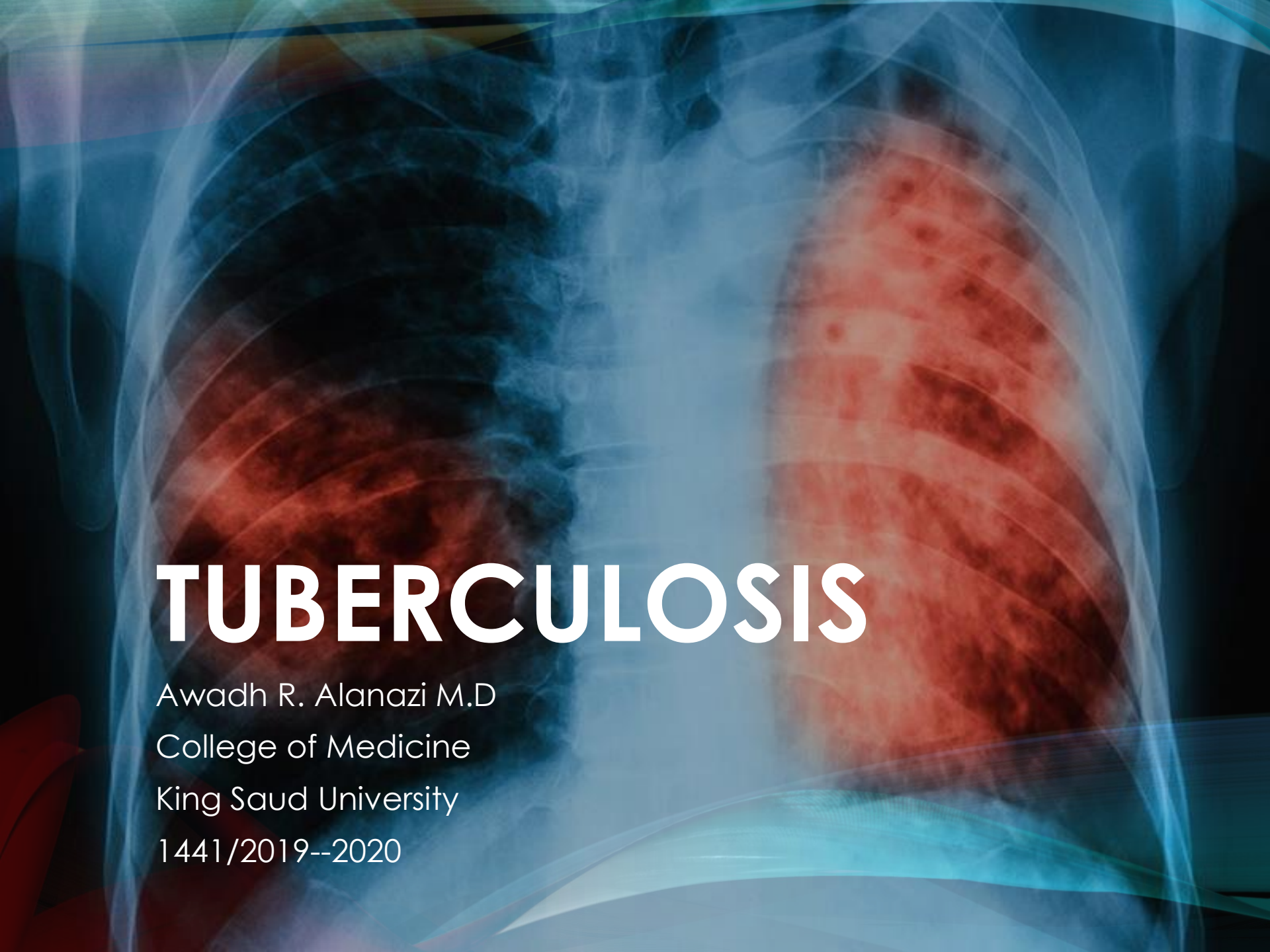

TUBERCULOSIS

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1441/2019--2020

OBJECTIVES

- By the end of this lecture, students should know the following about Tuberculosis:

  - Overview of Tuberculosis (TB) Epidemiology.
  - Transmission and Pathogenesis of TB.
  - Testing for TB Infection and Disease.
  - Diagnosis of TB Disease.
  - Treatment for Latent TB Infection.
  - Treatment for TB Disease.
  - TB Infection Control.

OVERVIEW OF TUBERCULOSIS (TB) EPIDEMIOLOGY

Bacterial infection.

Caused by Mycobacterium tuberculosis (also called tubercle bacillus).

Damages a person's lungs or other parts of the body.

Fatal if not treated properly.

EPIDEMIOLOGY

It is a world wide disease.

TB infects 1.7 billion with 3 million deaths/yr.

UK: 1st half of 20th century: a lot of death secondary to TB epidemic.

90% of cases and 95% of death occurred in developing countries.

Number of cases in developed countries has declined because of: case finding, RX and improved nutrition.

EPIDEMIOLOGY

- **Tuberculous infection:** a state in which the tubercle bacillus is established in the body without symptoms.

- **Tuberculous disease:** a state in which one or more organs of the body becomes diseased by the disease.

EPIDEMIOLOGY

What increases the spread of the disease:-

- crowding of living.
- migration of people from endemic area.

10% of infected people ---- active disease

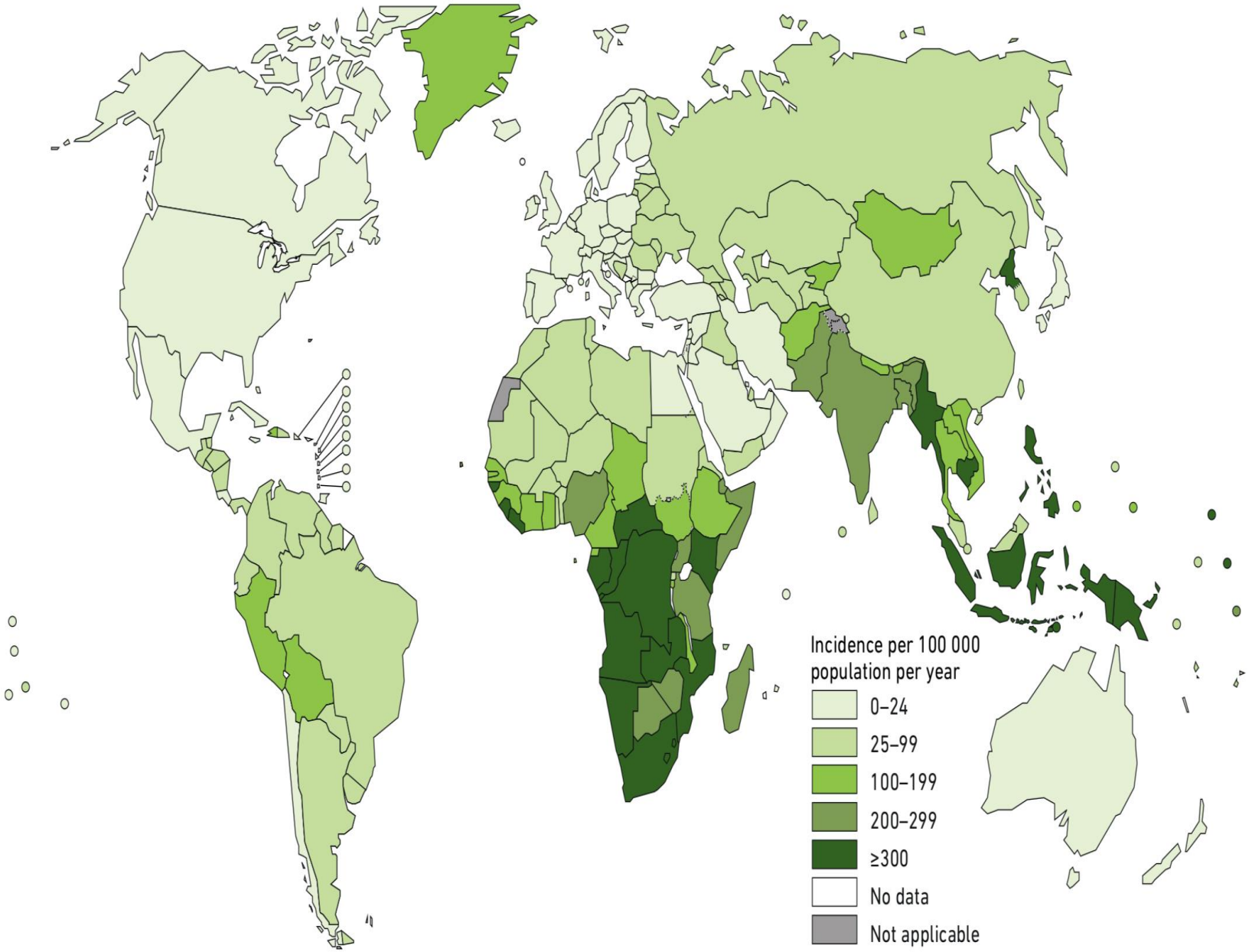
50%of active disease --- contagious

EPIDEMIOLOGY

What increases the risk of developing disease after TB infection :-

- Infecting dose.
- Host factors:
  - Age: under 5 yrs .
  - Debilitating illness and poor nutrition.
  - Alcoholism.
  - Gastrectomy.
  - Diabetes mellitus.

Estimated TB incidence rates, 2017



MODE OF SPREAD & TRANSMISSION

Inhalation of droplet nuclei.

Spreads through the air when a person with active TB:

- Coughs/ Speaks/ Laughs/ Sneezes/ Sings.
- Another person breathes in the bacteria and becomes infected.

TRANSMISSION OF *M. TUBERCULOSIS*

M. TB spread via airborne particles called droplet nuclei

Expelled when person with infectious TB coughs, sneezes, shouts, or sings

Transmission occurs when droplet nuclei inhaled and reach the alveoli of the lungs, via nasal passages, respiratory tract, and bronchi

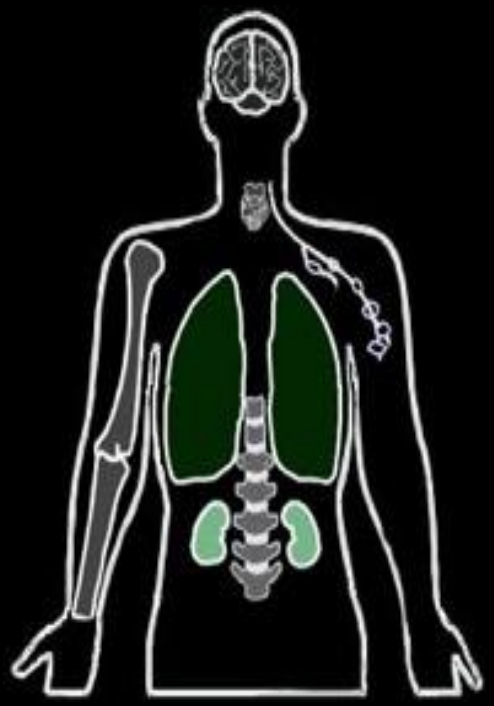
PATHOGENISIS

- Droplet nuclie ---terminal air space ---
- Multiplication … initial focus
  - Subpleural
  - 75%single
- Migration through blood and lymph node --- another focus
- Ingestion of the bacteria by the macrophage --- slow multiplication

PATHOGENISIS

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

PATHOGENISIS

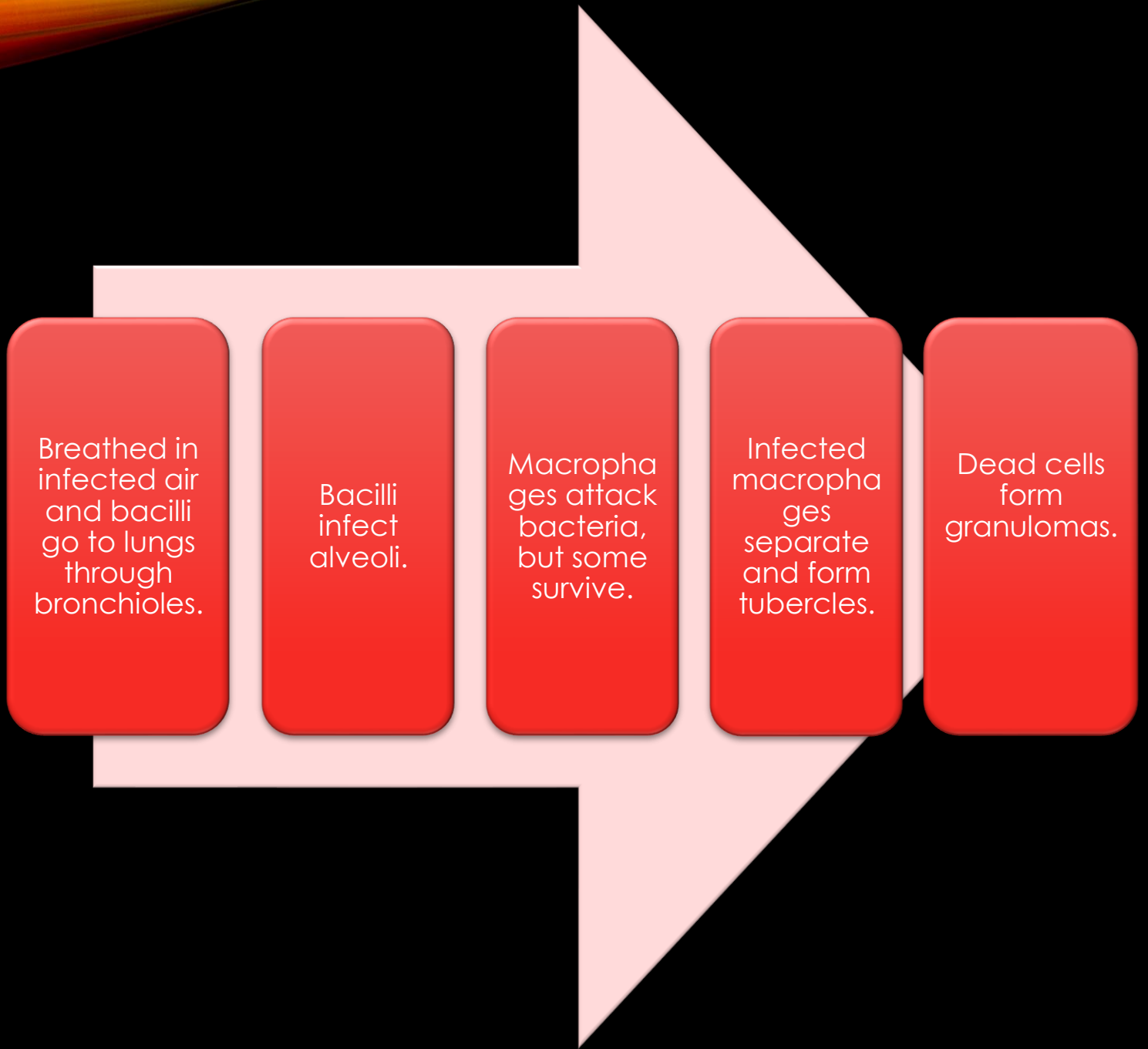


A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).

PATHOGENISIS

	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.

INSIDE THE BODY



INSIDE THE BODY (CONT.)

As a person breathes in infected air, the bacilli go to the lungs through the bronchioles. At the end of the bronchioles are alveoli, which are balloon-like sacs where blood takes oxygen from inhaled air and releases carbon dioxide into the air exhaled.

TB bacilli infect the alveoli and the body immune system begins to fight them. Macrophages — specialized white blood cells that ingest harmful organisms — begin to surround and "wall off" the tuberculosis bacteria in the lungs, much like a scab forming over a wound.

Then, special immune system cells surround and separate the infected macrophages. The mass resulting from the separated infected macrophages are hard, grayish nodules called tubercles.

INSIDE THE BODY (CONT.)

Active TB spreads through the lymphatic system to other parts of the body. In these other parts, the immune system kills bacilli, but immune cells and local tissue die as well. The dead cells form masses called granulomas, where bacilli survive but don't grow.

As more lung tissue is destroyed and granulomas expand, cavities develop in the lungs, which causes more coughing and shortness of breath. Granulomas can also eat away blood vessels which causes bleeding in the lungs, and bloody sputum.

IMMUNOLOGICAL FEATURE

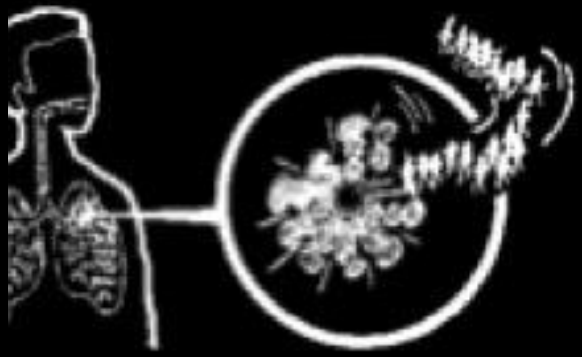
- TB require CMI(Cell Mediated Immunity) for its control.
- AB response is rich but has no role.
- Multiplication proceeds for weeks both in:
  - initial focus.
  - lymphohaematogenous metastatic foci.
- Until development of cell mediated immunity.

MICROBIOLOGY

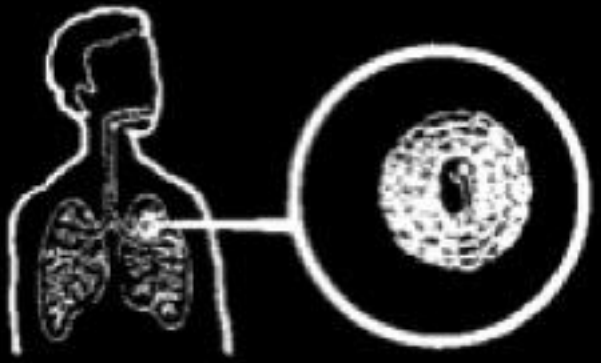
- Organism:
  - Mycobacterium tuberculosis.
  - Aerobic.
  - Non-spore forming ,non-motile.
  - Rod: 2—5 mm long.
  - Resistant to disinfectant.
  - Once stained it resists decolorization with acid and alcohol facultative intracellular organism.
- Humans are the main reservoir of MTB.

CLINICAL FEATURES ACTIVE VS. LATENT INFECTION

- Unhealthy person
- Bacilli overwhelm immune system.
- Bacilli break out of tubercles in alveoli and spread through bloodstream.
- This is (active) TB.



- Healthy person
- Initial infection controlled by immune system.
- Bacilli remain confined in tubercles for years.
- This is(latent) TB.



SYMPTOMS

- Cough.
- Fever.
- Weight loss.
- Night sweats.
- Loss of appetite.
- Fatigue.
- Swollen glands (lymph nodes).
- Chills.
- Pain while breathing.

CLINICAL FEATURES

- Pulmonary 80%.
- Extra pulmonary 20%.
- Pulmonary tuberculosis
- Primary: the lung is the 1st organ involved (middle and lower lobe).
- Health: asymptomatic .
- Heals spontaneously.
- CXR normal.

CLINICAL FEATURES

Post primary (reactivation):

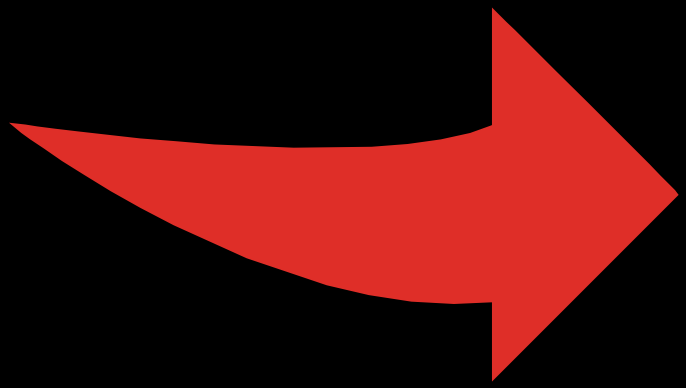
Result from endogenous reactivation of latent infection and manifest clinically:

- Fever and night sweat.
- Weight loss.
- Cough: non-productive then productive (may have hemoptysis).

Signs: rales in chest exam.

CLINICAL FEATURES (CONT.)

- Extra pulmonary
  - Lymph node.
  - Pleural.
  - Bone and joint.
  - Meninges.
  - Peritoneum.



CLINICAL FEATURES (CONT.)

Tuberculous lymphadenitis (25 %):

The commonest.

Localized painless swelling.

Common sites: cervical & supraclavicular.

Early: glands are discrete.

Late: glands are matted -/+ sinus.

Dx: FNA 30% in biopsy for histo and culture.

CLINICAL FEATURES (CONT.)

Pleural Tb:

Result form penetration by few bacilli into the pleural space resulting into:

Pleural effusion and fever.

DX; aspirate --- exudate.

AFB rarely seen.

Culture 30% positive.

BX 80% granuloma.

CLINICAL FEATURES (CONT.)

Skeletal Tb:

- Source:
  - Reactivation of hematogenous focus.
  - spread from an adjacent LN.
- Common sites: spine, hips and knees.

CLINICAL FEATURES (CONT.)

Spinal Tb:

- Dorsal site is the commonest site.
- Involve two vertebral bodies and destroy the disc in between.
- Advance disease .
- Collapse fracture of the bodies causing kyphosis and gibbus deformity.
- Paravertebral abscess(cold abscess).
- Dx: CT scan and MRI
- Biopsy: histopath& AFB stain & culture.

CLINICAL FEATURES (CONT.)

Tuberculous meningitis:

- Most often: children and may affect adults.

- Source:
  - Blood spread.
  - Rupture of a subependymal tubercle.

CLINICAL FEATURES (CONT.)

Symptoms:

- Fever.
- Headache.
- Neck rigidity.

- Disease typically evolve in 2 wks.
- Dx: CSF studies, AFB stain, WBC, cult, glucose, protein.

CLINICAL FEATURES

- Malnutrition.
- HIV.
- Severe cases:
  - primary lesion progress to clinical illness.
  - cavitating pneumonia.
  - lymphatic spread and lobar collapse due to LN.
- 40% hematogenous dissemination.

CLINICAL FEATURES

In children

Asymptomatic state may cause miliary tuberculosis and TB meningitis.

TB & AIDS

- Person with active TB are more frequent to have HIV than general population.
- AIDS in HAITIANS: almost all children are positive for PPD/TST, (active TB in 60%).
- New York: 50% of active TB patients are HIV+.

TB & AIDS

- Africans: 60% of active TB patients are HIV+.
- TB can appear at any stage of HIV infection but presentation varies with the stage.

TB & AIDS

Early:

- Typical pattern of upper lobe infiltrate -/+cavitation.

Late:

- Diffuse infiltrate .. no cavitation .. LN.

- Sputum is less frequent to be +ve for AFB with HIV than without.
- Extra pulmonary is more common (40%).

TB & AIDS

- Pulmonary TB and HIV --- diagnosis is difficult
  - sputum (-) in 40 %.
  - atypical CXR.
  - negativeTST(PPD).

LATENT TB INFECTION (LTBI)

Granulomas may persist (LTBI), or may break down to produce TB disease.

2 to 8 weeks after infection, LTBI can be detected via TST or interferon-gamma release assay (IGRA).

The immune system is usually able to stop the multiplication of bacilli.

Persons with LTBI are not infectious and do not spread organisms to others.

TB DISEASE

In some, the granulomas 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(laryngeal & open/smear+ve pulmonary TB).

Positive *M. tb* culture confirms TB diagnosis.

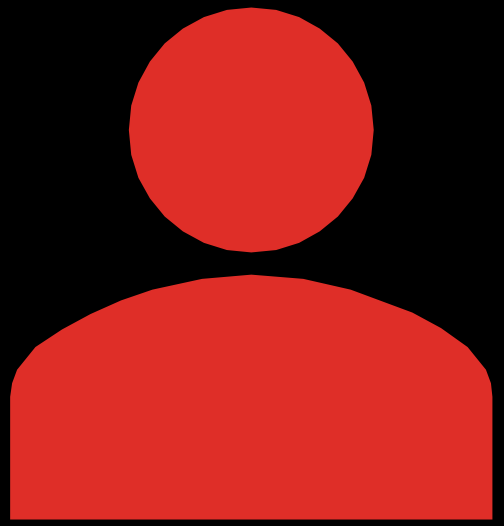
LTBI VS. TB DISEASE

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 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

MOST SUSCEPTIBLE

People at higher risk of TB infection:

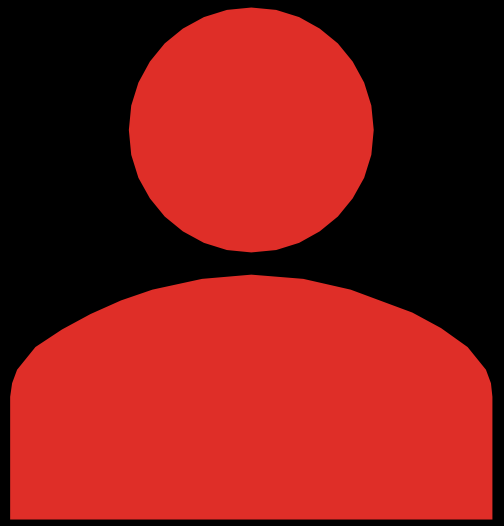
- Close contacts with people with infectious TB.
- People born in areas where TB is common.
- People with poor access to health care.
- People who inject illicit drugs.
- People who live or work in residential facilities.
- Health care professionals.
- The elderly.



MOST SUSCEPTIBLE (CONT.)

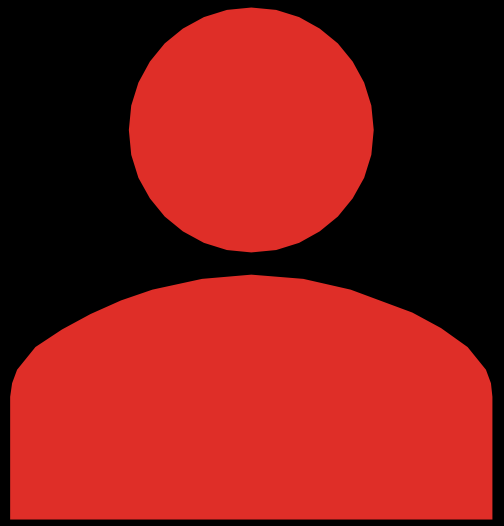
People at higher risk of active TB disease:

- People with weak immune systems (especially those with HIV or AIDS).
- People with diabetes or silicosis.
- People infected within the last 2 years.
- People with chest x-rays that show previous TB disease.
- Illicit drug and alcohol abusers.



PERSONS AT HIGHER RISK FOR EXPOSURE TO OR INFECTION WITH TB

- Close contacts of person known or suspected to have active TB.
- Foreign-born persons from areas where TB is common.
- Persons who visit TB-prevalent countries.
- Residents and employees of high-risk congregate settings.



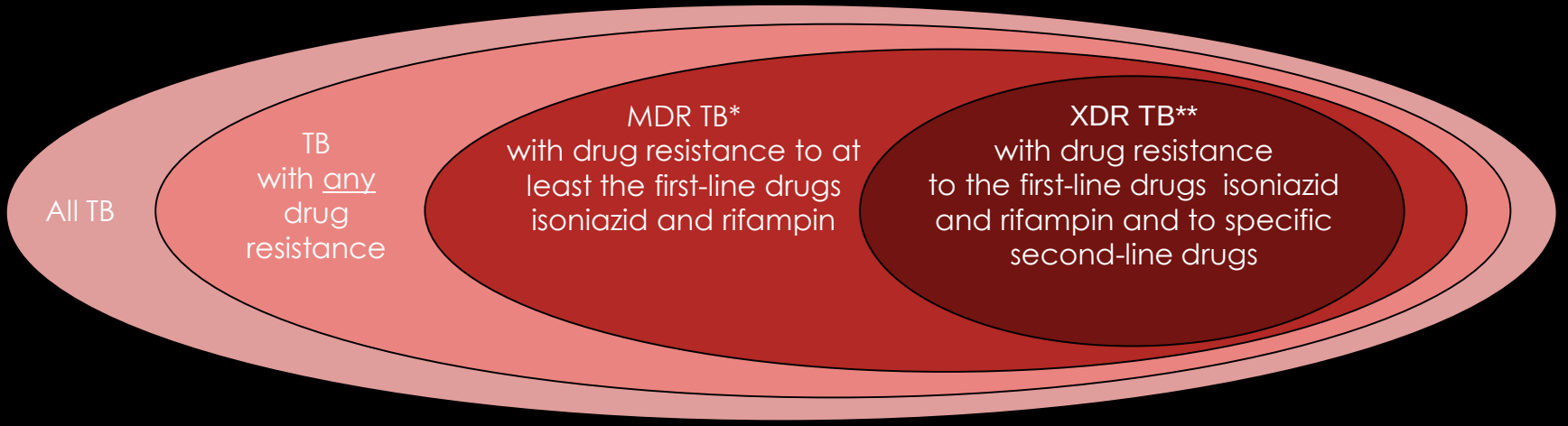
DRUG-RESISTANT TB

- Caused by organisms resistant to one or more TB drugs.
- Transmitted same way as drug-susceptible TB, and no more infectious.
- Delay in detecting drug resistance may prolong period of infectiousness because of delay in starting correct treatment.

MULTIDRUG-RESISTANT (MDR) AND EXTENSIVELY DRUG-RESISTANT (XDR) TB

- MDR TB caused by bacteria resistant to best TB drugs, isoniazid and rifampin.
- XDR TB caused by organisms resistant to isoniazid and rifampin, plus fluoroquinolones and ≥1 of the 3 injectable second-line drugs.

MULTIDRUG-RESISTANT (MDR) AND EXTENSIVELY DRUG-RESISTANT (XDR) TB



*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).

DIAGNOSIS

Medical Evaluation for TB:

- Medical history.
- Physical examination.
- Test for TB infection.
- Chest radiograph.
- Bacteriologic examination.

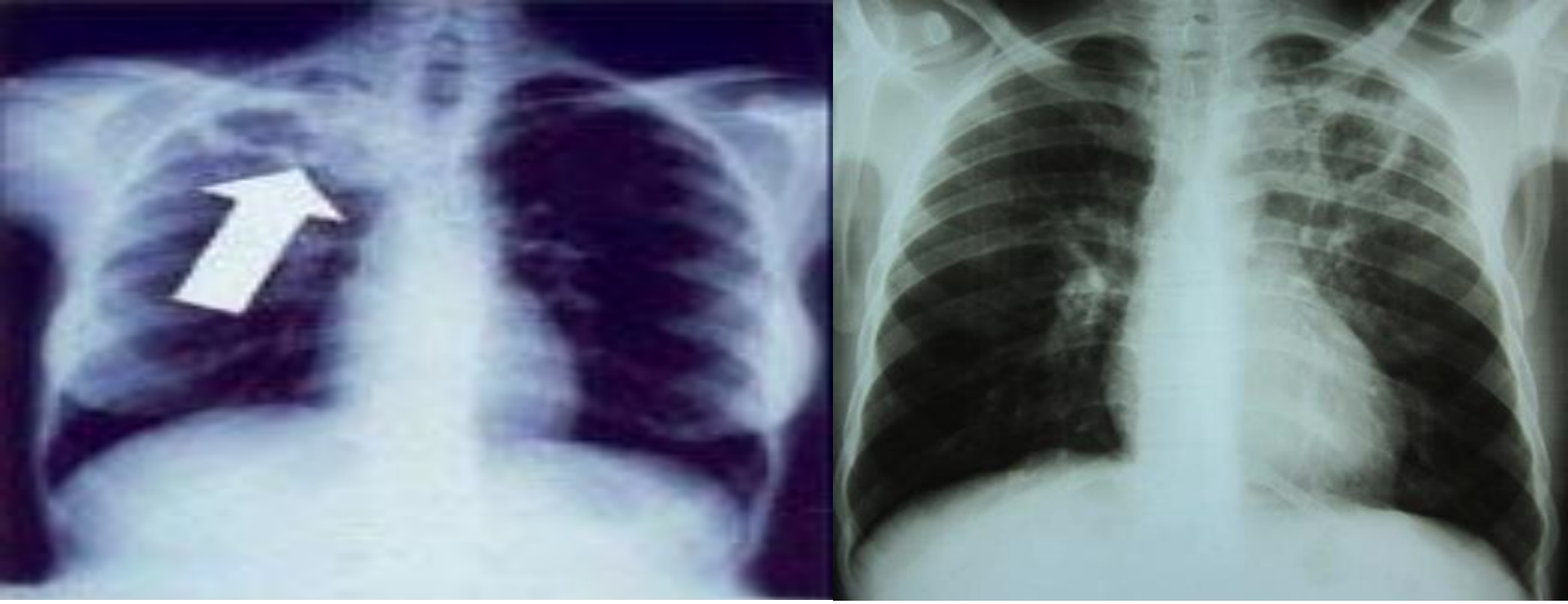
MEDICAL EVALUATION FOR TB (CONT.)
1. MEDICAL HISTORY (CONT.)

- **Symptoms of pulmonary TB:**
- Prolonged cough (3 weeks or longer), hemoptysis.
- Chest pain.
- Loss of appetite, unexplained weight loss.
- Night sweats, fever.
- Fatigue.

DIAGNOSIS

For any respiratory symptoms:

- Do chest x-ray … if abnormal ---
  - Sputum for:
    - Zn stain.
    - culture ..definite diagnosis.
  - Use lowenstein-jansen media.
- Slow growth … 3 - 6 wks.
- Bactic liquid media.



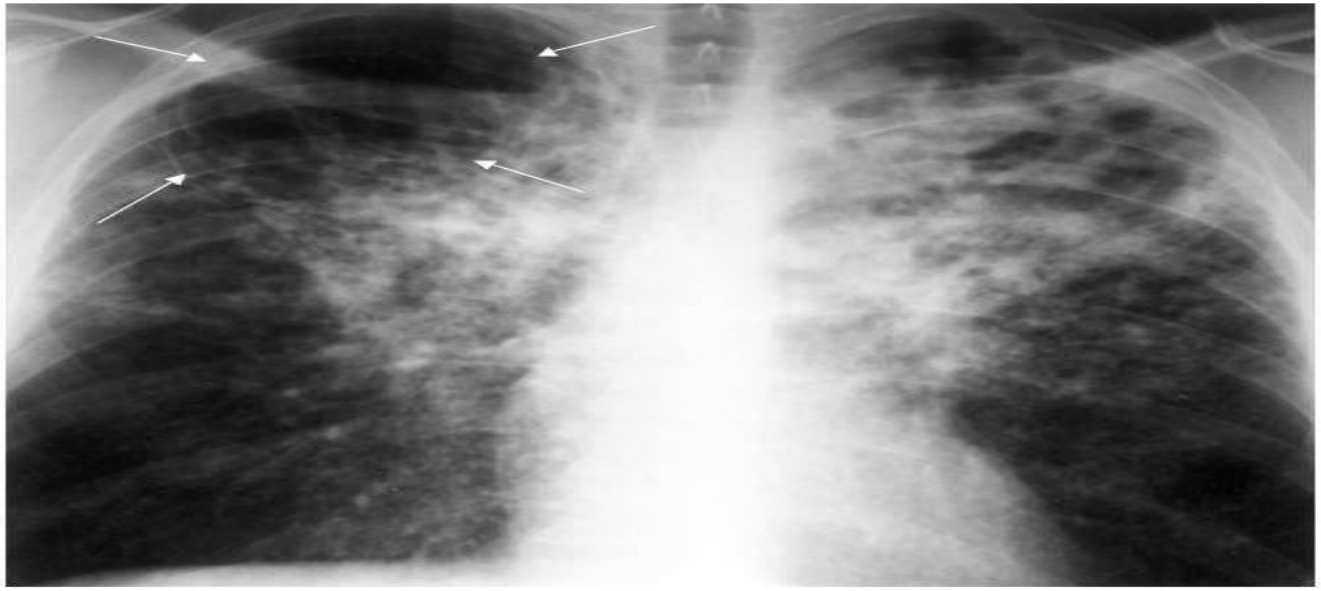
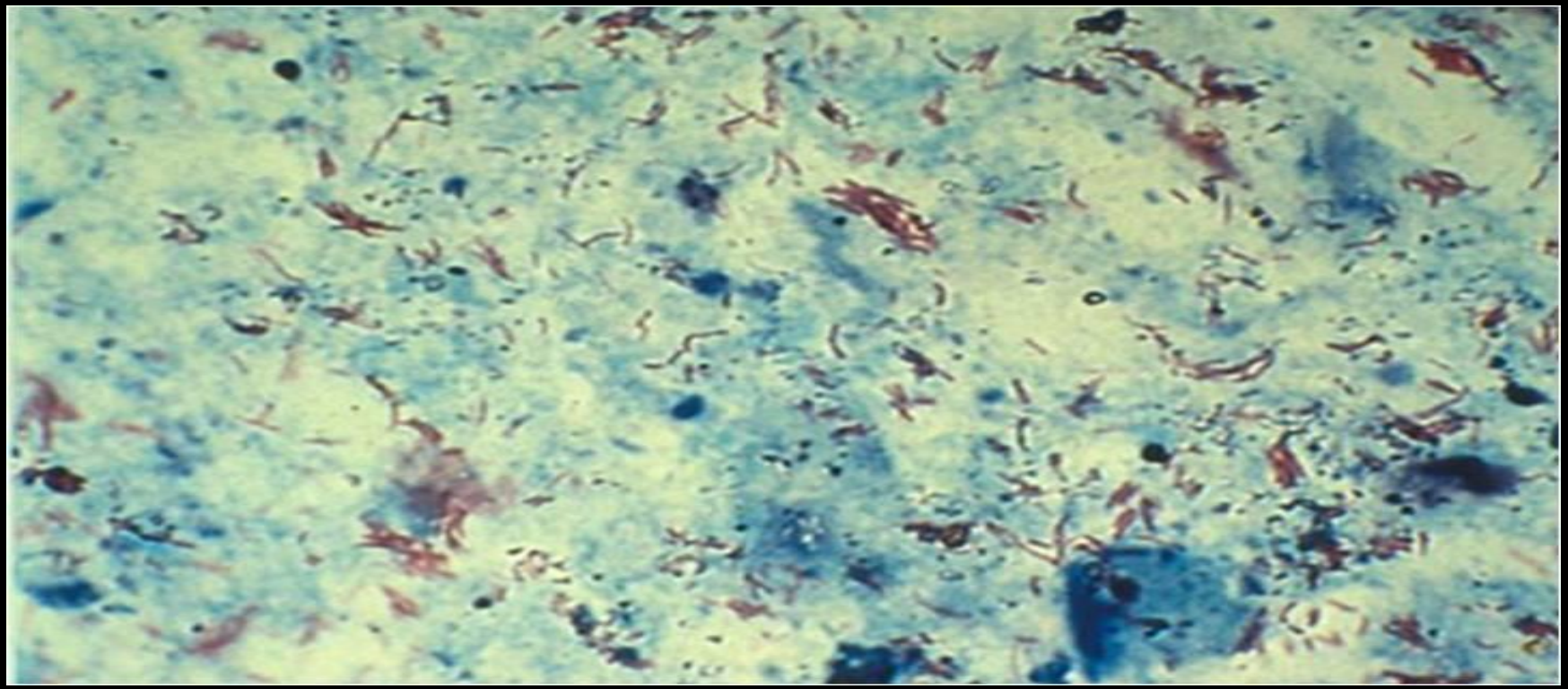


Figure 8. Chest x-ray with bilateral upper lobe opacities (white areas) with multiple cavities including a very large cavity in the right upper lobe (arrows).

AFB SMEAR
AFB (SHOWN IN RED) ARE TUBERCLE BACILLI



CULTURE

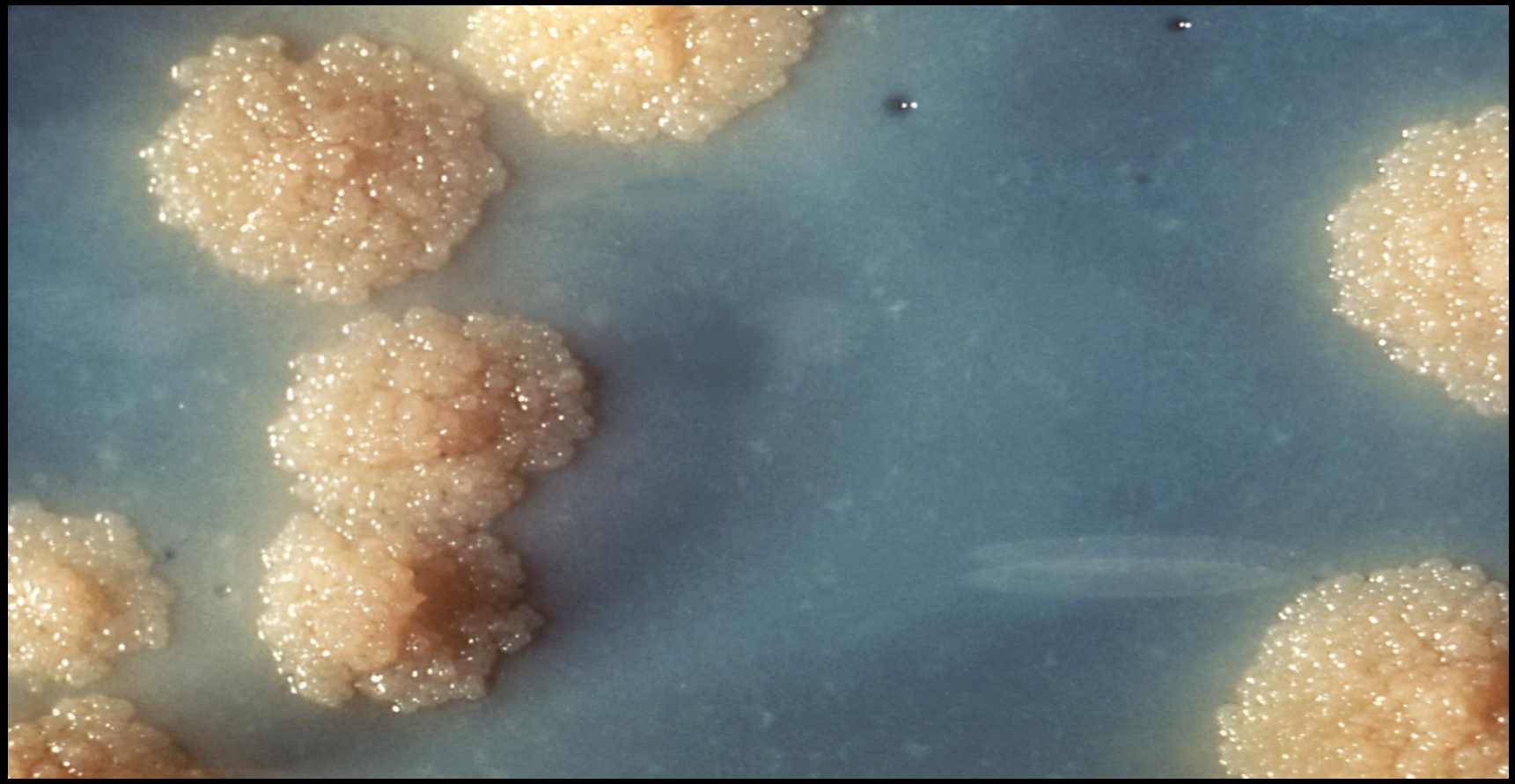
Remains gold standard for confirming diagnosis of TB.

Culture all specimens, even if smear or NAA negative.

Results in 4–14 days when liquid medium systems used.

Culture monthly until conversion, i.e., 2 consecutive negative cultures.

COLONIES OF *M. TUBERCULOSIS* GROWING ON MEDIA



DIAGNOSIS

- TST(PPD) … intradermally.
- 5 unit in o.1 ml.
- 10 mm: 90 % infected.
- More than 15 mm: 100% infected.

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BCG and positive TST(PPD):

- Unless very recent: positive TST(PPD) of more than 10mm should not be due to BCG

>15

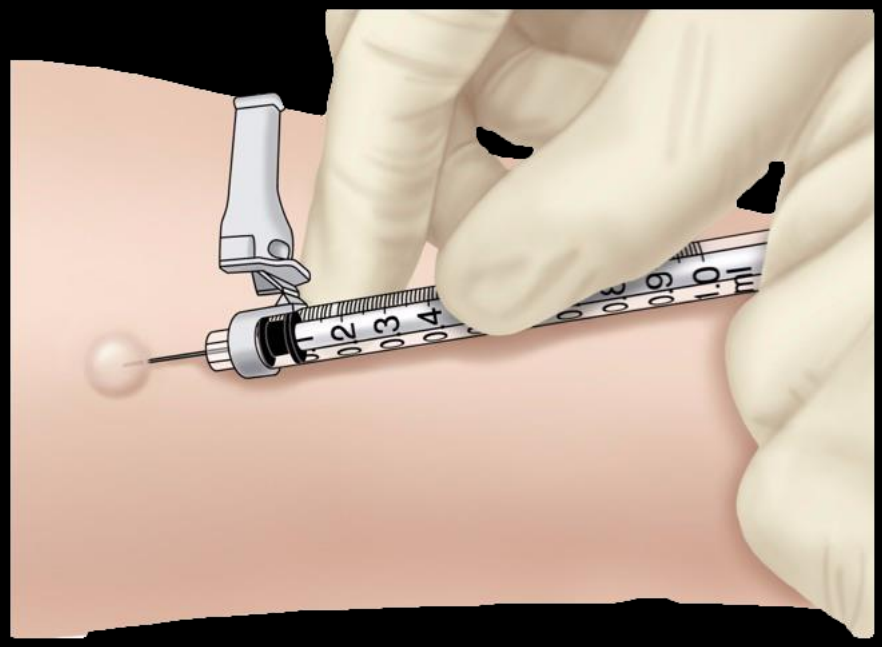
DIAGNOSIS

TST (Mantoux test),(PPD)

- TST(PPD) injected in forearm and examined 2-3 days later(24,48&72hrs).
- Induration around injection site indicates infection.
- Measure Induration NOT redness.
- Examine medical history, x-rays and sputum,
- Blood tests(B-interferone).
- PCR.

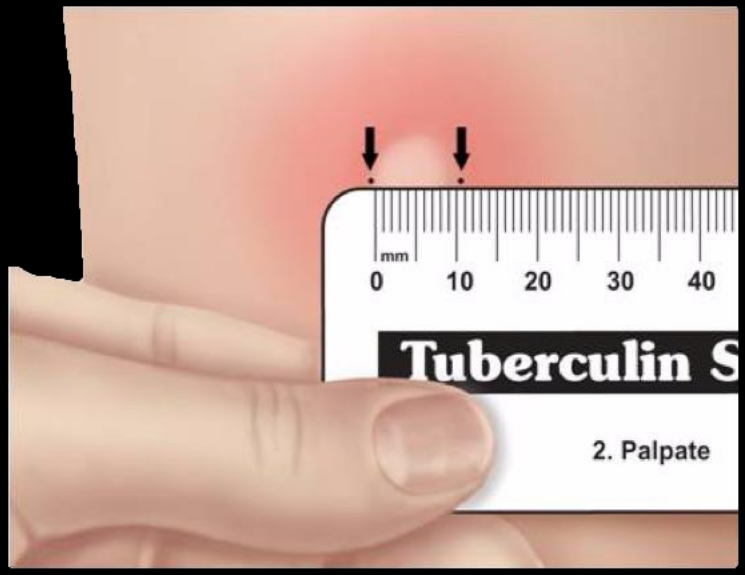
ADMINISTERING THE TST

- Inject 0.1 ml of PPD (5 tuberculin units) into forearm between skin layers.
- Produce wheal (raised area) 6–10 mm in diameter.
- Follow universal precautions for infection control.



READING THE TST

- Trained health care worker assesses reaction 48–72 hours after injection.
- Palpate (feel) injection site to find raised area.
- Measure diameter of induration across forearm; only measure induration, not redness.
- Record size of induration in millimeters; record “0” if no induration found.



MANTOUX TUBERCULIN SKIN TEST (TST)

- Purified protein derivative (PPD), derived from tuberculin, is injected between skin layers using the Mantoux technique
- Infected person's immune cells recognize TB proteins in PPD, respond to site, causing wheal to rise.
- Takes 2-8 weeks after exposure and infection for the immune system to react to PPD.
- Reading and interpretation of TST reaction must be done within 48–72 hours.

DIAGNOSIS

False negative TST:

- 20 % of active disease.
- Malnutrition.
- Sarcoid.
- Lymphoproliferative dis.(lymphoma).
- Viral infection.
- Steroid.
- TST(PPD): is of limited value because of low sensitivity and specificity

FACTORS THAT MAY AFFECT THE SKIN TEST REACTION

Type of Reaction	Possible Cause
False-positive	• Nontuberculous mycobacteria • BCG vaccination • Problems with TST administration
False-negative	• Anergy • Viral, bacterial, fungal coinfection • Recent TB infection • Very young age; advanced age • Live-virus vaccination • Overwhelming TB disease • Renal failure/disease • Lymphoid disease • Low protein states • Immunosuppressive drugs • Problems with TST administration

INTERFERON GAMMA RELEASE ASSAYS (IGRAS)

- IGRAs detect *M. tb* infection by measuring immune response in blood.
- Cannot differentiate between TB and LTBI; other tests needed.
- May be used for surveillance/screening, or to find those who will benefit from treatment.
- FDA-approved IGRAs are QFT Gold In-Tube and T-Spot.*TB* test.

BCG VACCINATION

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

BCG CONTRAINDICATIONS

Contraindicated in persons with impaired immune response from:

- HIV infection, congenital immunodeficiency.
- Leukemia, lymphoma, generalized malignancy
- High-dose steroid therapy.
- Alkylating agents.
- Antimetabolites.
- Radiation therapy.

BCG vaccination should not be given to pregnant women

GENERAL RECOMMENDATIONS FOR USING IGRAS

May be used in place of, but not in addition to, TST.

Preferred when testing persons:

- Who might not return for TST reading.
- Who have received BCG vaccination.

Generally should not be used to test children <5 years of age, unless used in conjunction with TST.

MEDICAL EVALUATION FOR TB (CONT.)
1. MEDICAL HISTORY (CONT.)

Symptoms of possible extrapulmonary TB:

- Blood in the urine (TB of the kidney).
- Headache/confusion (TB meningitis).
- Back pain (TB of the spine).
- Hoarseness (TB of the larynx).
- Loss of appetite, unexplained weight loss.
- Night sweats, fever.
- Fatigue

DIRECT DETECTION USING NUCLEIC ACID AMPLIFICATION (NAA)

NAA tests rapidly identify a specimen via DNA and RNA amplification.

Benefits may include:

- Earlier lab confirmation of TB disease
- Earlier respiratory isolation and treatment initiation
- Improved patient outcomes; interruption of transmission

Perform at least 1 NAA test on each pulmonary TB suspect.

A single negative NAA test does not exclude TB.

TREATMENT FOR LATENT TB INFECTION (LTBI)

- Treatment of LTBI essential to controlling and eliminating TB disease.
- Reduces risk of LTBI to TB disease progression.
- Use targeted testing to find persons at high risk for TB who would benefit from LTBI treatment.
- Several treatment regimens available.

CANDIDATES FOR TREATMENT OF LTBI (CONT.)

High-risk persons with positive IGRA test or TST reaction of ≥10 mm (cont.):

Persons with conditions that increase risk for TB:

- Silicosis.
- Diabetes mellitus.
- Chronic renal failure.
- Certain cancers (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung).
- Gastrectomy or jejunoileal bypass.
- Weight loss of at least 10% below ideal body weight.
- Children <4 yrs of age; children/adolescents exposed to adults in high-risk categories.

MAJOR GOALS OF TB TREATMENT

- Cure patient, minimize risk of death/disability, prevent transmission to others.
- Provide safest, most effective therapy in shortest time.
- Prescribe multiple drugs to which the organisms are susceptible.
- Never treat with a single drug or add single drug to failing regimen.
- Ensure adherence and completion of therapy.

CURRENT ANTI-TB DRUGS

10 or more drugs FDA-approved for treatment of TB:

- Isoniazid (INH).
- Rifampin (RIF).
- Pyrazinamide (PZA).
- Ethambutol (EMB).
- Rifapentine (RPT).
- Streptomycin (SM).
- Cycloserine.
- Capreomycin.
- *p*-Aminosalicylic acid.
- Ethionamide.

TREATMENT

Chemotherapy: cure

- Isonised.
- Rifampicin.
- Pyrazinamide.
- Ethambutol/streotomycin.

  - rapidly reduce the number of viable organism.
  - kill the bacilli.
  - slow rate of induction of drug resistance.

REGIMEN 1 FOR TREATMENT OF PULMONARY, DRUG-SUSCEPTIBLE TB

6-month standard regimen for most patients.

<u>Initial phase:</u>

- INH, RIF, PZA, EMB daily (7 or 5 days/week) for 8 weeks.

<u>4-month continuation phase options:</u>

- INH, RIF daily (7 or 5 days/week) for 18 weeks.
- INH, RIF intermittently (2 days/week or 1 day/week for INH, rifapentine) for 18 weeks.

TREATMENT CONT.

Drug failure:

- None compliance.
- Inappropriate drug.
- Drug resistance.

INFECTION CONTROL

Active pulmonary tuberculosis:

- Isolation of the patient (2wks).
- Isolation room should be negative pressure.
- Patient remain until 3 negative smears and there is clinical improvement.

TB INFECTION CONTROL MEASURES

TB infection control (IC) measures should be based on TB risk assessment for the setting.

The goals of IC programs are:

- Detect TB disease early and promptly.
- Isolate persons with known/suspected TB.
- Start treatment in persons with known/suspected TB.

THANK YOU FOR YOUR ATTENTION