  - M 5,9 mln; F 3,5 mln; children 1 mln
  - 56% in five countries: India, Indonesia, China, the Philippines, Pakistan
  - 600.000 MDR TB cases
- Deaths: 1,3 mln
  - 374.000 HIV+
  - 240 mila MDR-TB



OMS, "Global tubercolosis report 2016

Epidemiology – Europe, 2014



Epidemiology – Europe, 2014

- Cases notified: 329.270 (not reported from Italy and Liechtenstein)
- Estimated incidence: 340.000 = 37 per 100.000 population
- 45% cases 25-44 years
- 4,1% cases <15 years
- Incidence co-infection TB-HIV: 16.708

ECDC, "Tuberculosis surveillance and monitoring in Europe 2016"

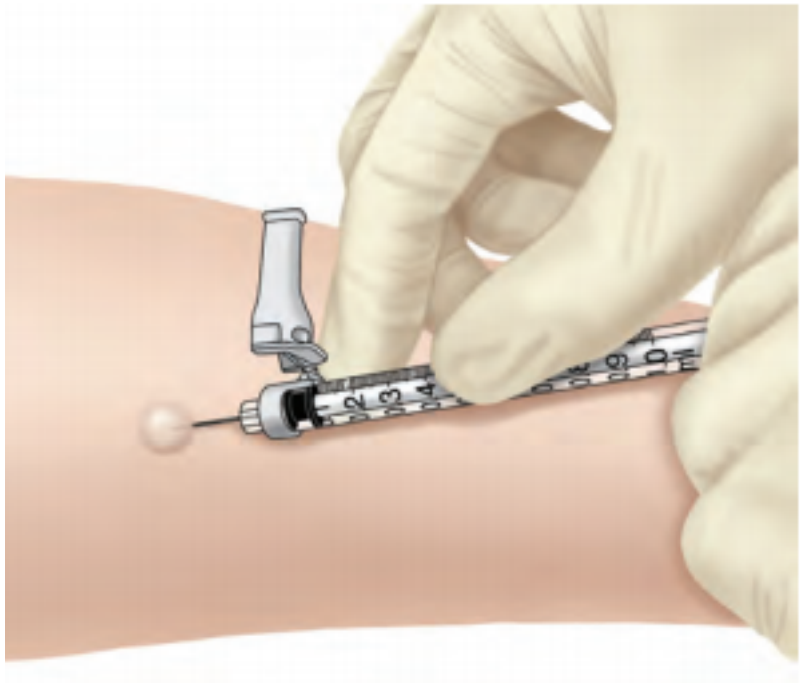
Diagnosis of LTBI

Currently, there are **two methods** available for the detection of M. tuberculosis infection:

- Mantoux tuberculin skin test (**TST**)
- Interferon-gamma release assays (**IGRAs**)
  - » QuantiFERON-TB Gold In-Tube test (QFT-GIT)
  - » T-SPOT.TB test

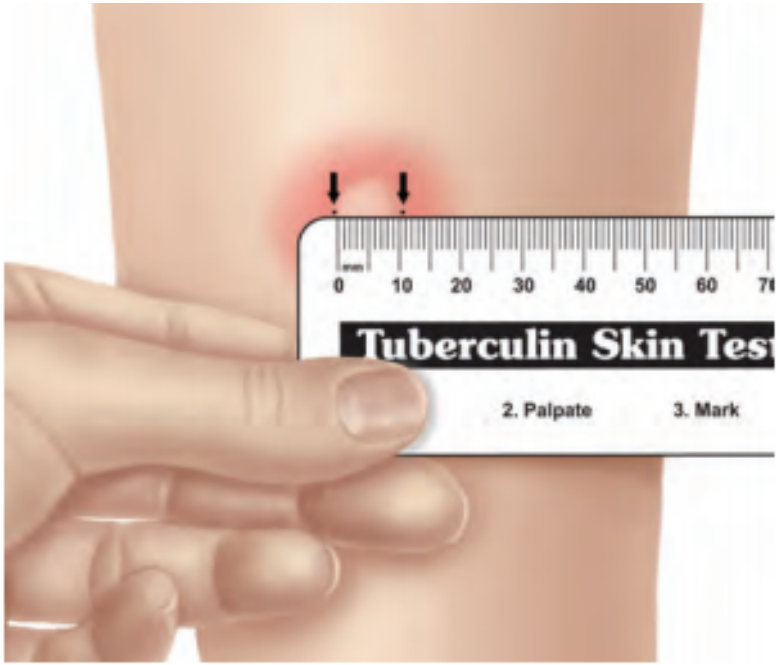
Mantoux Tuberculin Skin Test (TST)

- Intradermal injection of 0,1 ml of PPD
- Volar surface of the forearm
- producing of a discrete, pale elevation of the skin



Mantoux Tuberculin Skin Test (TST)

- reading 48 to 72 hours after the injection
- palpating the site of injection to find an area of induration



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Classification of the Tuberculin Skin Test Reaction

≥5 mm	≥10 mm	≥15 mm
- HIV-infected persons -A recent contact of a person with TB disease -Persons with fibrotic changes on chest radiograph consistent with prior TB -Patients with organ transplants -Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists)	- Recent immigrants (< 5 years) from high-prevalence countries -Injection drug users -Residents and employees of high-risk congregate settings -Persons with clinical conditions that place them at high risk	- persons with no known risk factors for TB

False-Positive Reactions

- Nontuberculous mycobacteria (NTM)
- BCG vaccination
- Administering of incorrect antigen
- Incorrect interpretation of TST result

False-Negative Reactions

- Anergy
- Recent TB infection
- Concurrent viral, bacterial or fungal infection (e.g., measles, mumps, HIV, typhoid fever, brucellosis…)
- Chronic renal failure
- Low protein states
- Diseases affecting lymphoid organs (e.g., Hodgkin's disease, lymphoma, chronic leukemia)
- Immunosuppressive drugs (e.g., medical steroids, TNF-alpha blockers)
- Very young or elderly persons

IGRA test

- **QuantiFERON®–TB Gold**
- **T-SPOT® TB test**

IGRAs detect TB infection by measuring the **release of interferon-gamma (IFN-g)** from patient T cells after stimulation of a whole blood sample with highly specific TB antigens

QuantiFERON-TB Gold Plus

It uses a peptide cocktail simulating:

1. PPD (*purified proteic derivative*)
2. ESAT-6 (*early secretory antigenic target* 6)
3. CFP-10 (*culture filtrate protein* 10)

ESAT-6 e CFP-10 sono codificati in una regione genica (RD1) che **manca nel BCG e in quasi tutti i MNT**

QuantiFERON-TB Gold Plus

Mitogen – Positive Control
Low response may indicate inability to generate IFN-γ

Nil – Negative Control
Adjusts for background IFN-γ

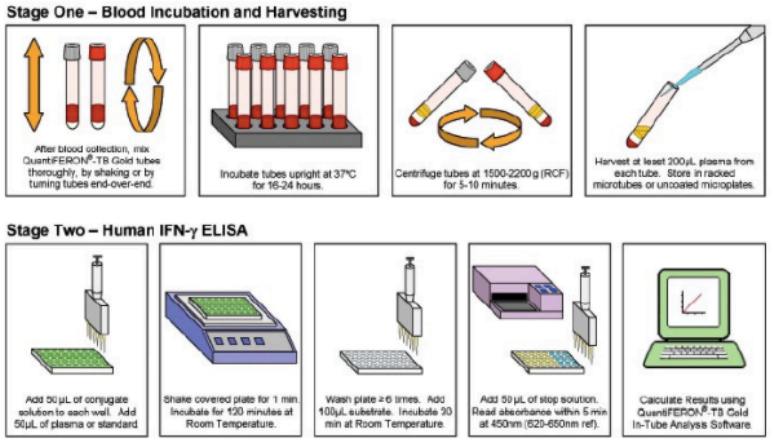
TB1 – Primarily detects CD4 T cell response

TB2 – Optimized for detection of CD4 and CD8 T cell responses

specificity of >97%
sensitivity of >94%

QuantiFERON-TB Gold Plus Procedure

1. Collect whole blood in a standard blood collection tube, or specialized QFT-Plus Blood Collection Tubes.
2. Incubate for 16 to 24 hours at 37°C.
3. Detect released IFNγ in harvested plasma by ELISA.
4. Analyze results using QFT-Plus Analysis Software.



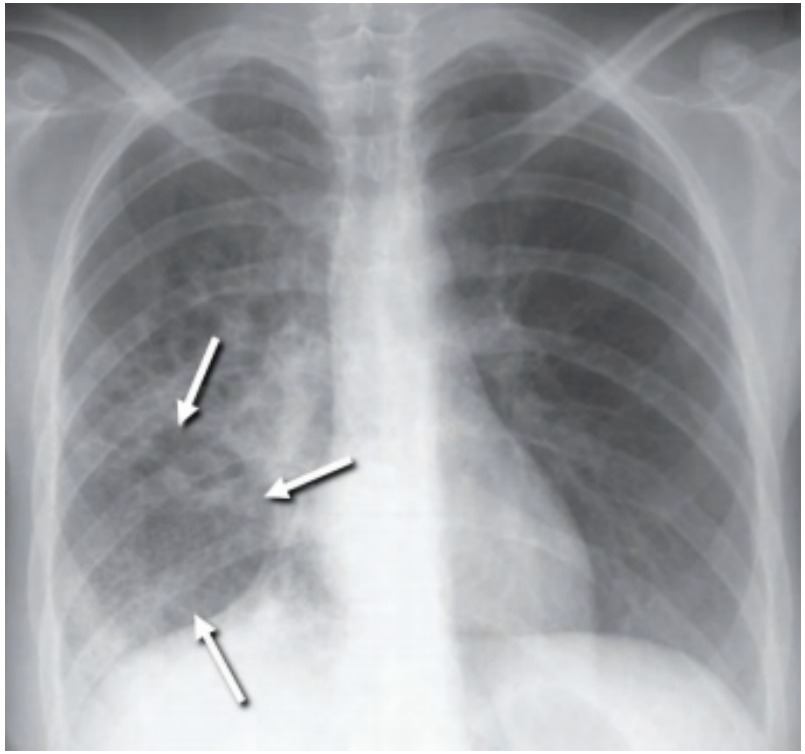
TST vs IGRA

TST	IGRA
Tuberculin is injected under the skin and produces a delayed-type hypersensitivity reaction if the person has been infected with *M. tuberculosis*	Blood is drawn for testing; test measures the immune response to the TB bacteria in whole blood
Requires two or more patient visits to conduct the test	Requires one patient visit to conduct the test
Results are available 48 to 72 hours later	Results can be available in 24 hours (depending on the batching of specimens by the laboratory and transport)
Can cause booster phenomenon	Does **not** cause booster phenomenon
Reading by HCW may be subjective	Laboratory test **not** affected by HCW perception or bias
BCG vaccination can cause false-positive result	BCG vaccination does **not** cause false-positive result and infection with most nontuberculous mycobacteria does **not** cause false-positive result
A negative reaction to the test does **not** exclude the diagnosis of LTBI or TB disease	A negative reaction to the test does **not** exclude the diagnosis of LTBI or TB disease

Diagnosis of Tuberculosis Disease

A complete medical evaluation includes the following five components:

1. Medical history
2. Physical examination
3. Test for M. tuberculosis infection
4. Chest radiograph
5. Bacteriologic examination of clinical specimens.

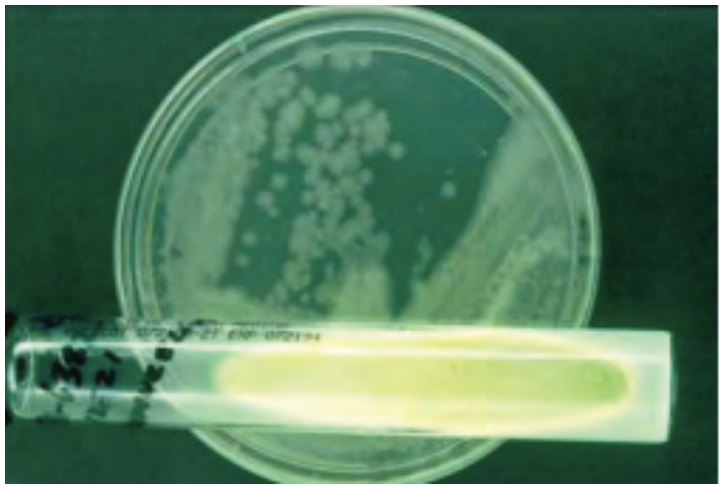


Bacteriologic examination of clinical specimens

- Specimen collection, processing, and review
- AFB smear classification and results
- Direct detection of M. tuberculosis in clinical specimen using nucleic acid amplification (NAA)
- Specimen culturing and identification
- Drug-susceptibility testing

Bacteriologic examination of clinical specimens

- At least three consecutive sputum specimens
- each collected in 8 to 24 hour intervals
- at least one being an early morning specimen
- collection from: coughing, induced sputum, bronchoscopy, gastric aspiration
- other clinical specimens: **urine, cerebrospinal fluid, pleural fluid, pus, or biopsy specimens**



Bacteriologic examination of clinical specimens

- Detection of acid-fast bacilli in stained and acid-washed smears examined microscopically may provide the first bacteriologic evidence of the presence of mycobacteria in a clinical specimen.
- Culture remains **the gold standard** for laboratory confirmation of TB disease, and growing bacteria are required to perform drug-susceptibility testing and genotyping

Treatment

Major goals of treatment:

- Cure the individual patient;
- Minimize risk of death and disability;
- Reduce transmission of M. tuberculosis to other persons.

Four-drug therapy

Treatment

First line TB drug

- Isoniazid (H/Inh)
- Rifampicin (R/Rif)
- Pyrazinamide (Z/Pza)
- Ethambutol (E/Emb)
- Streptomycin (S/Stm)

Second line TB drug

- Amikacin (Amk), kanamycin (KM)
- para-aminosalicylic acid (Pas)
- Fluoroquinolones
- cycloserine (Dcs)
- thionamide

Treatment of LTBI

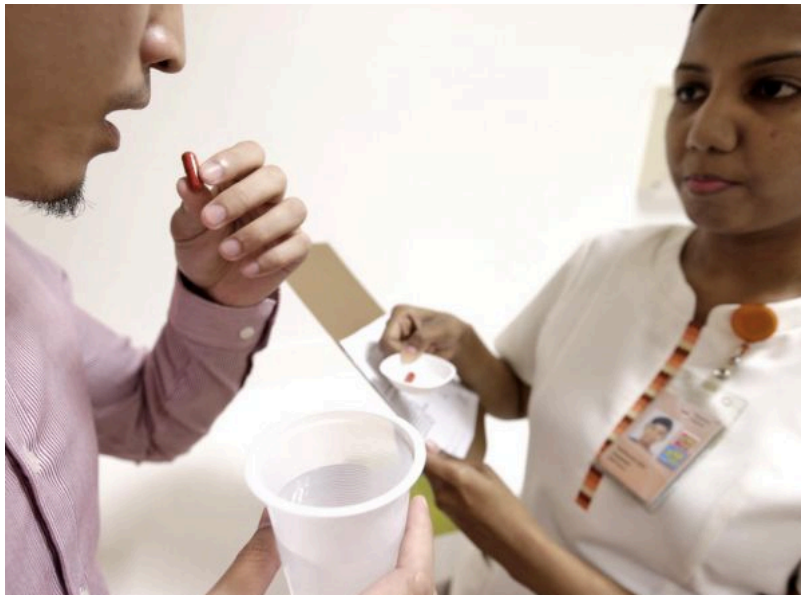
Drugs	Duration	Interval	Minimum doses
Isoniazid	9 months	Daily	270
		Twice weekly*	76
Isoniazid	6 months	Daily	180
		Twice weekly*	52
Isoniazid & Rifapentine	3 months	Once weekly*	12
Rifampin	4 months	Daily	120

Treatment of TB disease

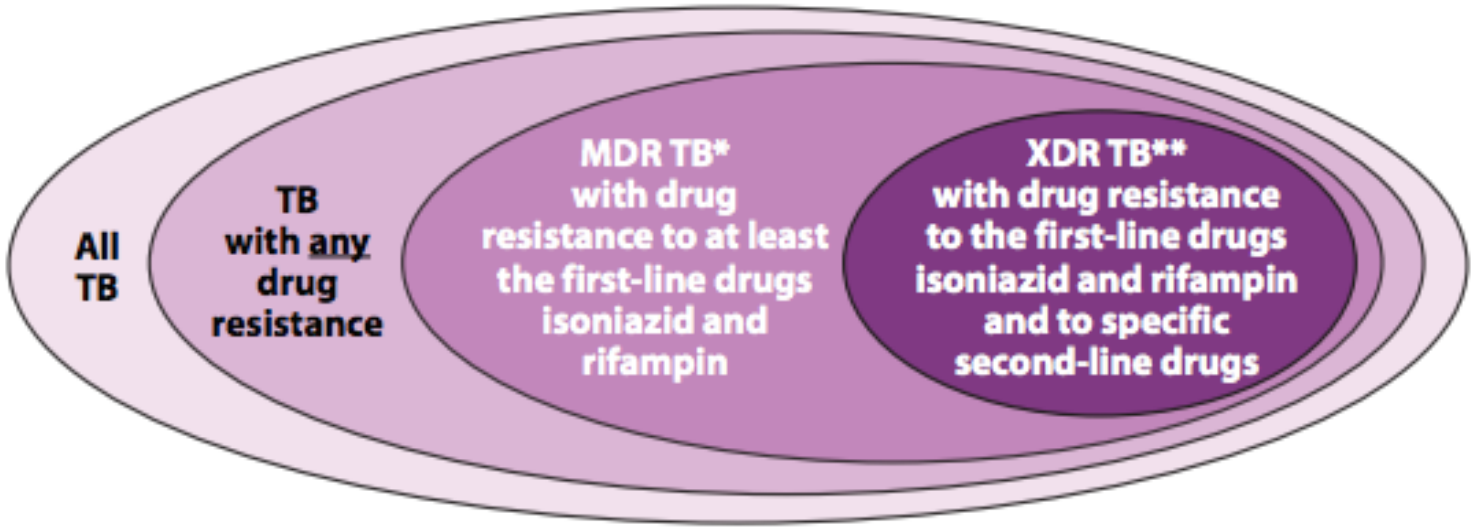
	INTENSIVE PHASE		CONTINUATION PHASE				
Regimen	Drugs[a]	Interval and Dose[b] (minimum duration)	Drugs	Interval and Dose[b,c] (minimum duration)	Range of Total Doses	Comments[c, d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)	INH RIF	7 days/week for 126 doses (18 weeks) *or* 5 days/week for 90 doses (18 weeks)	182 to 130	This is the preferred regimen for patients with newly diagnosed pulmonary TB.	Greater
2	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	110 to 94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 days/week for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 weeks)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease. If doses are missed then therapy is equivalent to once weekly, which is inferior.	Lesser

Directly Observed Therapy (DOT)

- DOT helps ensure patients adhere to therapy.
- A trained health-care worker watches a patient swallow each dose of anti-TB drugs and documents it.
- DOT can reduce the development of drug resistance, treatment failure, or relapse after the end of treatment.



Drug-Resistant TB (MDR and XDR)



* Often resistant to additional drugs

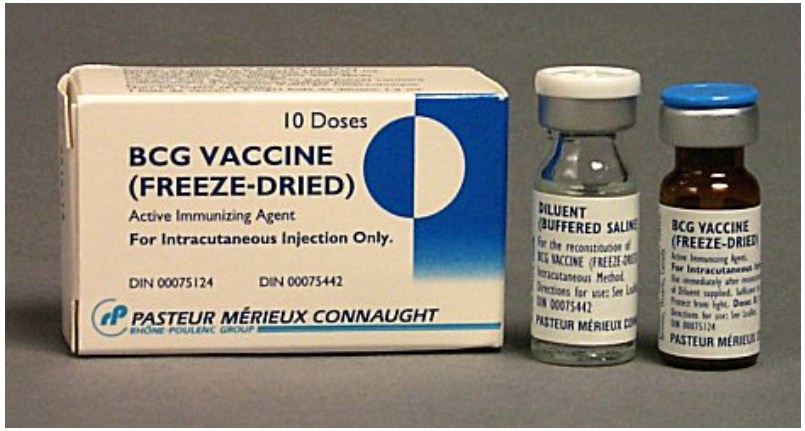
** Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)

Recommended Examinations for Baseline Monitoring

Patient	Recommended Test
All patients	Measure aminotransferases (i.e., AST, ALT), bilirubin, alkaline phosphatase, and serum creatinine and a platelet count
Patients at risk for hepatitis B or C (e.g., injection drug user, born in Asia or Africa, or HIV infected)	Conduct serologic tests
Patients who are taking EMB	Test visual acuity (Snellen chart) and color vision (Ishihara)
HIV-infected patients	Obtain CD4+ lymphocyte count

BCG Vaccination

- Vaccine made from live, attenuated (weakened) strain of *M.bovis*
- Early version first given to human in 1921
- Many TB prevalent countries vaccinate infants to prevente severe TB disease



Contact Investigation

Primary goal:

- Identify persons who were exposed to an infectious case of TB
- Ensure that contacts receive:
  - Testing for M. tuberculosis infection;
  - Screening for TB disease;
  - Medical evaluation, if indicated;
  - Prompt initiation of treatment for latent tuberculosis infection (LTBI) if at high risk for developing TB
  - A complete, standard course of treatment, unless medically contraindicated.

Contact Investigation

Pulmonary, **laryngeal**, or **pleuropulmonary disease** with either:

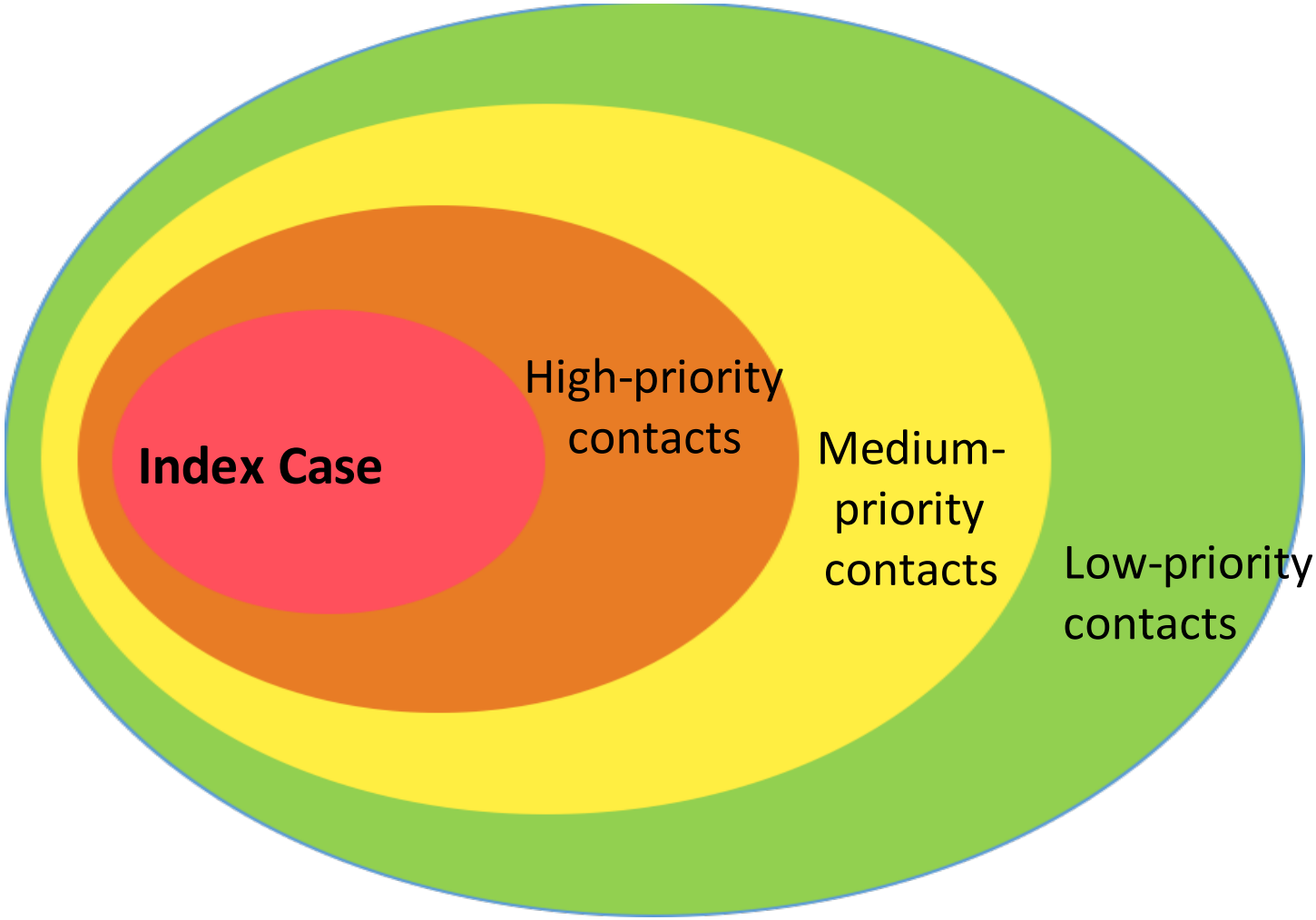
- Pulmonary cavities or
- Respiratory specimens that have acid-fast bacilli (AFB) on microscopy or
- (Especially) both.

Contact Investigation

Index patient factors increasing transmission risk

Characteristics of the Index Patient	Behaviors of the Index Patient
• Pulmonary, laryngeal, or pleuropulmonary tuberculosis (TB) • Positive acid-fast bacilli sputum smear results • Cavitation on chest radiograph • Adolescent or adult patient • Lack of treatment or ineffective treatment of TB disease	• Frequent coughing • Sneezing • Singing • Close social network

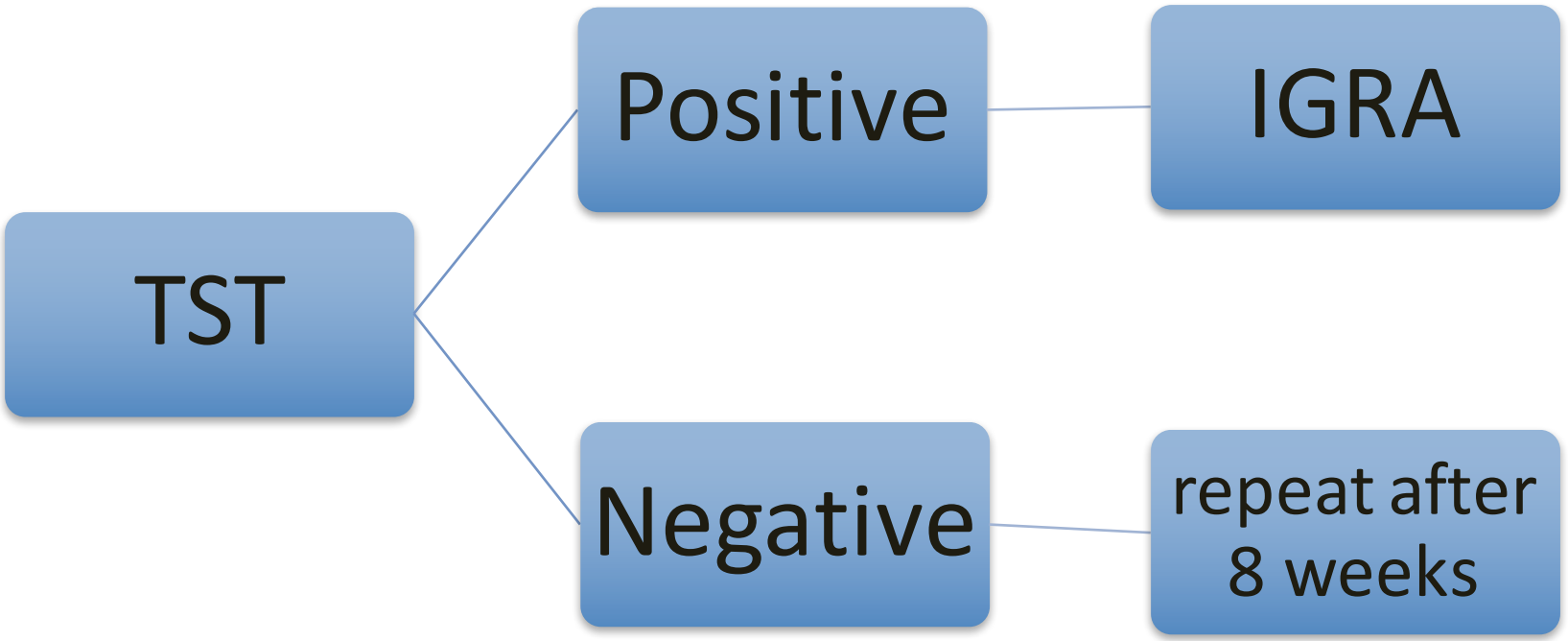
Contact Investigation
Contact Priorities



Contact Investigation
Prioritization of contacts

High-Priority Contacts	Medium-Priority Contacts	Low-Priority Contacts
• Household contacts • Contacts <5 years old • Contacts with human immunodeficiency virus (HIV) infection or other immunocompromising condition • Contacts with exposure during a medical procedure such as bronchoscopy, sputum induction, or autopsy • Contacts with exposure in a congregate setting • Contacts whose exposure occurs in poorly ventilated areas and for significant periods of time*	• Contacts not in high-priority groups • Contacts 5–15 years old • Contacts whose exposure occurs in poorly ventilated areas and for significant periods of time*	• Contacts not in high-priority groups • Contacts not in medium-priority groups

Contact Investigation – T0



Contact Investigation – T0