Zaporizhzhia State Medical University
Department of phthisiology and pulmonology
R.N. Yasinskiy
(assistant of department)
e-mail: yarn85@mail.ru

Importance of tuberculosis as scientific and practical problem. Tuberculosis epidemiology in the world. Etiology and pathogenesis of tuberculosis. Immunity at tuberculosis

What is Tuberculosis?

- Tuberculosis is defined as an infectious disease caused by a bacterium; that most commonly affects the lungs.
- It can also be a crippling and deadly disease, and is on the rise in both developed and developing worlds. Globally, it is the leading cause of deaths resulting from a single infectious disease.
- Currently, it kills “three million people” a year and could claim up to 30 million lives if not controlled.

These numbers are expected to increase in the coming years because of the acquired immune deficiency syndrome (AIDS) pandemic – a high percentage of the patients with human immunodeficiency virus (HIV) are co-infected with MBT, and the emergence of drug-resistant strains of the TB organisms. This alarming increase in morbidity and mortality highlights the need to strengthen control measures.

Accurate and rapid diagnosis is essential for controlling the disease, yet the traditional tests for TB produce results that are either inaccurate or take too long to be definitive.

People who have healthy immune systems can often fight off a tuberculosis infection after breathing in MBT.

These people have no symptoms and are not sick, because the immune system is able to prevent the MBT from growing and multiplying.

This is called latent tuberculosis. People with latent tuberculosis are not contagious and cannot spread the disease to others.

However, anything that stresses the immune system, such as the development of a chronic disease, can allow the bacteria to become active and begin to multiply in the body.

The magnitude of the problem:

- Tuberculosis kills more than 3 million people per year
- Tuberculosis produces 25% of all avoidable deaths in developing countries
- Tuberculosis produces more death than any other single infectious disease , so its the deadliest one
- About the 1/3 of the world population are infected by tuberculosis

Tuberculosis uniqueness:

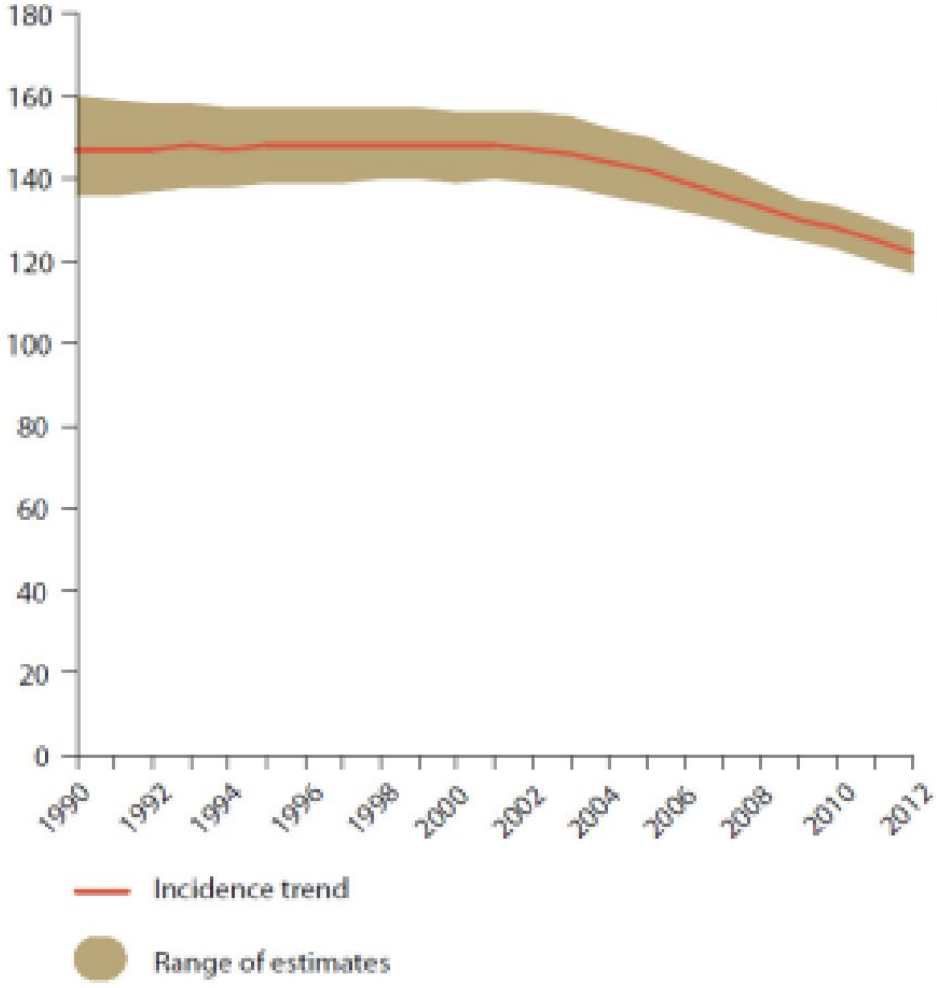
- the most ancient among known infection
- the most ubiquitous infection
- infection which can coexist with the human being without producing the disease
- infection from which human being isn't able to deliver

Main reasons for tuberculosis reappearance as a global challenge:

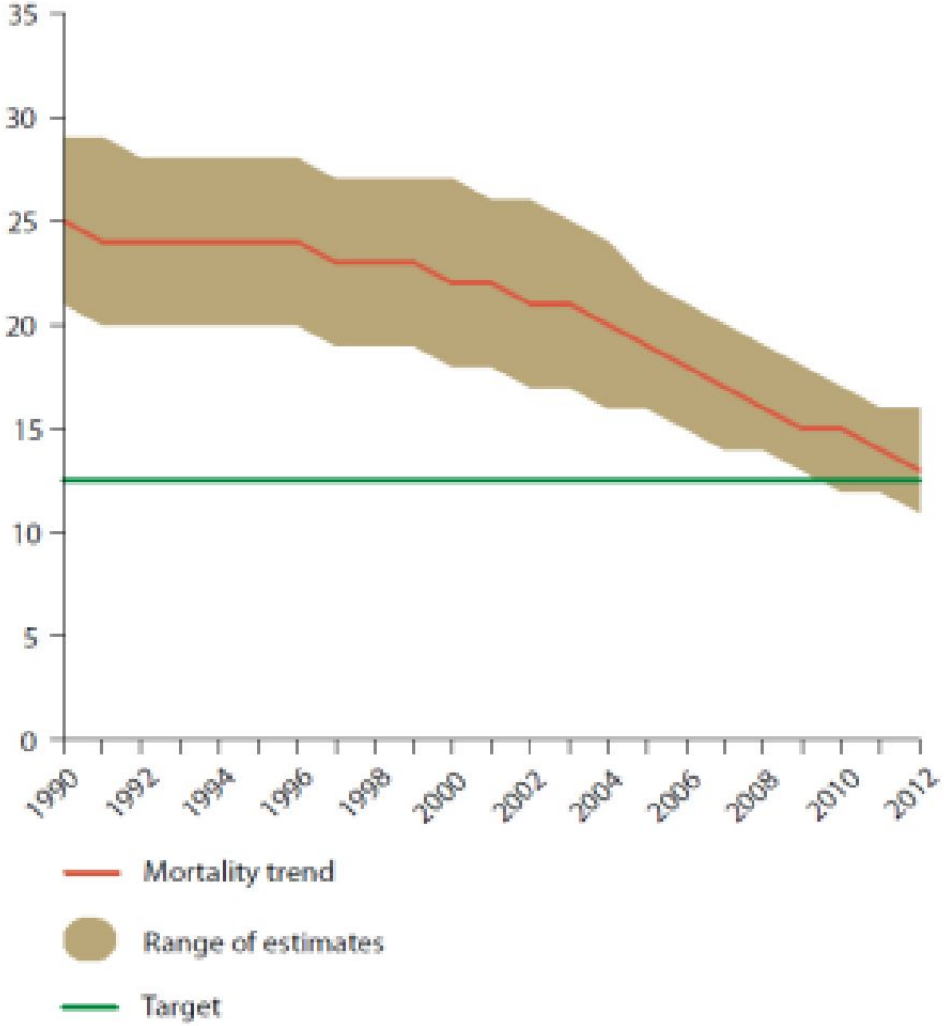
- Drug-resistance
- Human immunodeficiency virus (HIV)
- Social disturbances

EPIDEMIOLOGY

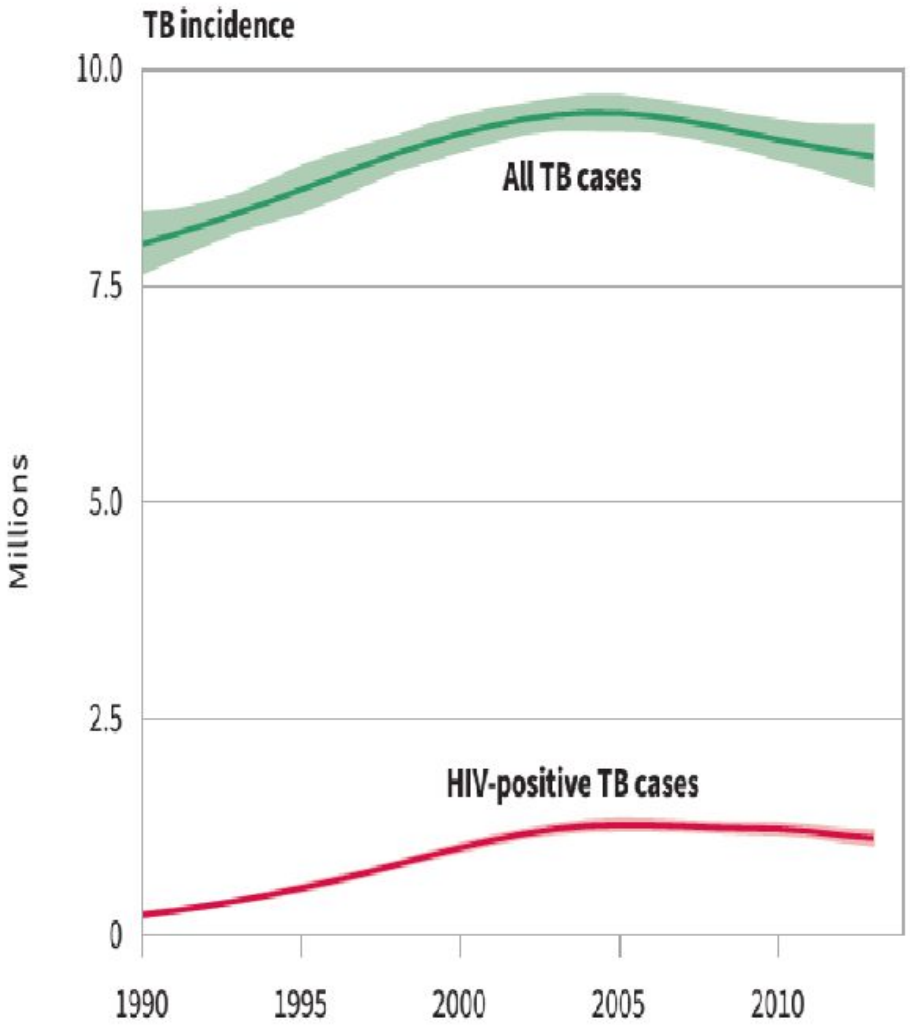
Estimated number of new tuberculosis cases per 100,000 population including people who are HIV-positive, 1990–2012

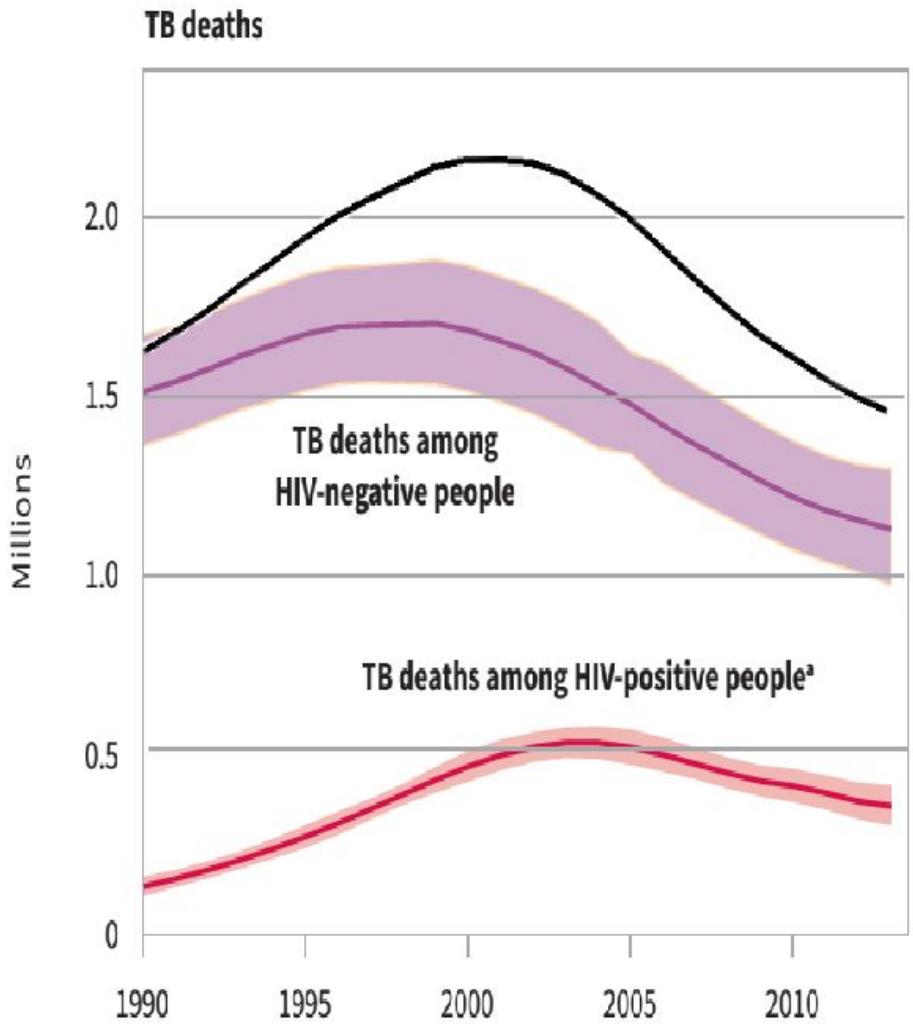


Estimated number of deaths due to tuberculosis per 100,000 population excluding people who are HIV-positive, 1990–2012



Estimated absolute numbers of estimated TB cases and deaths (in millions per year), 1990–2013



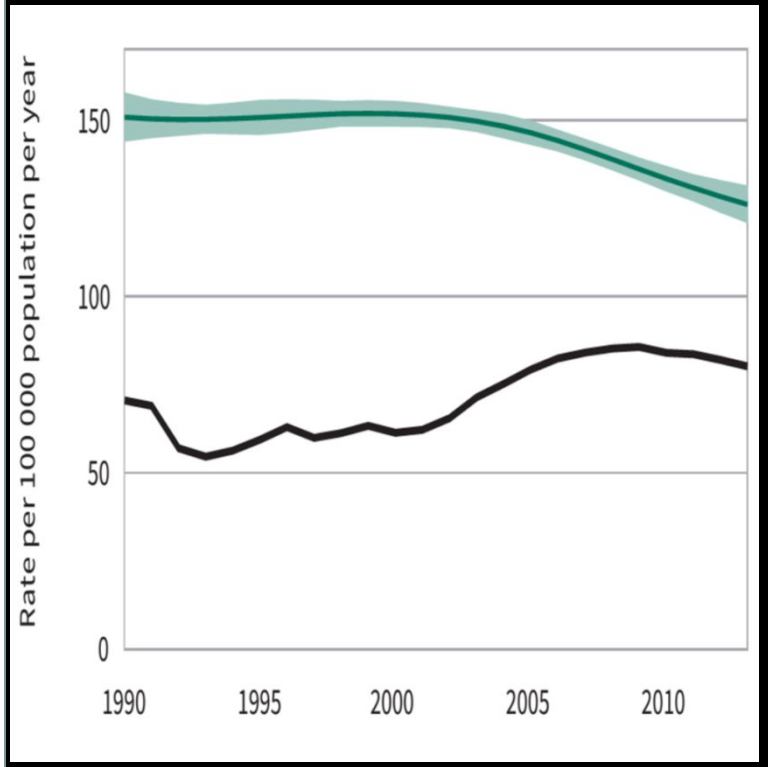


[a] HIV-associated TB deaths are classified as HIV deaths according to ICD-10.

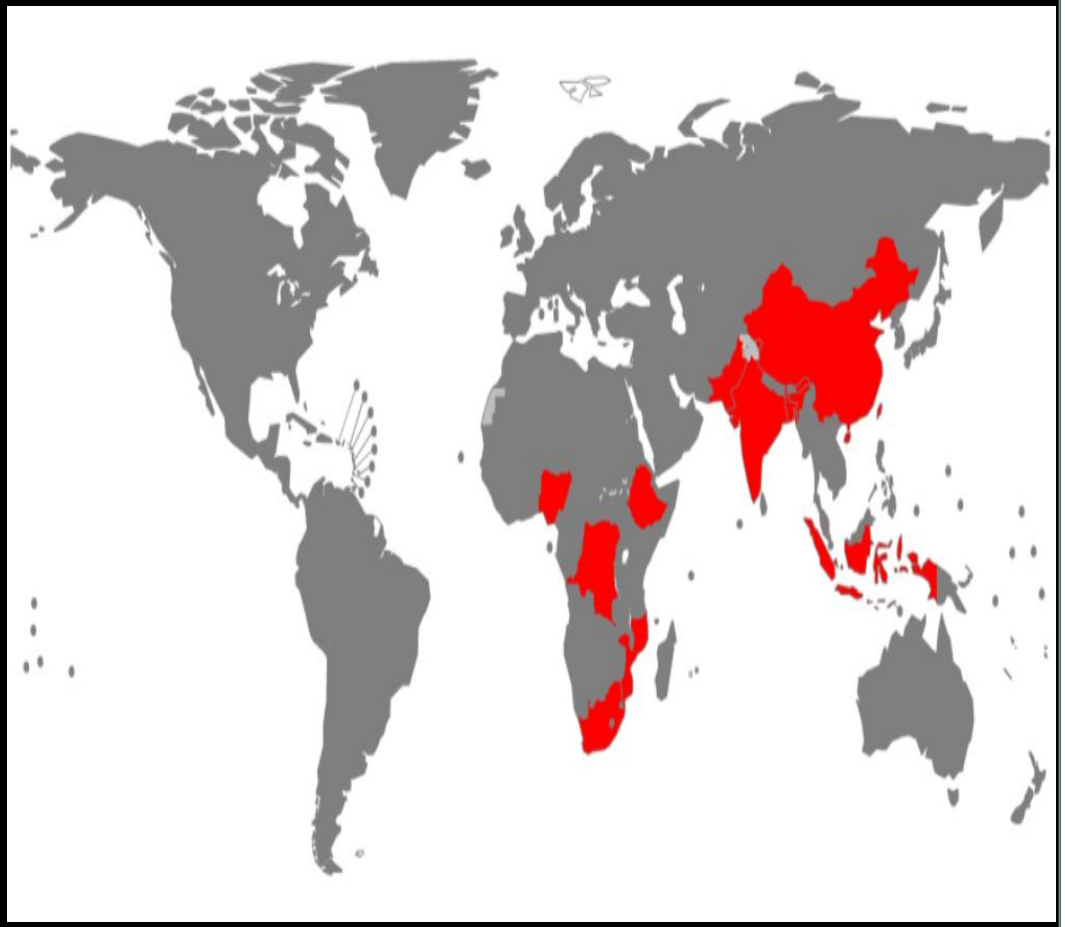
5 PRIORITIES TO ELIMINATE TB

- Reaching the "missed" cases (3 million not in the system)
- Address MDR-TB as crisis
- Accelerate response to TB/HIV
- Increase financing to close resource gaps
- Intensify research and ensure rapid uptake of innovations

Reaching the "missed" cases early means cutting transmission

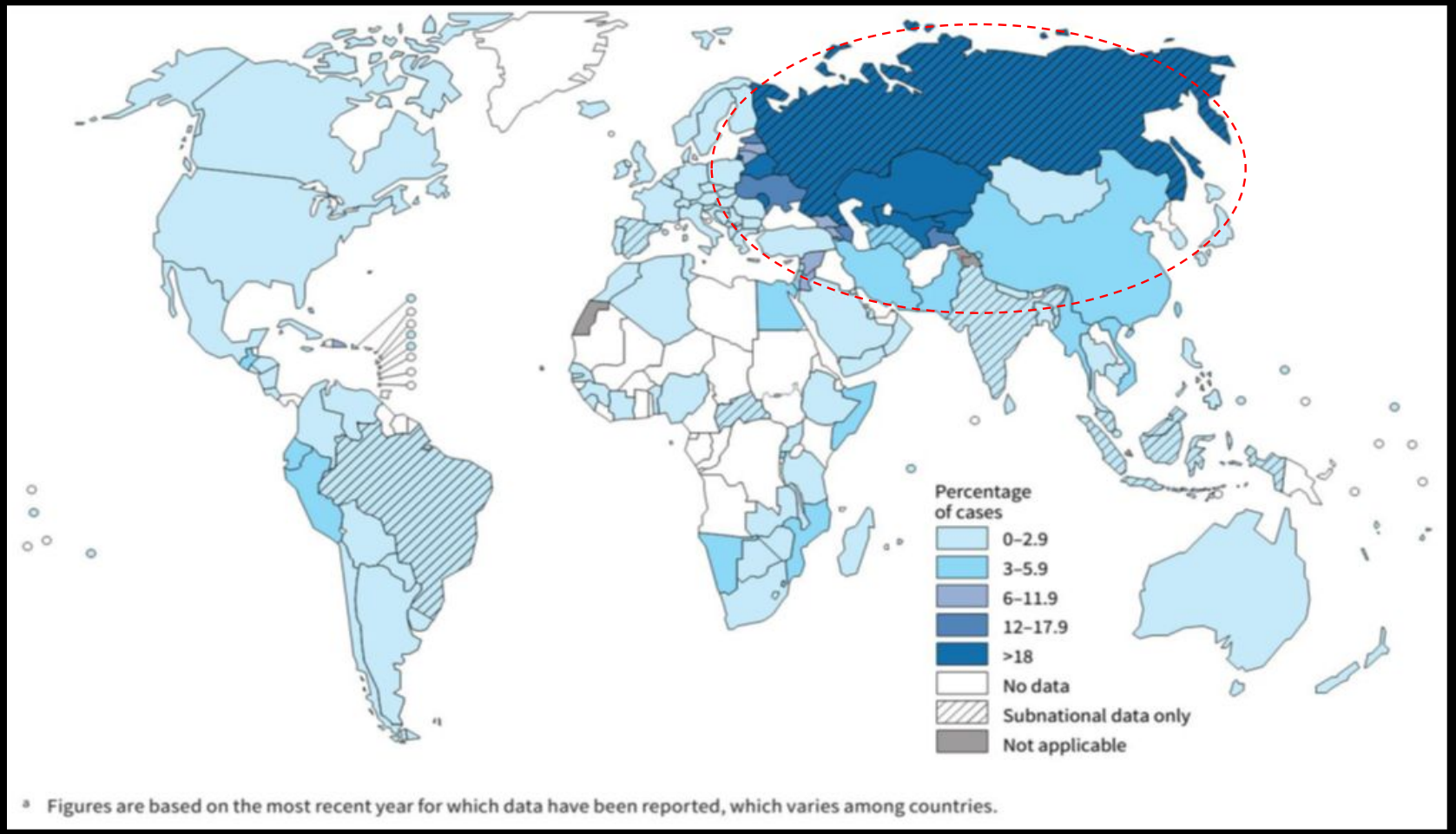


Share of total missed cases



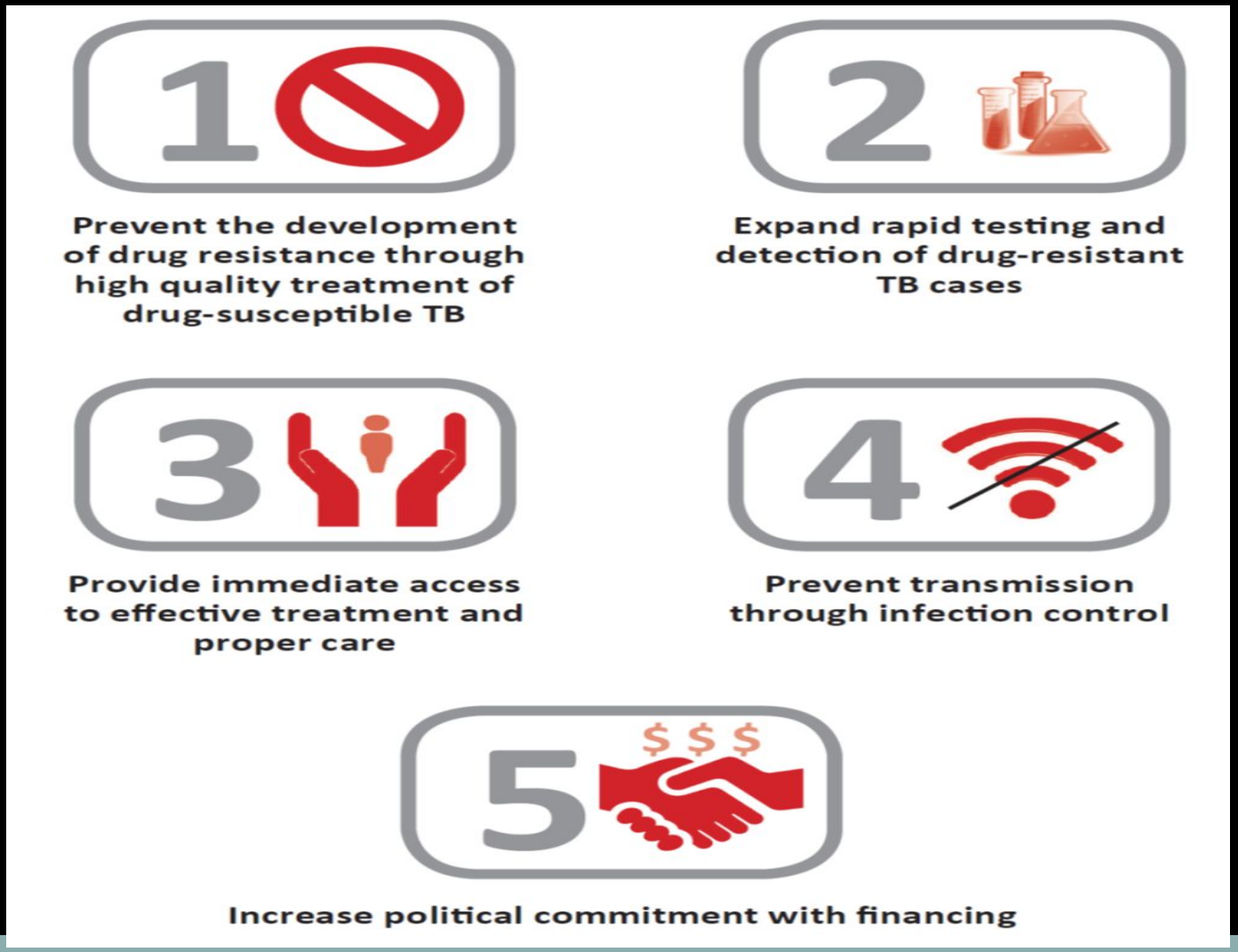
Addressing MDR-TB as a crisis

Percentage of new TB cases with MDR-TB



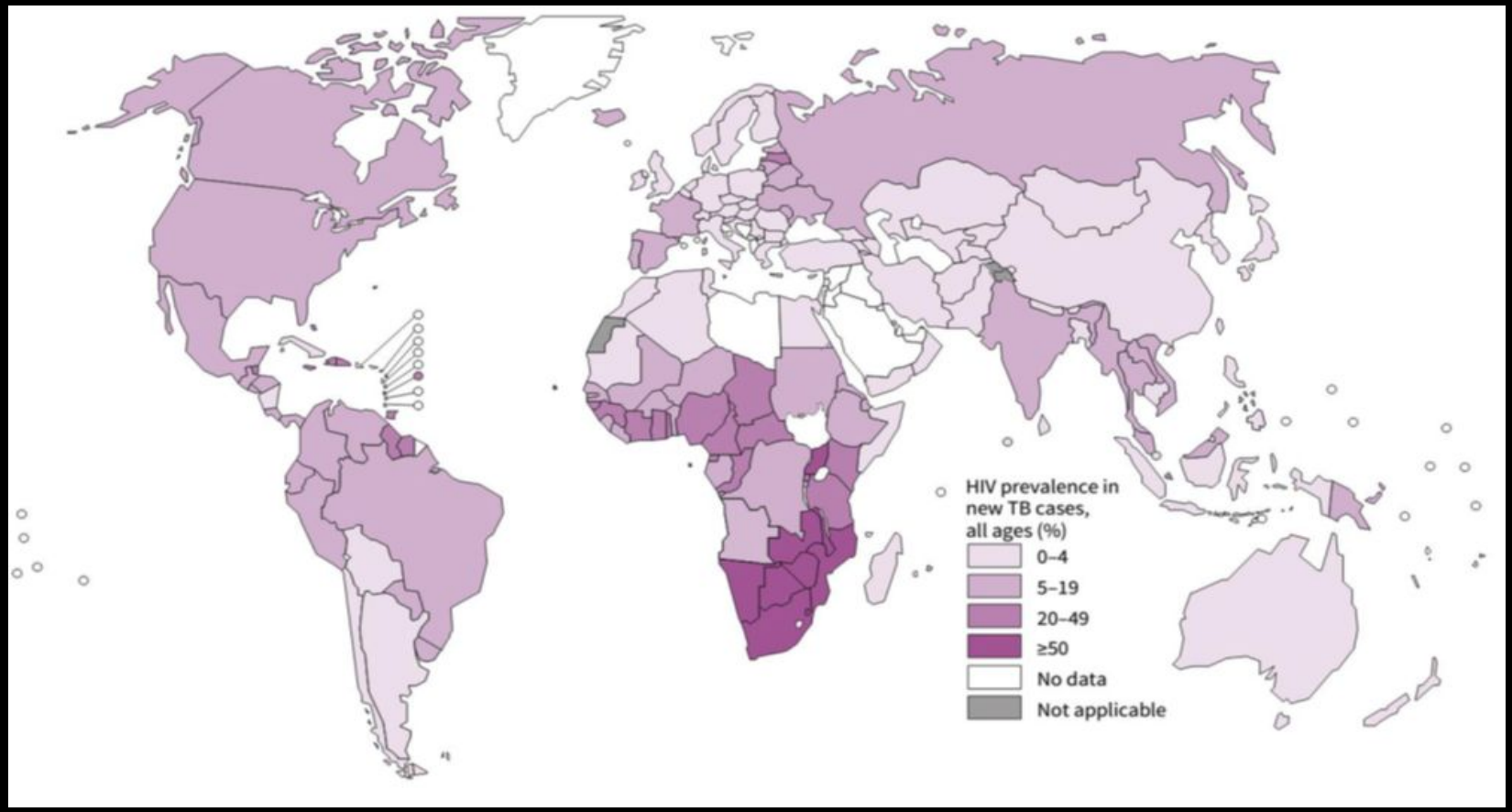
[a] Figures are based on the most recent year for which data have been reported, which varies among countries.

Five priority actions to address the global MDR-TB crisis



Accelerating response to TB/HIV means cutting transmission and mortality

Estimated HIV prevalence in new TB cases, 2013



67th World Health Assembly, Geneva, May 2014

THE END TB STRATEGY

SIXTY-SEVENTH WORLD HEALTH ASSEMBLY WHA67.1

Agenda item 12.1 21 May 2014

Global strategy and targets for tuberculosis prevention, care and control after 2015

The Sixty-seventh World Health Assembly,

Having considered the report on the draft global strategy and targets for tuberculosis prevention, care and control after 2015;[1]

Acknowledging the progress made towards the achievement of Millennium Development Goal 6 (Combat HIV/AIDS, malaria and other diseases) for 2015 following the United Nations Millennium Declaration and related 2015 tuberculosis targets, through the adoption of the DOTS strategy, the Stop TB Strategy and the Global Plan to Stop TB 2006–2015, as well as the financing of national plans based on those frameworks, as called for, inter alia, in resolution WHA60.19 on tuberculosis control;

The End TB Strategy – Components

1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION

A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and

high-risk groups

B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support

C. Collaborative tuberculosis/HIV activities, and management of co-morbidities

D. Preventive treatment of persons at high risk, and vaccination against tuberculosis

2. BOLD POLICIES AND SUPPORTIVE SYSTEMS

A. Political commitment with adequate resources for tuberculosis care and prevention

B. Engagement of communities, civil society organizations, and public and private care providers

C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational

use of medicines, and infection control

D. Social protection, poverty alleviation and actions on other determinants of tuberculosis

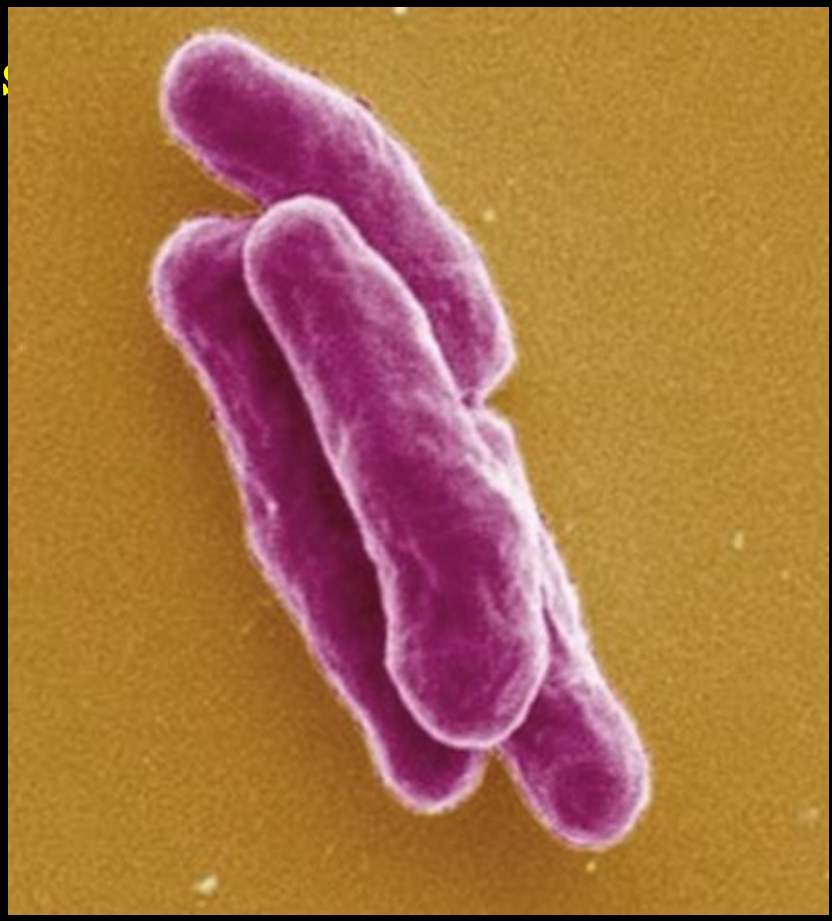
3. INTENSIFIED RESEARCH AND INNOVATION

A. Discovery, development and rapid uptake of new tools, interventions and strategies

B. Research to optimize implementation and impact, and promote innovations

Mycobacteria types

1. **M. causing tuberculosis**
   - **M. tuberculosis (human)**
   - **M. bovis.**
   - **M. Africans.**
2. **Non-patogenous M.**
   - **M.avium-intracellulare.**
   - **M.smegmaticus.**
   - **M. xenopi**
   - **M. scrofulaceum.**
3. **M. causing leprosy**
   - **M. leprae**



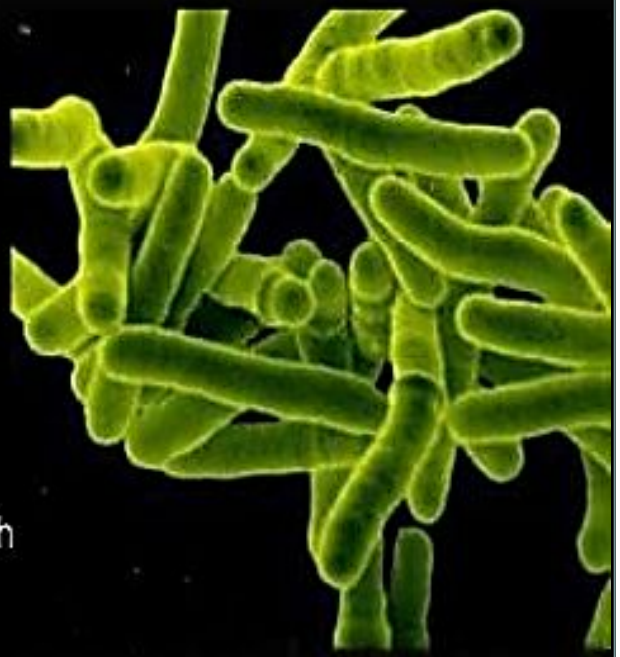
Important Mycobacterium

***Mycobacterium tuberculosis*, along with *M. bovis*, *M. africanum*, and *M. microti* all cause the disease known as tuberculosis (TB) and are members of the tuberculosis species complex. Each member of the TB complex is pathogenic, but *M. tuberculosis* is pathogenic for humans while *M. bovis* is usually pathogenic for animals**

The Causative agent of tuberculosis is opened by R. Kokh on March, 24, 1892

MYCOBACTERIUM TUBERCULOSIS- CHARACTERISTICS

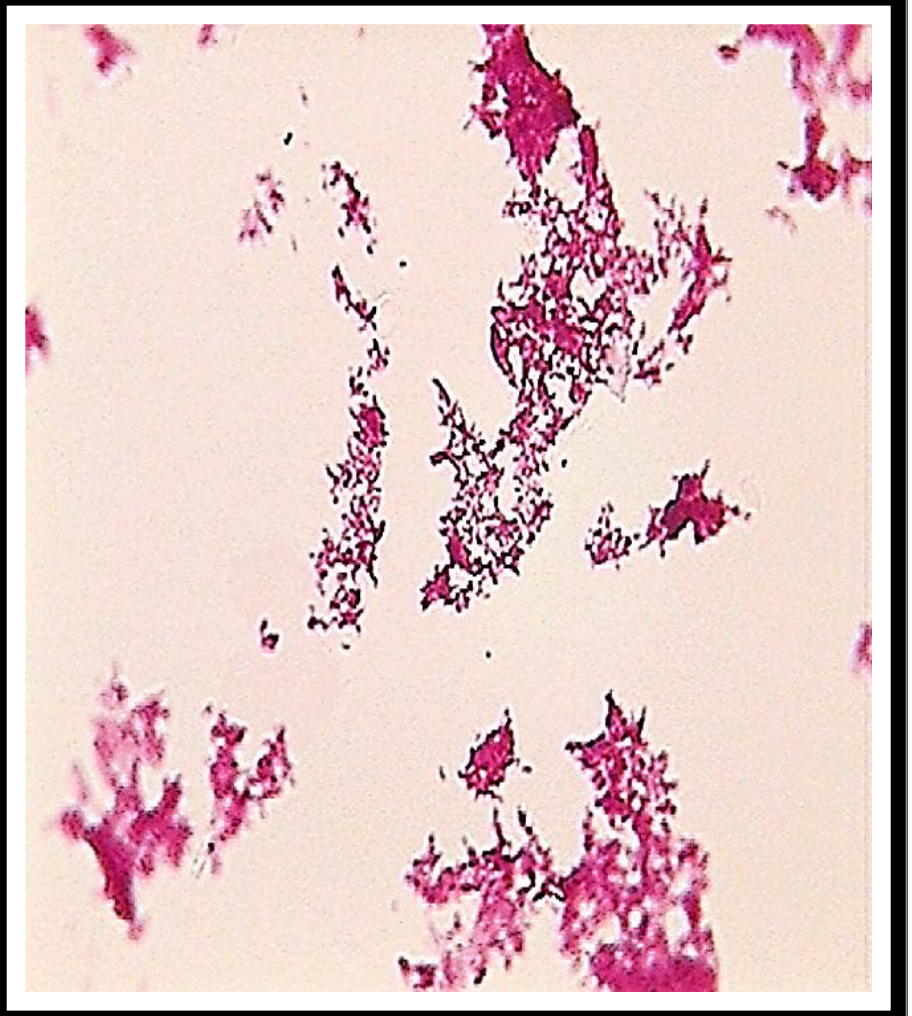
- Gram positive
- Obligate aerobe
- Non-spore-forming
- Non-motile rod
- Mesophile
- 0.2 to 0.6 x 2-4um[1]
- Slow generation time: 15-20 hours
  - May contribute to virulence[1]
- Lipid rich cell wall contains mycolic acid—50% of cell wall dry weigh
  - Responsible for many of this bacterium's characteristic properties
  - Acid fast—retains acidic stains
  - Confers resistance to detergents, antibacterial



Scanning Electron Micrograph of Mycobacterium tuberculosis

Morphology of Mycobacterium tuberculosis

- Straight, slightly curved Rod shaped 3 x 0.3microns
- May be single, in pairs or in small clumps
- On conditions in growth appears as filamentous, club shaped, or in Branched forms.

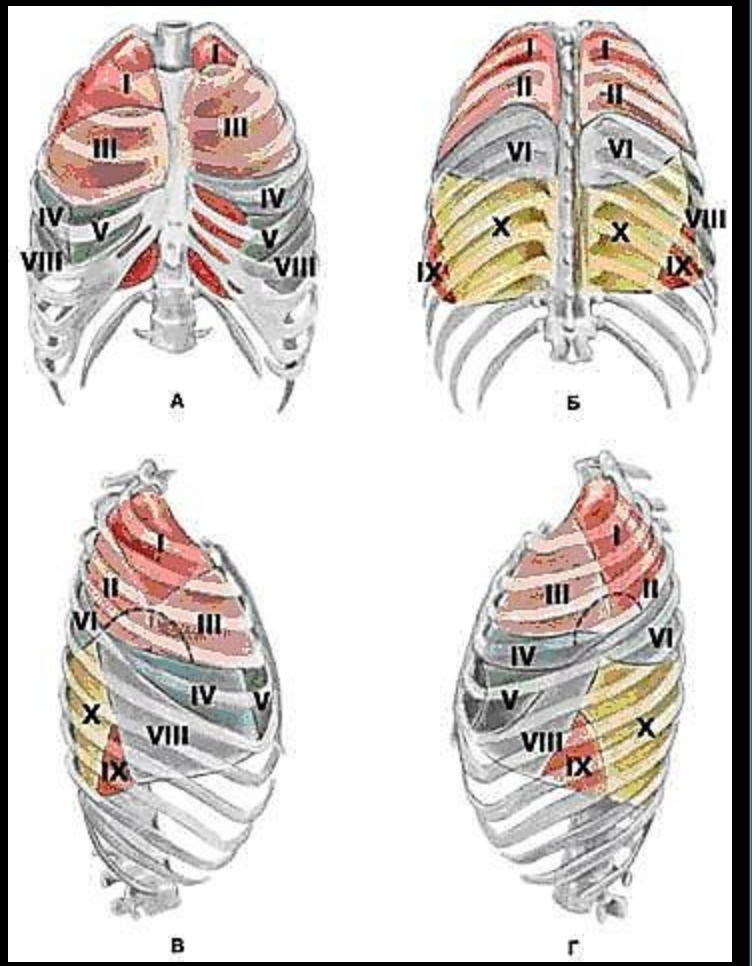


Atypical Mycobacterium

- **Photochromogens**
- **Scotochromogens**
- **Non Photochromogens**
- **Rapid growers**

The lungs are the basic organs affected by tuberculosis. The lungs are comprised of lobes. The right lung has 3 lobes, (superior, medial, inferior), left – 2 lobes (superior and inferior).

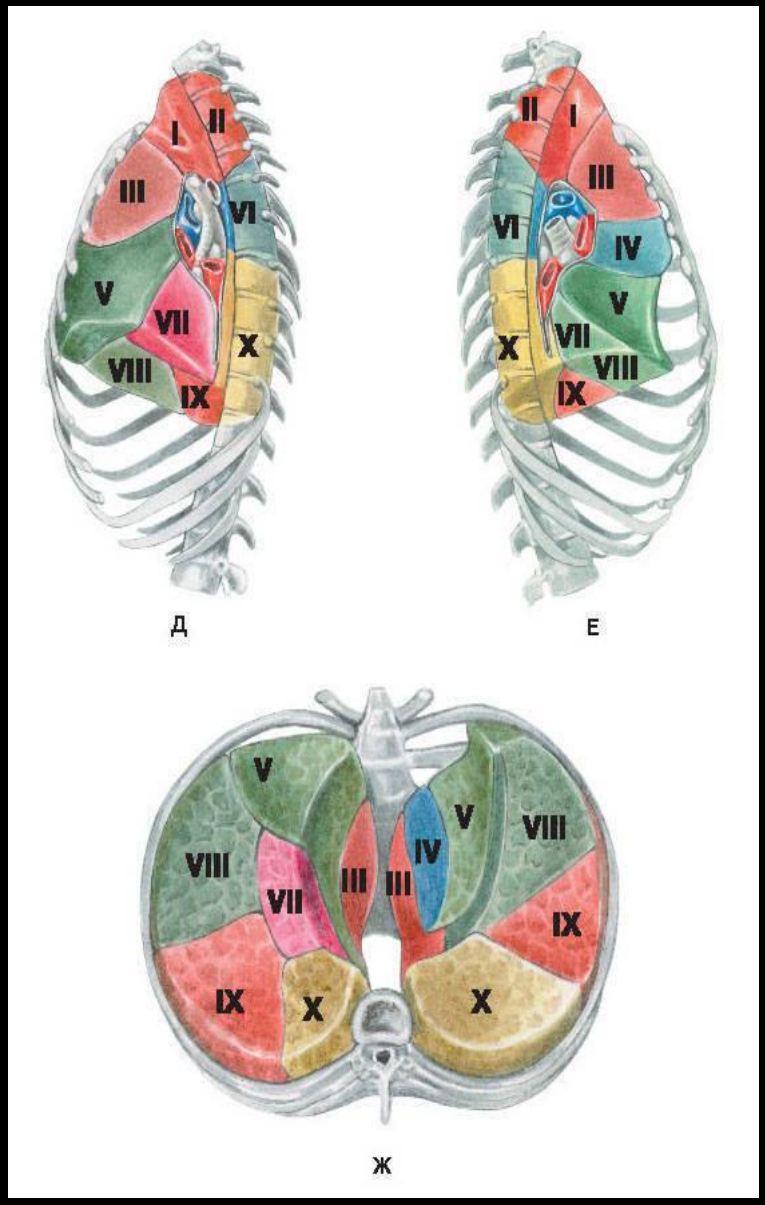
The lobes are divide into segments. In the right lung there are 10 segments and in left lung there are 9. The segments are comprised from lobules. In both lungs, there are about 1000 lobules. In general the size of lobule is 1-1.5 cm. The collection of the lobules comprise sub-segment. The collection of the lobules comprise sub-segment. Several sub-segments form a segment.



Each lung segment contains a bronchus and artery that are almost arranged in a parallel order.

The bronchi-lung segments have a triangular shape with the apex facing medially and the base facing peripherally.

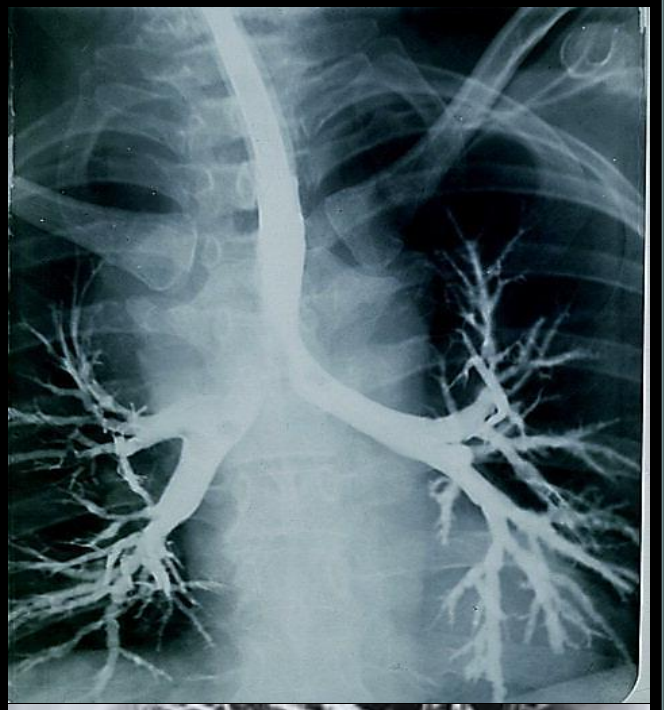
Each lung segment is separated from one another by a layer of connecting tissue.

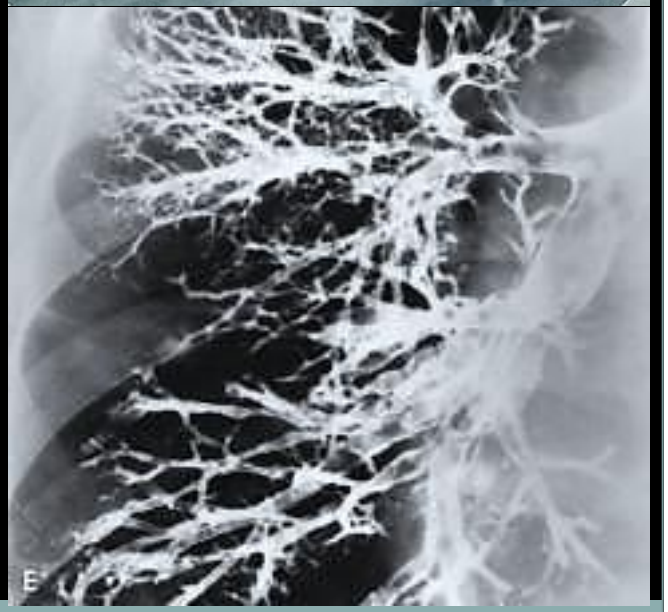


Bronchial Airways

The two bronchi proceed from the bifurcation of the trachea opposite to the 4-th thoracic vertebra to their corresponding lungs.

Upon entering the lungs, the bronchi divide into branches in which each of these branches divide and subdivide dichotomously to their ultimate termination (smallest bronchi).



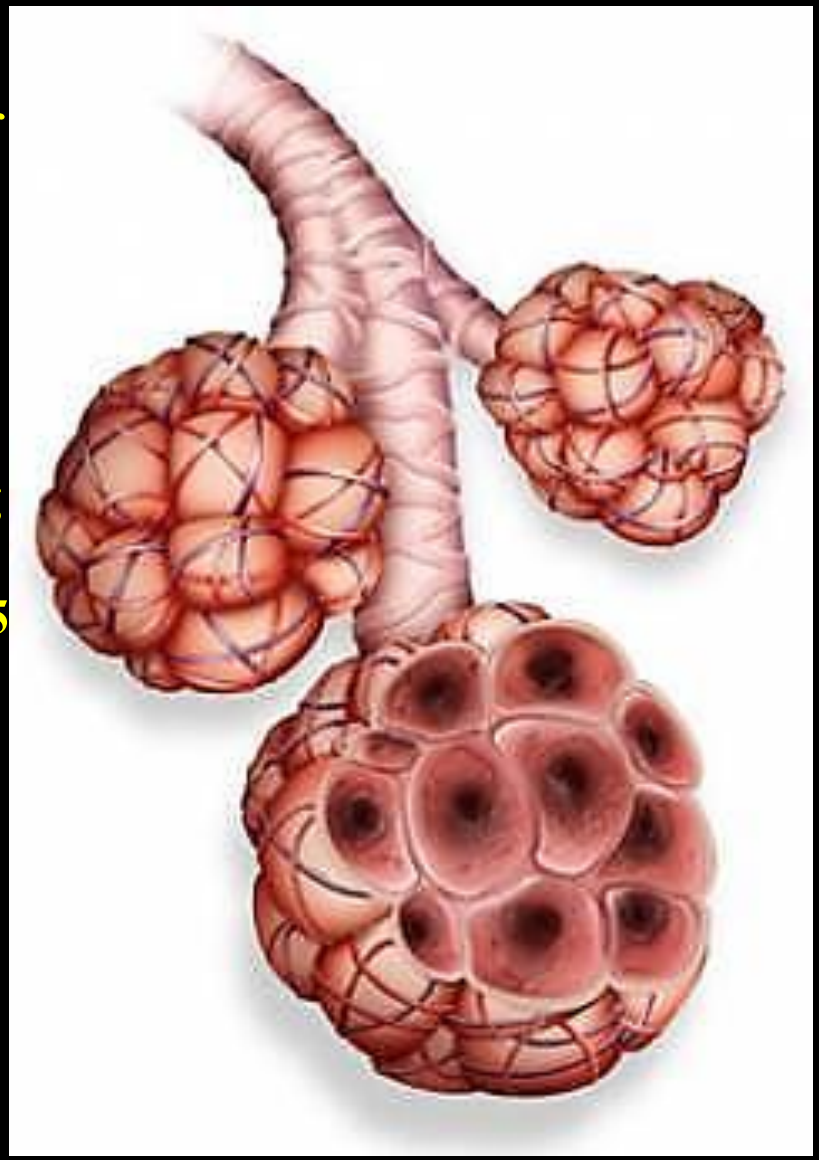


The structure of the lung parenchyma

The finniest, independent functional unit of the lung parenchyma is an acinus.

It is a miniature lung about 1,5 mm in diameter. The acinus is ventilated by the smallest bronchioles (bronchiolus or bronchulus terminalis) – finniest branching of the bronchial tree. The group of acinus forms lobulus, whose diameter reaches 1-1,5 cm.

The mucous membrane lining the bronchi has a ciliated columnar epithelium as far as their termination. However, in the alveolar passages and air-cells the mucous membrane becomes thin and transparent coated with a squamous epithelium.

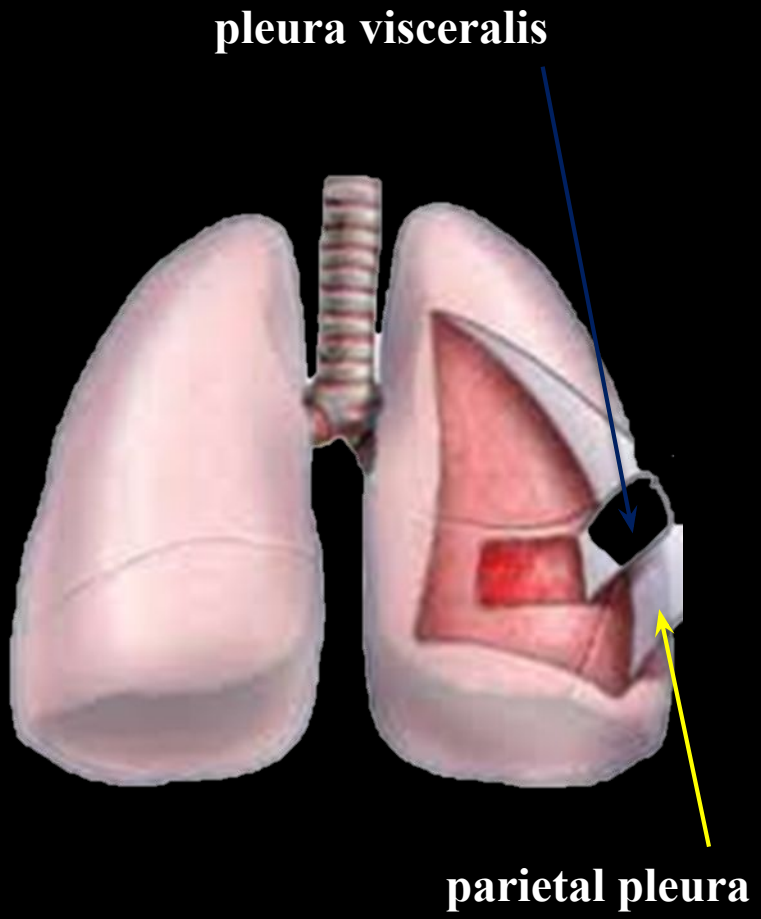


Pleura

Each lung is enclosed and its structure supported by a serous membrane, the pleura, which invests it as far as the root, and is then reflected on the parietals of the chest.

That portion of the membrane which is in relation with the lung is called (pleura visceralis s. pleura pulmonalis), and that in contact with the parietes, pleura costalis, pleura diaphragmatica and (pleura mediastinalis).

The pulmonary pleura is very thin, elastic, and inseparably connected with the structure of the lung; the costal pleura is thick and strong, has very little elasticity, and can be readily stripped off the ribs and intercostal muscles which it covers.

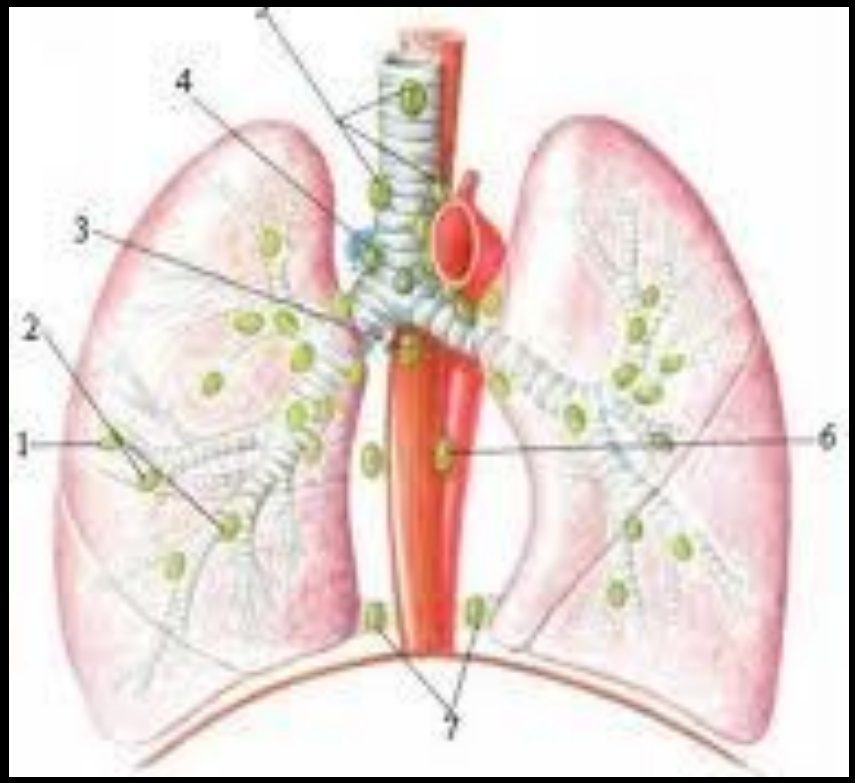


The lymphatic lung system

The lung surface is formed of a thin sub-pleural network of lymphatic vessels that communicate with the pleural cavity by a system of pores.

The lung parenchyma consists of 2 types of lymphatic structures.

The 1st type forms an elaborate network located beneath the bronchi's mucous membrane.



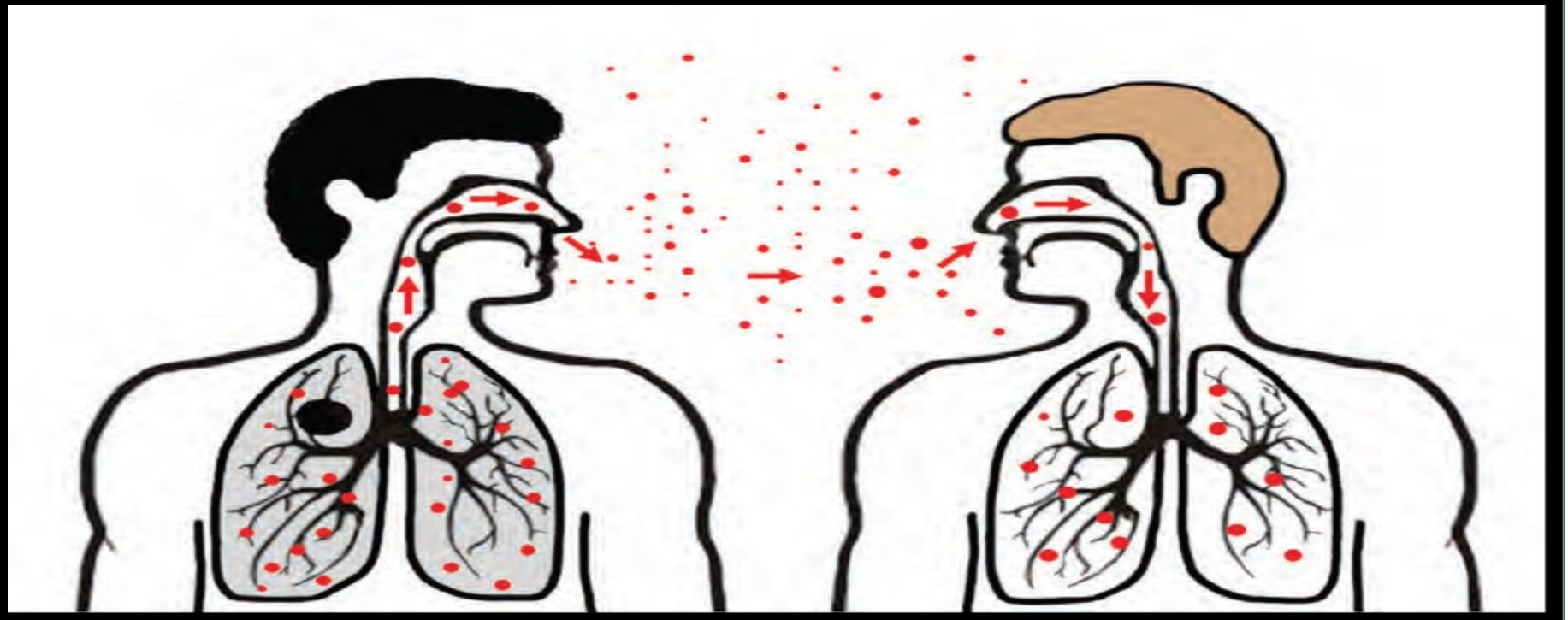
The 2nd type originates in the capillaries between alveolar ducts and alveolar sacs.

Lymphatic vessels of both types terminate in the broncho-pulmonary nodes in the hilus of the lung. These numerous and large nodes are located around the bronchi and within the tracheal bifurcation.

Transmission of tuberculosis

TB is spread from person to person through the air. The dots in the air represent droplet.

The dots in the air represent droplet nuclei containing tubercle bacilli.



The ways of the transmission:

- **Inhalation (about 90%)**
  - **Dusty**
  - **Droplet**
- **Alimentary**
- **Contact**
- **Vertical**

Factors that determine the probability of transmission of *M. Tuberculosis*

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**

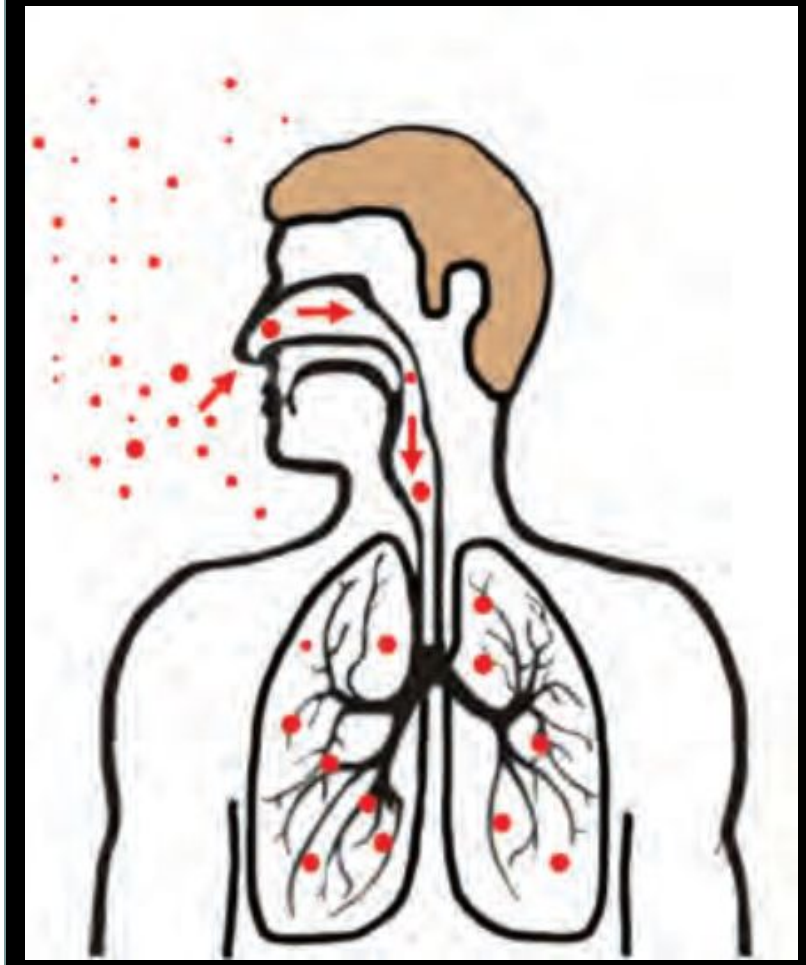
Characteristics of a patient with TB disease that are associated with Infectiousness

Factor	Description
Clinical	Presence of cough, especially lasting 3 weeks or longer 1. Respiratory tract disease, especially with involvement of the larynx (highly infectious) 2. Failure to cover the mouth and nose when coughing 3. Inappropriate or inadequate treatment (drugs, duration)
Procedure	1. Undergoing cough-inducing or aerosol-generating procedures (e.g., bronchoscopy, sputum induction, administration of aerosolized medications)
Radiographic and laboratory	1. Cavitation on chest radiograph 2. Positive culture for *M. tuberculosis* 3. Positive AFB sputum smear result

Proximity and length of exposure factors that can affect transmission of *M. Tuberculosis*

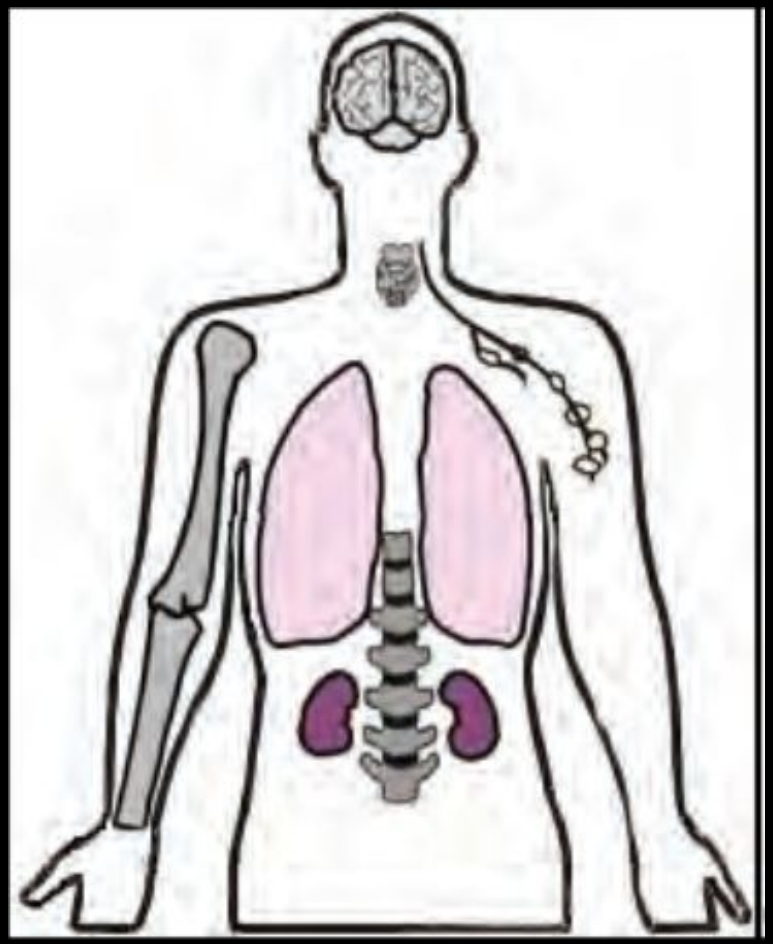
Factor	Description
Duration of exposure to a person with infectious TB	The longer the duration of exposure, the higher the risk for transmission
Frequency of exposure to infectious person	The more frequent the exposure, the higher the risk for transmission
Physical proximity to infectious person	The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

Pathogenesis of TB

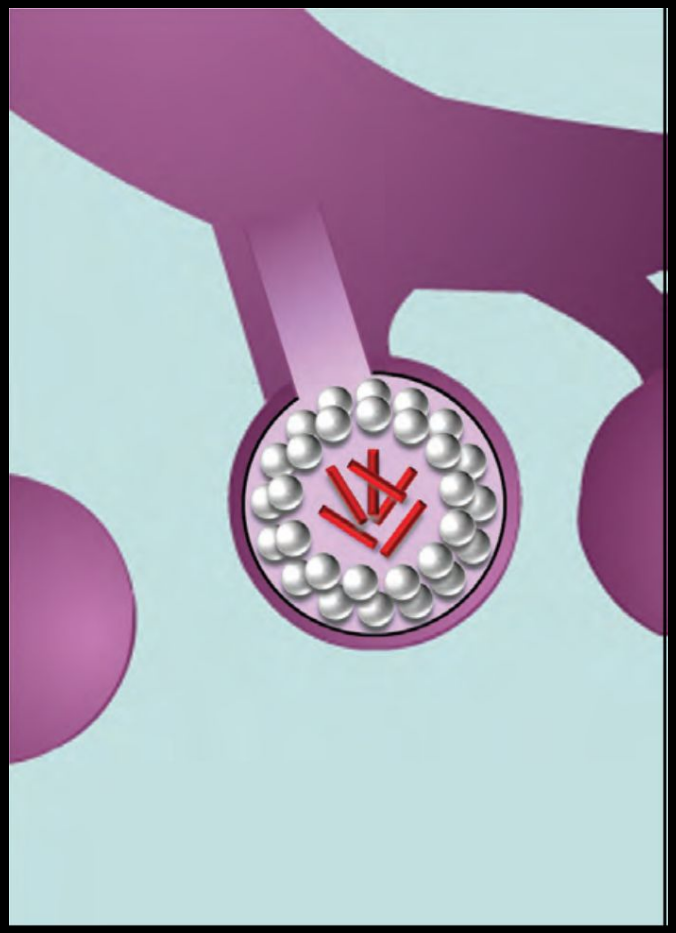


Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.

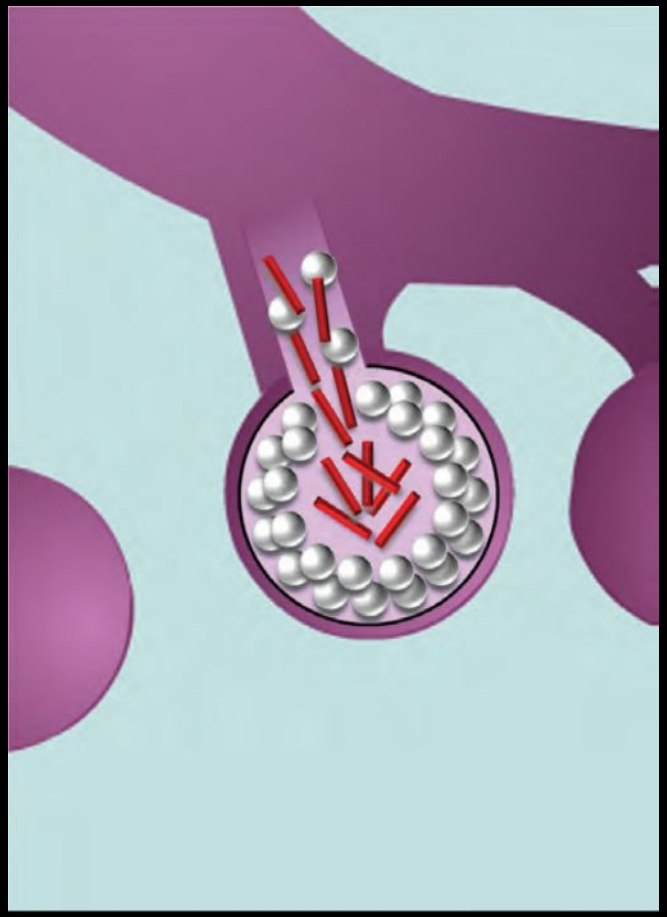
Tubercle bacilli multiply in the alveoli.



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).



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



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 Tuberculosis Infection (LTBI)

Persons with LTBI have M. tuberculosis in their bodies, but do not have TB disease and cannot spread the infection to other people. A person with LTBI is not regarded as having a case of TB. The process of LTBI begins when extracellular bacilli are ingested by macrophages and presented to other white blood cells. This triggers the immune response in which white blood cells kill or encapsulate most of the bacilli, leading to the formation of a granuloma. At this point, LTBI has been established. LTBI may be detected by using the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) . It can take 2 to 8 weeks after the initial TB infection for the body's immune system to be able to react to tuberculin and for the infection to be detected by the TST or IGRA. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression.

Persons with LTBI have M. tuberculosis in their bodies, but do not have TB disease and cannot spread the infection to other people.

TB Disease

In some people, the tubercle bacilli overcome the immune system and multiply, resulting in progression from LTBI to TB disease . Persons who have TB disease are usually infectious and may spread the bacteria to other people. The progression from LTBI to TB disease may occur at any time, from soon to many years later. Body fluid or tissue from the disease site should be collected for AFB smear and culture, Positive culture for M. tuberculosis confirms the diagnosis of TB disease.

Persons who have TB disease may spread the bacteria to other people.

Risk of developing TB disease over a lifetime

Without treatment, approximately 5% of persons who have been infected with *M. tuberculosis* will develop disease in the first year or 2 after infection, and another 5% will develop disease sometime later in life. Thus, without treatment, approximately 10% of persons with normal immune systems who are infected with *M. tuberculosis* will develop TB disease at some point in their lives.

Risk of LTBI Progressing to TB Disease

Anyone who has LTBI can develop TB disease, but some people are at higher risk than others. HIV infection is the greatest risk factor for the development of TB disease in persons with LTBI, due to a weakened immune system. The risk of developing TB disease is 7% to 10% each year for persons who are infected with both *M. tuberculosis* and HIV and who are not receiving highly active treatment for HIV; it is 10% over a lifetime for persons infected only with *M. tuberculosis*. Children younger than 5 years of age are also at increased risk for progression of LTBI to TB disease.

Persons at Increased Risk for Progression of LTBI to TB Disease

Risk Factor	Risk of Developing TB	Description
TB infection and no risk factors	About 10% over a lifetime	For people with TB infection, no risk factors, and no treatment, the risk is about 5% in the first 2 years after infection and about 10% over a lifetime.
TB infection and diabetes	About 30% over a lifetime	For people with TB infection and diabetes, and with no treatment, the risk is three times as high, or about 30% over a lifetime.
TB infection and HIV infection	About 7% to 10% PER YEAR	For people with TB infection and untreated HIV infection and with no LTBI treatment, the risk is about 7% to 10% PER YEAR, a very high risk over a lifetime.

The tubercular inflammation

The tubercular inflammation, like any other inflammation is a manifestation of alteration, exudation, proliferation, leading to the formation of tubercular granuloma (Tuberculum, tubercular tumor).

The term granuloma is derived from the diminutive of the Latin term for a grain, granulum, which was first used by Rudolf Virchov [1818] to describe tumors that may ulcerate and give rise to granulation tissue.

The tubercular granuloma is not a mere collection of inflammatory cells but is an active site of action of numerous enzymes and cytokines in the very complex process of removing the causative agent MBT.

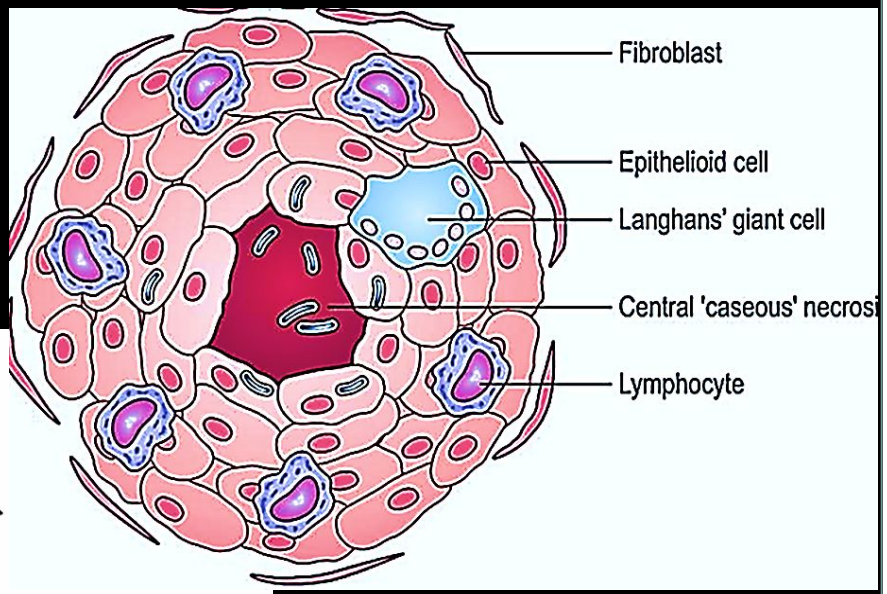
Participate in the formation of tubercular granuloma

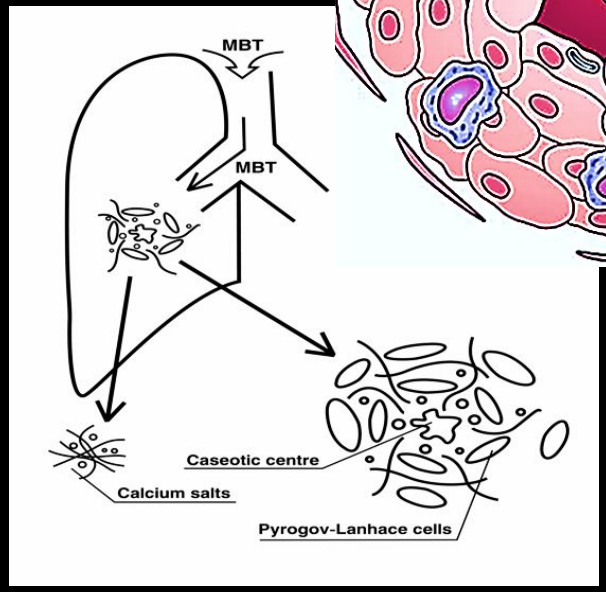
- **hematogenic elements (lymphocytes, monocytes, polymorphonuclear leucocytes),**

- **histiogenic elements (histocytes, macrophages, fibroblasts, reticular cells, endothelium of blood vessels, plasmatic and mast cells),.**

The tubercular granuloma has the following structure:

- The center consists of amorphous tissue detritus (due to alteration and necrosis), the peripheral region contains several layers of epithelial cells.
- Lymphoid and plasma cells are present in the external layers of the tuberculum.
- Giant multinucleated Pirogov – Langhans cells can be seen among the epithelial cells.





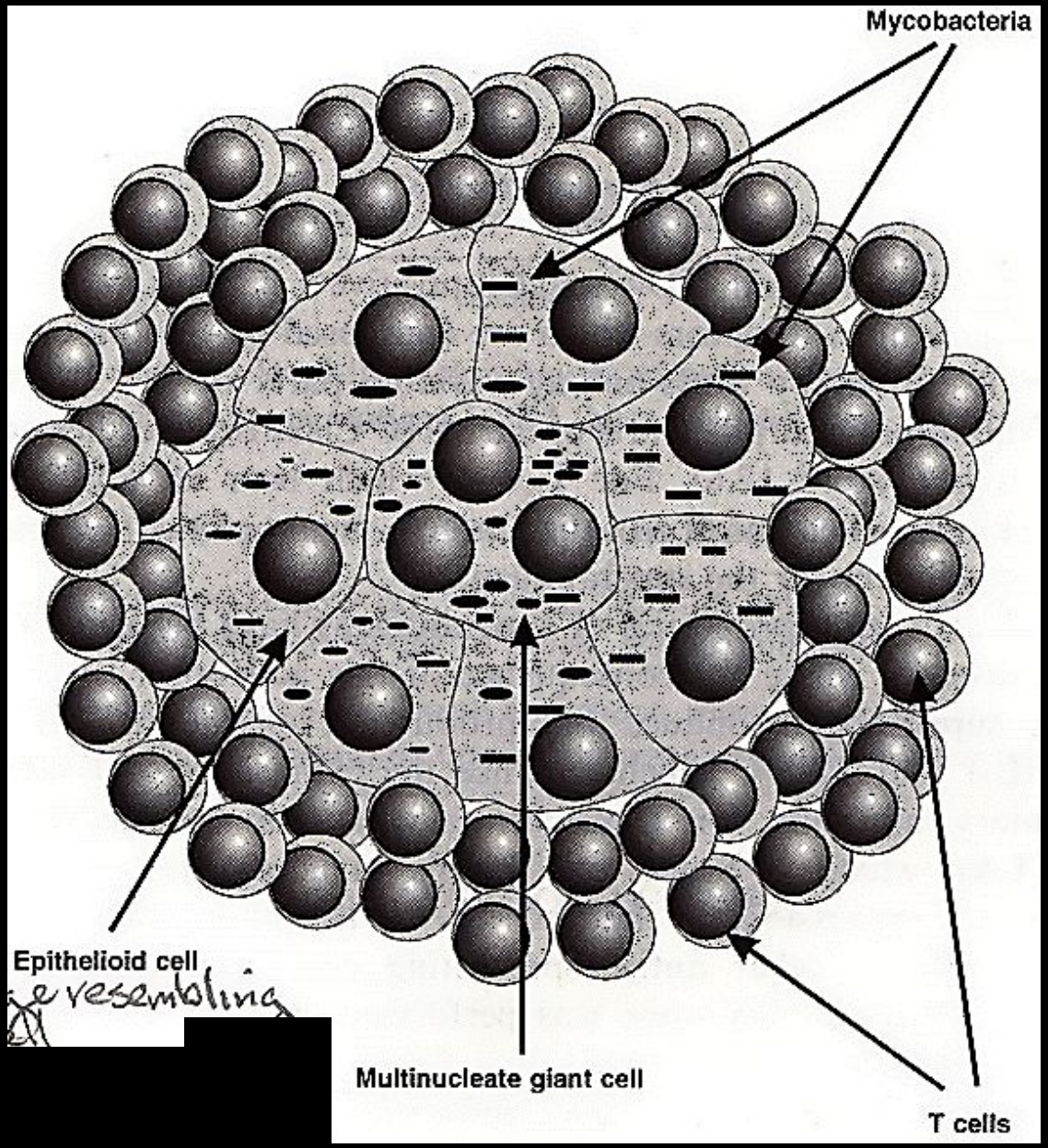
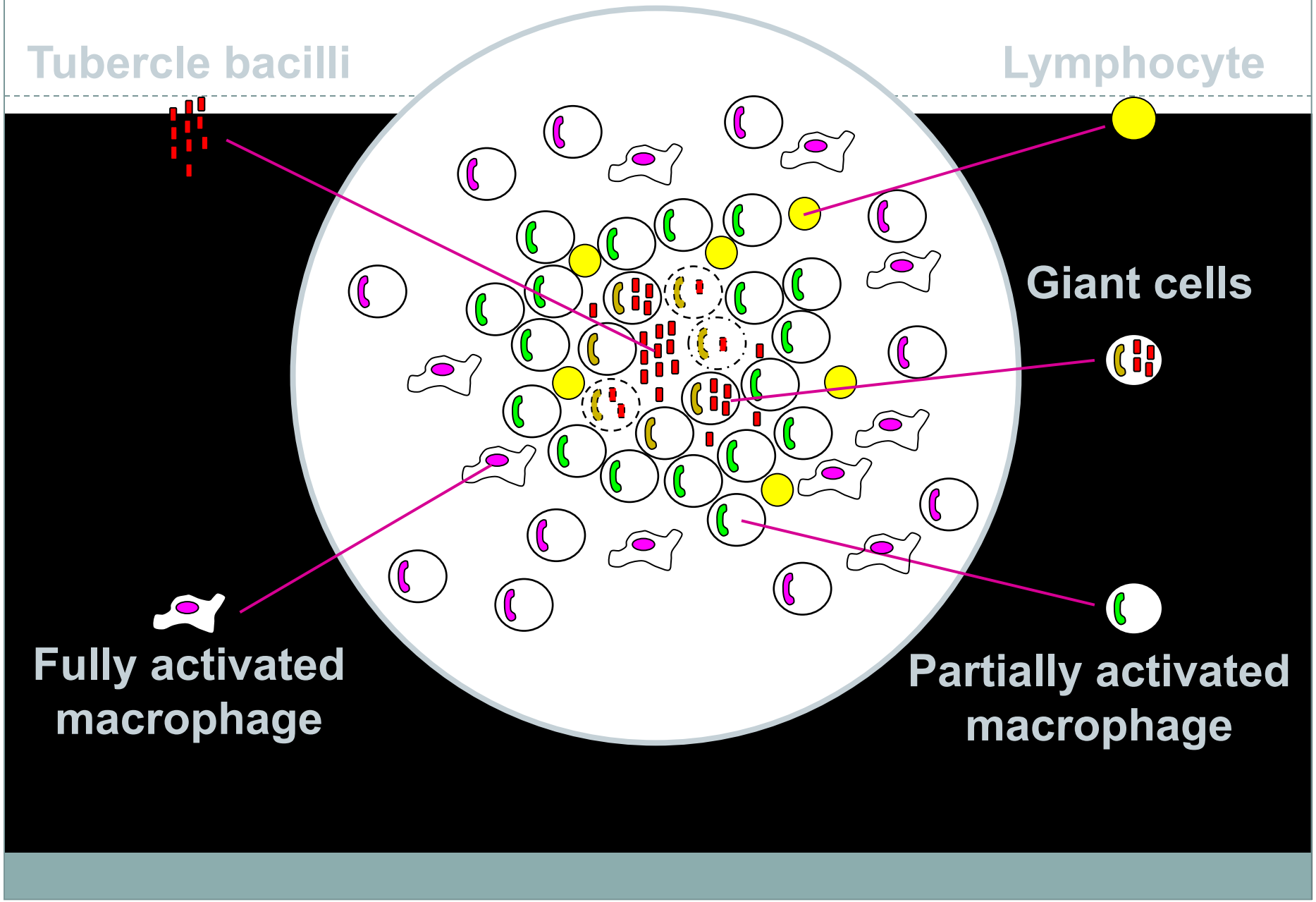


Diagram of a Granuloma

NOTE: ultimately a fibrin layer develops around granuloma (fibrosis), further "walling off" the lesion.

Typical progression in pulmonary TB involves caseation, calcification and cavity formation.


Tubercle bacilli
Lymphocyte
Giant cells
Fully activated macrophage
Partially activated macrophage

The tuberculum histogenesis depends on the development of the inflammation process, which is either progressive or regressive.

When there is a decreased host resistance to tuberculosis, progression of the tubercular inflammation takes place.

The tissue exudative reaction develops with the formation of cheesy necrosis which might develop within the tuberculum and surrounding tissues.

These tissues will generally be impregnated with serous-fibrinous exudates.

Various foci of different sizes of cheesy necrosis arise during the further progression of specific tubercular inflammation.

Foci of cheesy necrosis can spread and merge into bigger foci from which foci with sites of caseation (infiltrates) are formed.

Caseation is diluted under the action of proteolytic enzymes and is coughed out through the bronchi.
Cavities of disintegration appear in these sites of the lungs but ulcers appear on the mucous membrane and skin.

The cavity formed during the disintegration of caseation will be the source of dissemination of MBT in other parts of the lungs and formation of new foci and cavities.

The particular danger is represented by vascular blood erosion supplying sites of lungs where caseous degeneration occurred.

During cavity formation, blood from the damaged vessels penetrates the bronchi and from there, either penetrates other parts of lungs or is expectorated externally.

Reversible development of process (regression) occurs during high resistance of the organism the tuberculum will be substituted by fibrosis and calcification. (Chronic development of tuberculous inflammation).

The morphological and biochemical components of microbial cells cause various reactions in the host.

The basic biochemical components of MBT are:

– proteins;
– carbohydrates;
– lipids.

Proteins (tuberculoproteids) is the basic carrier of MBT antigenic properties.

Delayed-type hypersensitivity (DTH)

The substances, which are included in the MBT wall structure, induce tissue specific inflammation reaction and granuloma formation, with the development of the delayed-type hypersensitivity (DTH), which could be detected by a positive tuberculin test reaction, and a weak antibody formation.

In general, term DTH is used for characteristics of a type IV immune response (induration at the site of intradermal injection of tuberculin develops after 48 hours) among individuals who are infected with Mycobacterium tuberculosis.

DTH is to be concerned as an immune response from the damaged tissue factors.

The cycle of tuberculosis development from MBT contamination till the occurrence of its clinical manifestations and distribution of MBT in envi-ronment conditionally is classified into 5 stages.

Stages:

1. **Spreading of infection (contamination).**
2. **Beginning of infection, proliferation and dissemination in an infected host.**
3. **Formation of immune reaction in the host.**
4. **Formation of caseous necrosis, and proliferation of bacteria.**
5. **Secondary spreading of infection (ability to infect).**

Primary tuberculosis

Primary tuberculosis develops after the first contact of macroorganism with MBT.

MBT fill in the peripheral parts of the lungs when tiny particles containing MBT are inhaled through the superior respiratory tract.
The mycobacterium remains there and reproduces slowly forming the primary pulmonary affection (focus).

In this way, mycobacterium falling into the lymph through which they are transported to the lymph nodes.

The classical form of morphological manifestation of primary tuberculosis is the primary tuberculosis complex.

In the primary lung focus, alveolitis develops, which is quickly replaced by the typical development of caseosis necrosis. In the centre of primary focus, caseosis forms but in the periphe- ry-elements of non specific inflammation occur.

The primary lung affect localizes more often just under pleura, therefore frequently pleura is involved in the inflammation process.

The lymphatic vessels expand, their walls becoming infiltrated and tubercles appear.

In the regional lymphatic nodes, there are elements of inflammations converting into specific caseous changes with necrosis

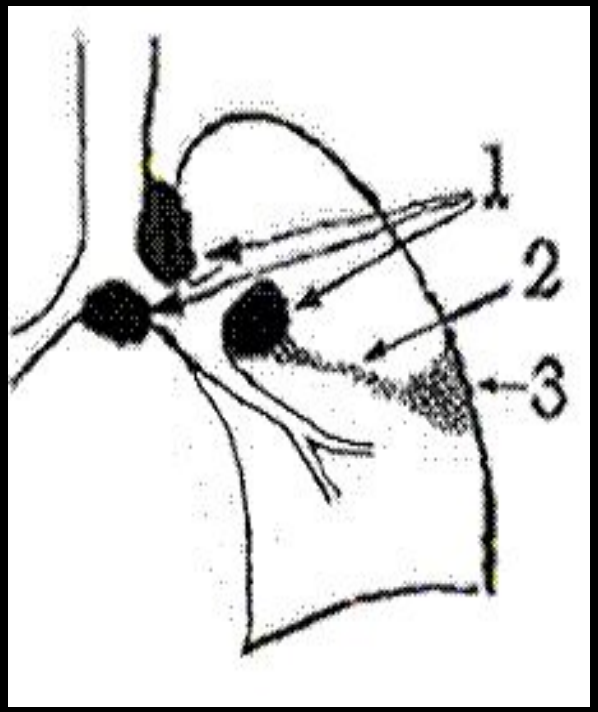
Perifocal inflammation around the lymph nodes will spread in the mediastinum and surround the lung tissues.

The inflammation process within the lymph nodes is most intense in the primary affection area.

Therefore, reparative changes in the lymph nodes will be slower.

The dynamic study of primary pulmonary processes among children has allowed to allot 4 phases of the primary tuberculosis course:

1) pneumonic;
2) phase of dissolving;
3) phase of condensation;
4) formation of Gohn's focus.



phase 1 (pneumonic)

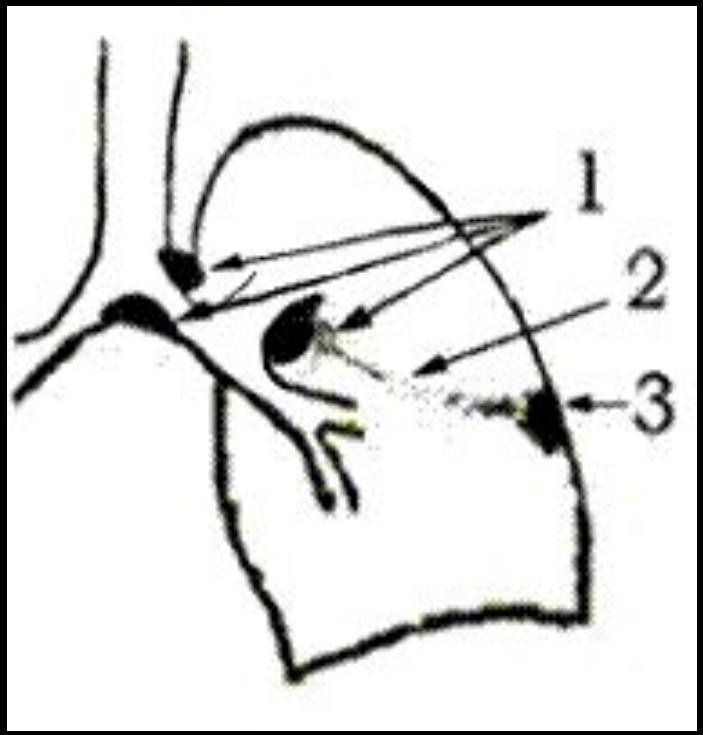
In the first phase (pneumatic) the focus of broncho-lobular pneumonia (3) is determined with a size of 1,5-2 till 5 cm.

The form of the lung focus (3) is round or irregular, with heterogenous character and dim contours.

Enlarged regional lymphatic nodes (1) are determined simultaneously (the picture of infiltrative bronchoadenitis) and there is an amplification of bronchial vessels picture – lymphangitis (2) between the focus and the lung root.

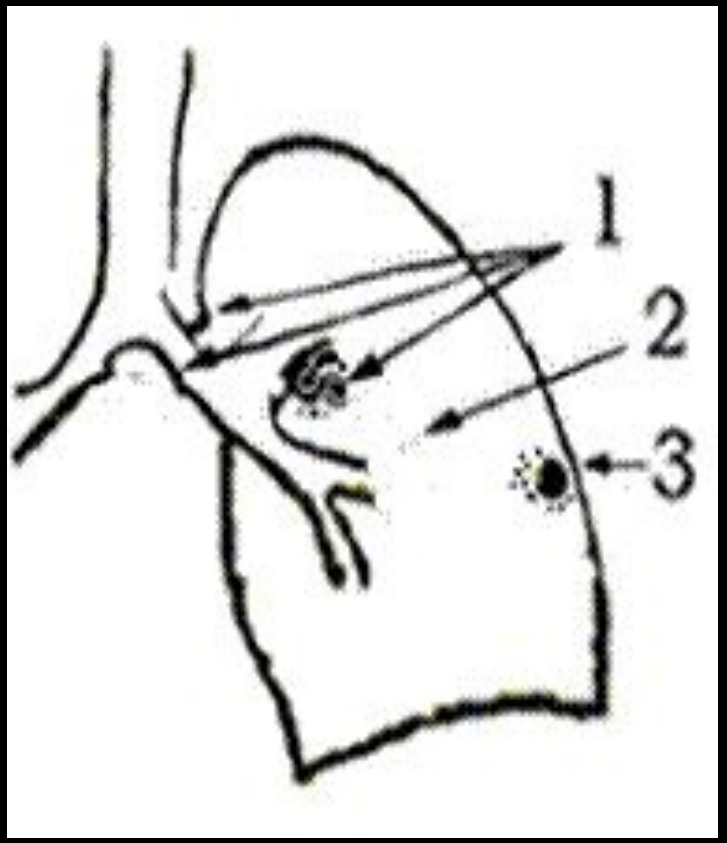
In the second phase of dissolving (bipolarity) the reduction of the perifocal zone of inflammation (3) is observed.

The centrally located caseous focus becomes more prominent.



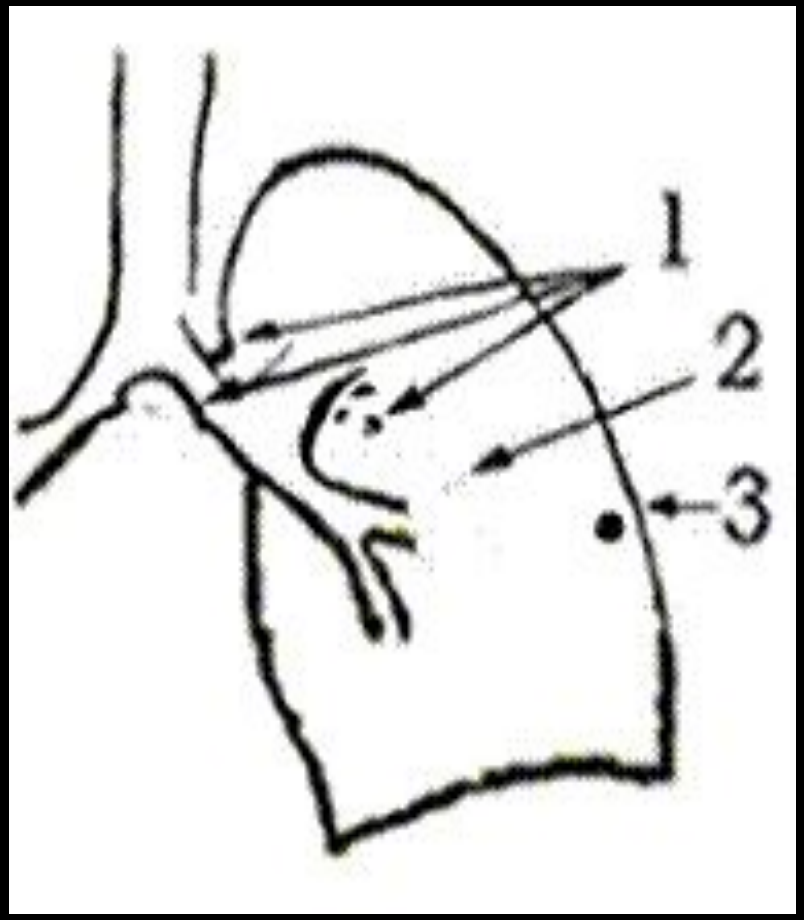
phase 2 of dissolving (bipolarity)

The signs of inflammation in regional lymphatic nodes (1) and in the zone of bronchopulmonary vessels are decreaseding (2).



the phase 3 – condensation

In the third phase, the phase of condensation: the primary focus is well outlined (3), its contours are cleared, on periphery of the focus there is the beginning of calcification as fine pieces; at peripheral regions of lung bronchial lymphatic nodes calcification is also present (1).



phase 4 formation of Gohn's focus

In the fourth phase, in the place of broncho-lobular pneumonia (3) calcification become compact, the focus is round with regular precise contours, its size does not exceed 3-5 mm. This formation is called Gohn's focus.

Outcomes of the primary tubercular complex may be in the following way:

1) healing with encapsulation, calcification or ossification;

2) progression and generalization of the inflammation process. It may be accompanied with additional complications such as atelectasis, pneumosclerosis, etc.

There are 2 types of generalization of the tubercular complex progression:

1) hematogenic;
2) lymphogenic
3) bronchogenic.

At progression of hematogenous disseminated tuberculosis the cavities are formed.

The formation of cavities is the result of cheesy disintegration and dissolution of necrotic masses.

The cavities are usually thin-walled, multiple and settled down symmetrically in both lungs.

In an origin of such cavities, important role plays damage of blood vessels, their thrombosis and obliteration.

The blood supply of these focuses is disturbed in lungs and destruction is formed resembling trophic ulcers.

During the formation of the cavities, the possibility of bronchogenic dissemination of healthy regions of lungs can appear.

Immunity at tuberculosis

Natural resistance to tuberculosis is inherited. It involves non-specific antimicrobial humoral factors (non-immunological phenomena). These factors inactivate MBT and prevent their multiplication as well as destroy their toxins.

These factors include:

- **lysozyme in alveolar macrophages;**
- **higher contents of lactic acid in cells;**
- **lipoprotein lipase, an enzyme which decomposes protein and lipid complexes of MBT cell wall, producing bacteriostatic non-etherized fat acids;**
- **cytokines (IL-1, α-interferon, components of compliment).**

Phagocytosis plays special role in natural resistance. Primary contact MBT and the host triggers phagocytosis of bacilli by macrophages.

Following facts are important about phagocytosis:

5% of MBT is destroyed by macrophages (completed phagocytosis). Damaging activity of macrophages depends on the susceptibility of the host and virulence of MBT.

Fagocitosis

Completed phagocytosis

It is one of mechanisms
natural resistance
to tuberculosis

Uncompleted phagocytosis

The result of him is education
geared-up makrofaga (only
the T-cell will co-operate with such
macrophages)

Results of phagocytosis

Immunity in tuberculosis consists from five basic reactions: cell reaction, humoral factor, allergy, immune memory and immune tolerance. Chief role belongs to T-lymphocyte cell-mediated immune reactions.

Populations of T-helpers (CD4+), T-killers and T-suppressors (CD8+) are studied best among all T-lymphocytes. Helpers are inducted at first contact with antigen and condition the immunity, suppressors balance the process and killers play active role in phagocytosis.

Cell-mediated immunity. Cell-mediated immunity is based on interaction of macrophages and T-lymphocytes.

Only under these conditions T-helper (CD4+) may recognize antigen peptide of MBT.
- At the same time macrophage produce interleukyn-1 (IL-1) which makes T-helper to produce interleucin-2 (IL-2) and gamma- interferon. These mediators influence:
a) macrophages, activating their migration to MBT and increasing their enzyme and bactericidal activity leading to the death of intracellular MBT (compete phagocytosis).
b) T-killers (CD8+) which destroy infected macrophages (macrophages with phagocytized MBT).
c) B- lymphocytes (humoral immunity) produce specific antibodies.

T- suppressors depress activity of IL-1 and IL-2.

Classical example of cell-mediated immunity is increased slow type sensitivity, found with 2 IU tuberculin skin test and provided by T- lymphocytes and macrophages. T-killers may exert cytotoxic effect that is they may ruin macrophages leading to hyperergic reaction at tuberculin skin test.

Proof of the role of T- lymphocytes in anti-tubercular immunity:

- injection of T- lymphocytes suspension from immunized animals to non- immunized increased resistance of the latter against tuberculosis infection;

- injection of anti- lymphocyte suspension leads to quick and malignant course of tuberculosis in animals. This also leads to emptying of thymus -dependent areas of spleen and lymph nodes. Injection of corticosteroids has the same effect;

- resection of thymus in newborn animals decreases their resistance to tuberculosis, and infection takes malignant course.

As immune response builds up multiplication of Mycobacteria slows down, their general number decreases, as specific inflammation. But compete elimination of pathogen is not achieved even with adequate interaction of macrophages and T-lymphocytes. Certain population of MBT remains in the host as biologically changed cells (such as L-forms). They locate in tubercular granulomas surrounded by dense fibrotic capsule.

Remaining MBT are located within cells and prevent formation of phagolysosome, thus becoming inaccessible to enzymes of lysosomes. Due to preservation of Mycobacteria anti-tubercular immunity is called non-sterile. MBT remaining in the host support population of sensitized T-lymphocytes and secure effectiveness of immune defense. Patient infected with Mycobacteria retains them for a long time, sometimes for life. With failure of immune balance retained Mycobacterial population may activate and cause tuberculosis.

Thank you for your attention!