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RECENT DRUGS FOR THE TREATMENT OF TUBERCULOSIS

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Abstract:

Tuberculosis (TB) is caused by a bacterium called Mycobacterium tuberculosis_usually attack the lungs, but it can attack any part of the body such as kidneys, spine, and brain. In 2010 it was estimated the total cases of TB were 8.8 million cases, while in 2011 it was estimated 8.7 million cases. 6.1 million Cases were reported in 2012. In 2013, drastic increase in cases which raised to 54.2% in world population. In 2014, a slight decrease in spread of disease count to 42%. Combined ratios of 10 million cases were recorded in 2015&2016. The same number of cases was repeated in 2019. Even during pandemic condition also they recorded 10 million cases in 2020.In 2022, the slight decrease is taking place to 28 thousand people got affected through TB. Due to Tb bacteria it is still responsible for more deaths in Worldwide each year than any other infectious disease. Tuberculosis is a major disease for the human population after HIV/AIDS. To overcome this TB disease it requires spreading awareness and understanding of tuberculosis worldwide. When someone's immune system is weakened, chances of developing Tb are increased on average 10% of the infected individuals develop the disease during their lifetime. In latest survey 3% of new cases and 12 to17% of patients had MDR [Multiple Drug Resistant]-TB and they got treated. The major goals of treatment for TB disease are to Cure the individual patient; Minimize risk of death and disability; and reduce transmission of M. tuberculosis to other persons.

Key Words: *Mycobacterium tuberculosis, Immune system, Multidrug-resistant, Population, Disability, Transmission.*

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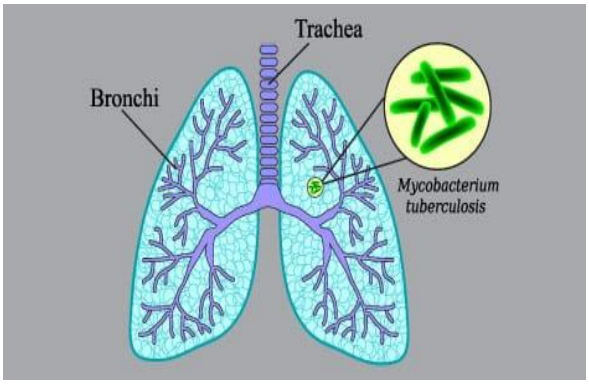
INTRODUCTION:

Tuberculosis (TB) is a bacterial infection spread through inhaling tiny droplets of saliva from the cough or sneeze of an infected person.[1]This is due to array of events that begins with the virulence of Mycobacterium Tuberculosis, the highly contagious and persistent bacterium responsible for TB infection.[2] TB most commonly attacks the lungs (Pulmonary TB)but can also affect the CNS, The Lymphatic system, The Circulatory system, The Genitourinary system, Bones, joints, and even The Skin. TB is spread from one person to the next through the air when people who have active Tb in their Lungs, Cough, and split, speak or Sneeze. Most infections show No symptoms, in which case it is known as Latent Tuberculosis. When someone's immune system is weakened, chances of developing Tb are increased on average 10% of the infected individuals develop the disease during their lifetime.[3] Tuberculosis is a chronic Granulomatous disease and a major health problem in developing countries. TB kills more adults in India than any other Infectious disease. In 2012, the Government of India has declared Tb to be a Noticeable disease. Latest survey in India 3% of new cases and 12 to17% of previously treated patients has MDR (Multiple Drug Resistant)-TB. [4] Reasonable progress has been made over the 70 years. TB is still a Life threatening problem in this country, and it impacts people across states. TB knows No Borders, and people in the states are suffering from the TB. Anyone can get TB. [5] TB germs spread through the air. The Tb germs are put into the air when a person with Tb disease (on the left) of the lungs or throat coughs, speaks, are sings. People nearby may breathe in these germs (Illustrated by the Person on the right) and become infected. The person on the left has TB disease and is put in Tb germs into the air. The person on the right is breathing in the Tb germs into their lungs. [6,7]



THE BEST WAY TO STOP TB SPREAD IS TO:

- Identify people who have TB
- Isolate those who are Contagious
- Provide treatment as soon as possible to anyone who is contagious.
- People with Tb disease are most likely to spread it to people they spend time with every day, including Family members, friends, Coworkers, or Schoolmates.[8]

TB IS NOT SPREAD BY:

- Sharing tooth brushes
- Shaking someone's Hand
- Touching bed linens or toilets
- Sharing food, Drink, or Utensils.

When a person breathes in Tb bacteria, the bacteria can settle in the lungs and begin to grow. From there, they can move through the blood to other parts of the body, such as kidney, Spine, and Brain. This means that the bacteria can spread to other people. TB in other parts of the body such as the kidney, spine, is usually not infectious. [8]

TYPES:

There are three types of TB disease:

1. Active tuberculosis
2. Miliary tuberculosis
3. Latent tuberculosis

ACTIVE TUBERCULOSIS:

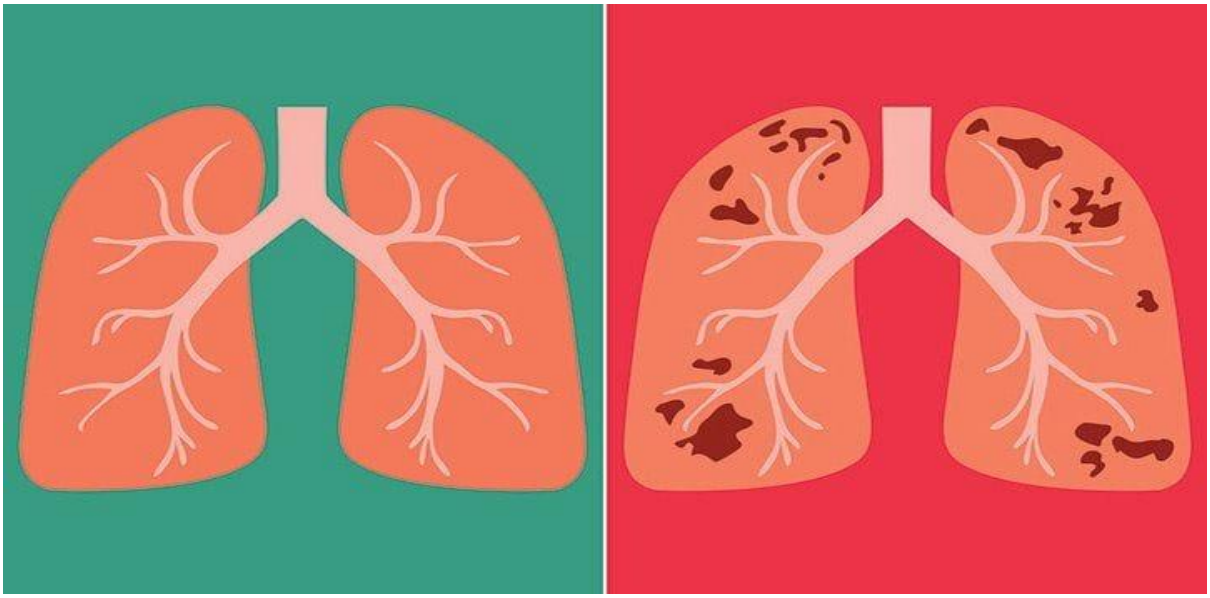
Active tuberculosis is an illness in which the TB bacteria are rapidly multiplying and invading different organs of the body. The typical symptoms of active TB variably include cough, phlegm, chest pain, weakness, weight loss, fever, chills, and sweating at night. A person with active pulmonary TB disease may spread TB to others by air bone transmission of infectious particles coughed into the air. If you are diagnosed with an Active Tb disease be prepared to give a careful, detailed history of every person with whom you had contact. Since the active form may be contagious, these people will need to be tested, as well. [9, 10]

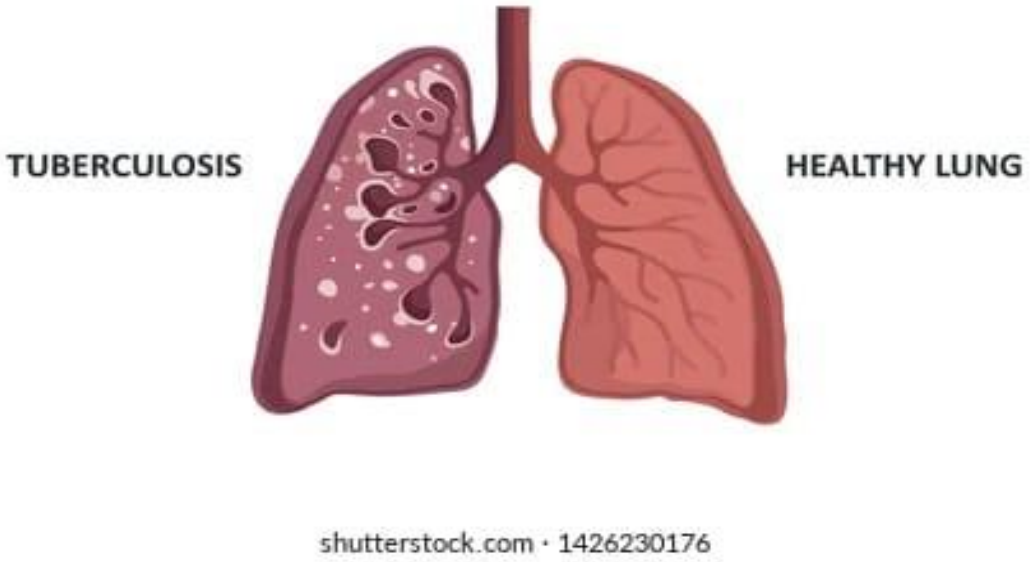
MILIARY TUBERCULOSIS:

Miliary tuberculosis is a rare form of active disease that occurs when TB bacteria find their way into the blood stream. In this form, the bacteria quickly spread all over the body in tiny nodules and affect multiple organs at once. This form of Tb can be rapidly fatal. [9, 10]

LATENT TUBERCULOSIS:

Many of those who are infected with TB do not develop over disease. They have no symptoms and their chest x-ray may be normal. The only manifestation of this encounter may be reaction to the tuberculin skin test (TST) or interferon-gamma release assay (IGRA). However, there is an ongoing risk that the latent infection may escalate to active disease. The risk is increased by other illnesses such as HIV or medications which compromise the immune system. To protect against this, the United States employs a strategy of preventive therapy or treatment of latent TB infection. [9, 10]





ETIOLOGY OF TUBERCULOSIS:

Persons having weak resistance power due to immunodeficiency, malnutrition, alcoholism, or chronic diseases frequently and easily get infected by TB. Other than these general causes, a person can also get infected through**:** [11]

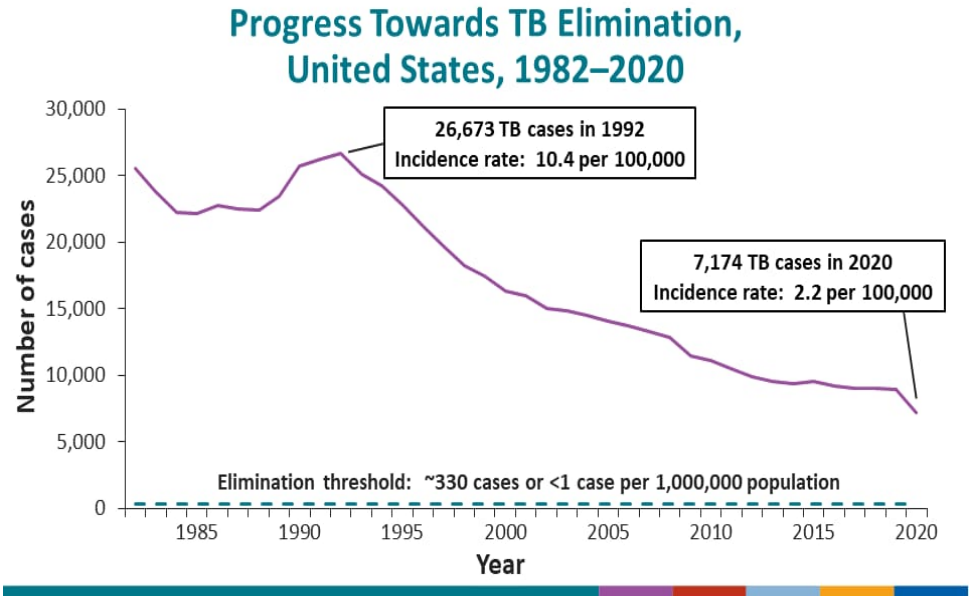
1. **DROPLET INFECTION**:
   Transmission of M. tuberculosis occurs by inhalation of the oral droplets released by an infected person
2. **INTAKE OF UNPASTEURISED COW MILK**:
   TB may also be caused by M. bovis (causing infection in cows) present in the unpasteurised milk.
3. **RE- INFECTION**:
   The degree of protection provided by the primary infection is limited. This is likely to be overpowered in case of massive re infection. So in the case if the re infecting organism is more virulent, re infection may break the protective barrier provided by the primary infection.
4. **DISEASED CONDITIONS**:
   Presence of diseases like diabetes, alcoholism, liver cirrhosis, congenital heart diseases, whooping cough, Influenza, and numerous other devitalising diseases decrease the body resistance against diseases, thus making the body prone to tuberculosis.

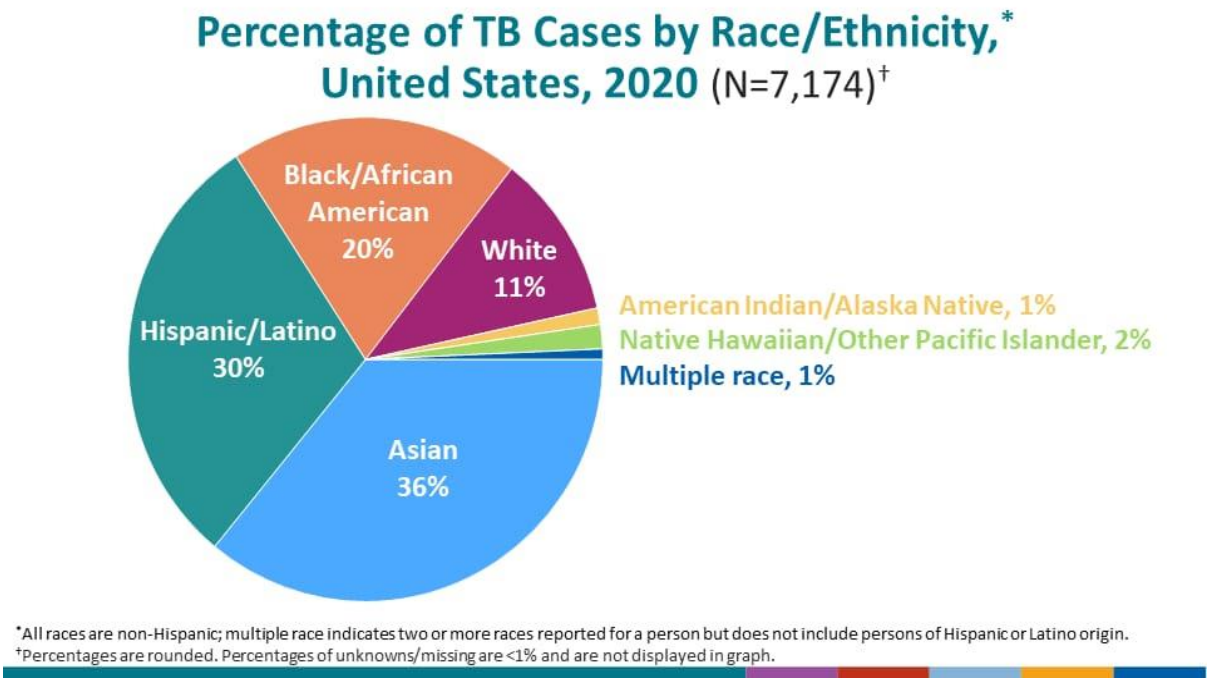
EPIDEMOLOGY:

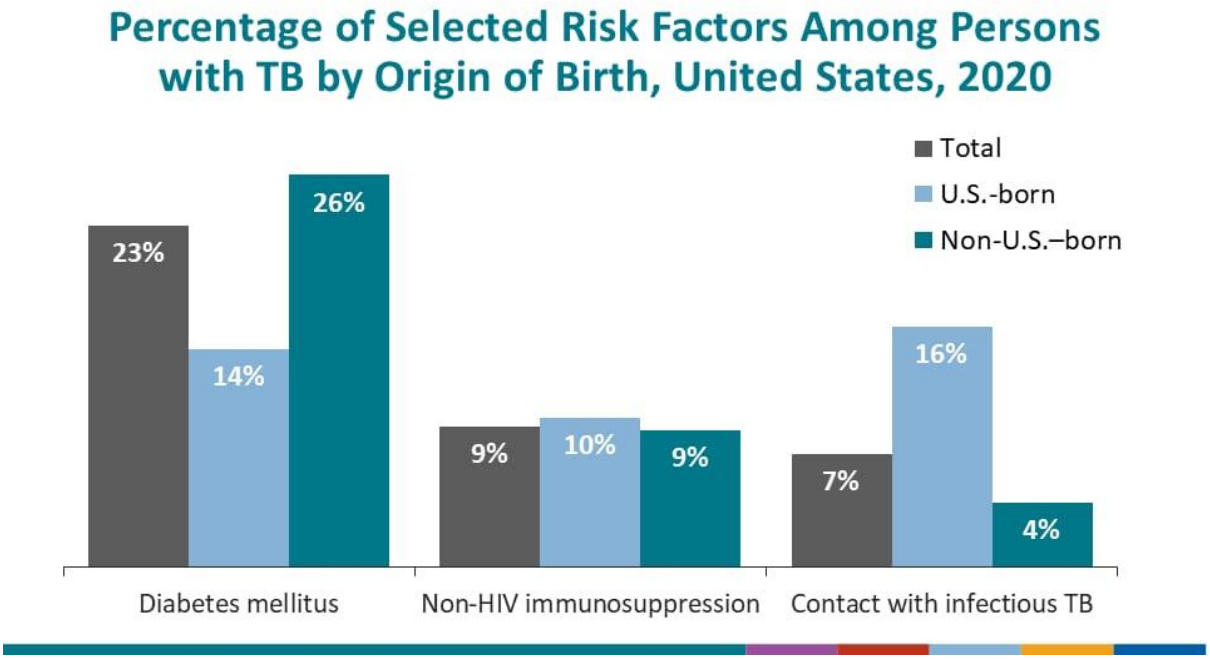
More than 1.7 billion people (approximately 22 percent of the world population) are estimated to be infected with *M. tuberculosis*. The global incidence of TB peaked around 2003 and appears to be declining slowly. According to the World Health Organization (WHO), in 2020, 9.9 million individuals became ill with TB and 1.5 million died.

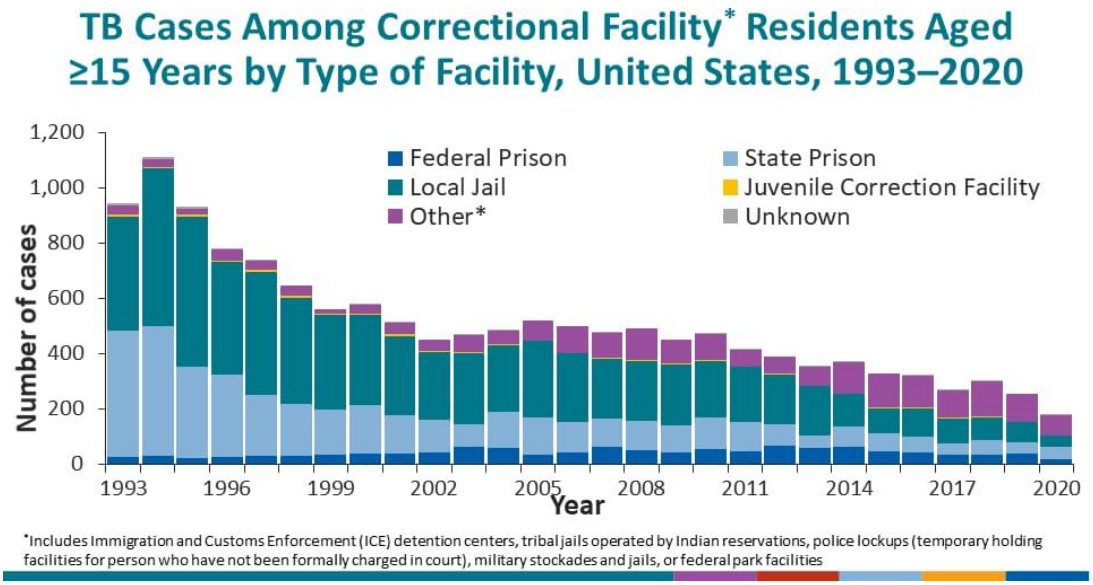
Tuberculosis is present globally developing countries for a disproportionate share of tuberculosis disease burden. In addition to the six countries listed above, several countries in Asia, Africa, Eastern Europe, and Latin and Central America continue to have an unacceptable high burden of tuberculosis. In advanced countries, high burden tuberculosis is seen among recent arrivals from tuberculosis-endemic zones, health care workers, and HIV-positive individuals. The use of immunosuppressive agents such as long-term corticosteroid therapy has also been associated with an increased risk. More recently, the use of a monoclonal antibody targeting the inflammatory cytokine, tumor necrotic factor alpha (TNF-alpha) has been associated with an increased risk. Antagonists of this cytokine include several monoclonal antibodies (biologics) used for the treatment of inflammatory disorders[12]

ANALYSIS OF TUBERCULOSIS:




Percentage of TB Cases by Race/Ethnicity,* United States, 2020 (N=7,174)†
Black/African American 20%
White 11%
Hispanic/Latino 30%
Asian 36%
American Indian/Alaska Native, 1%
Native Hawaiian/Other Pacific Islander, 2%
Multiple race, 1%
*All races are non-Hispanic; multiple race indicates two or more races reported for a person but does not include persons of Hispanic or Latino origin.
†Percentages are rounded. Percentages of unknowns/missing are <1% and are not displayed in graph.

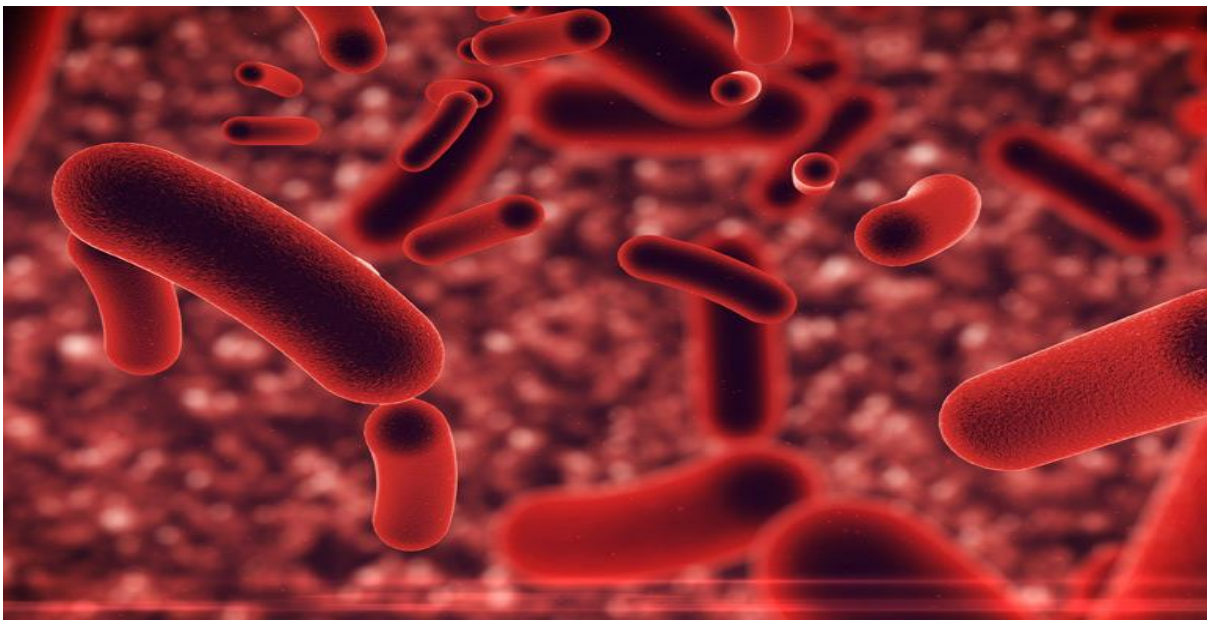

Percentage of Selected Risk Factors Among Persons with TB by Origin of Birth, United States, 2020
Total
U.S.-born
Non-U.S.–born
23%
14%
26%
9%
10%
9%
7%
16%
4%
Diabetes mellitus
Non-HIV immunosuppression
Contact with infectious TB



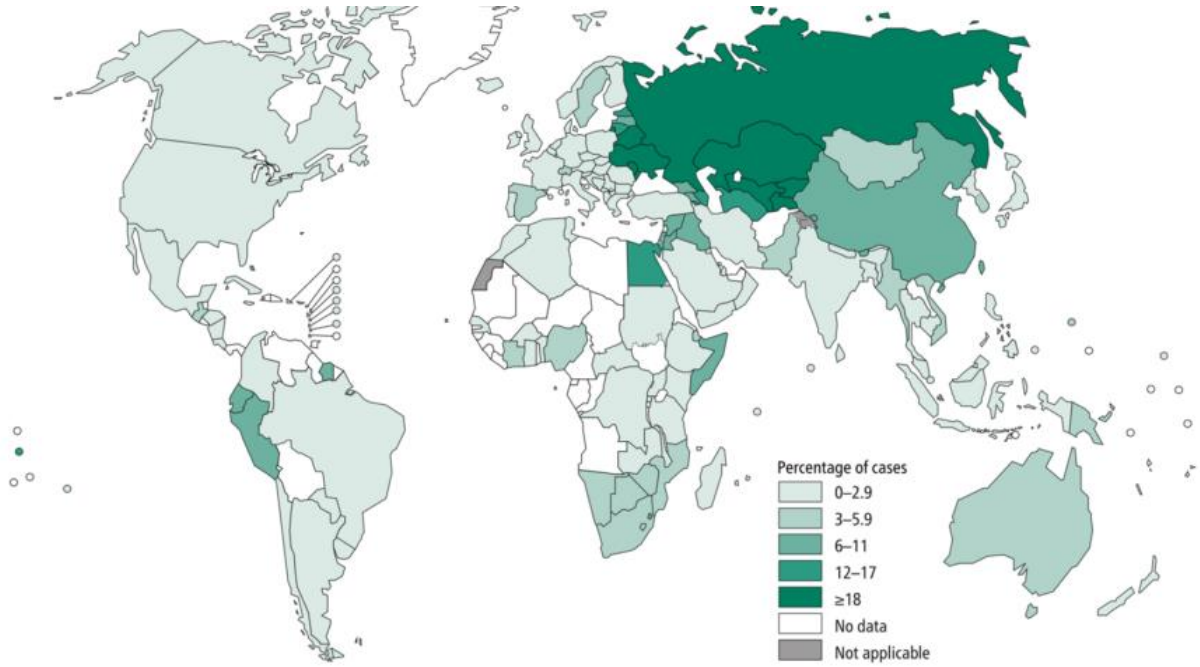
Multi-Drug Resistant Tuberculosis (MDR-TB) and Extremely Multi-Drug Resistant Tuberculosis (XDR-TB)

MDR-TB

This refers to tuberculosis with strains of Mycobacterium which have developed resistance to the classic anti-tuberculosis medications. TB is especially a problem among patients with HIV/AIDS. Resistance to multiple anti-tuberculosis medications including at least the two standard anti-tuberculosis medications, Rifampicin or Isoniazid, is required to make a diagnosis of MDR-TB. Seventy-five percent of MDR-TB is considered primary MDR-TB, caused by infection with MDR-TB pathogens. The remaining 25% are acquired and occur when a patient develops resistance to treatment for tuberculosis. Inappropriate treatment for tuberculosis because of several factors such as antibiotic abuse; inadequate dosage; incomplete treatment is the number one cause of acquired MDR-TB.

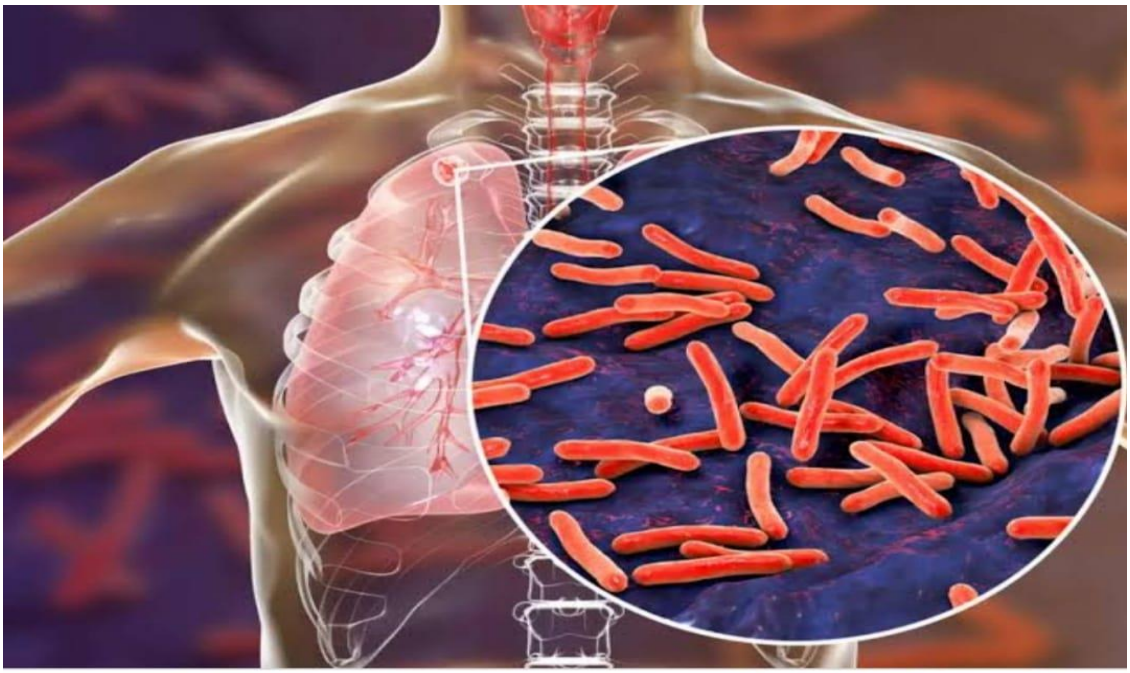


Multi drug resistant tuberculosis (MDR_ TB)

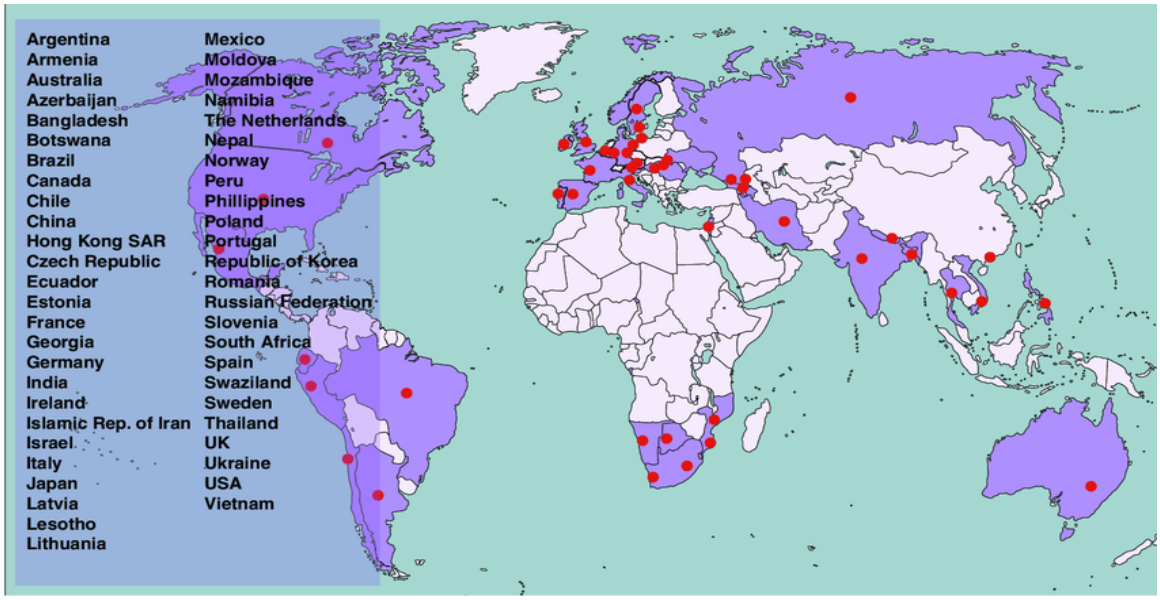


XDR-T.B

This is a more severe type of MDR-TB. Diagnosis requires resistance to at least four anti-tuberculosis medications including resistance to Rifampicin, Isoniazid, and resistance to any two of the newer anti-tuberculosis medications. The newer medications implicated in XDR-TB are the fluoroquinolones (Levofloxacin and moxifloxacin) and the injectable second-line aminoglycosides, Kanamycin, Capreomycin, and amikacin.The mechanism of developing XDR-TB is similar to the mechanism for developing MDR-TB.XDR -TB is an uncommon occurrence.



Extensively drug resistant tuberculosis(XDR_TB)



PATHOGENESIS:

Mycobacterium bacilli inhales

↓

Transmitted through airways to alveoli

↓

Multiplication

↓

Transfer to lymph system and blood stream

↓

Immune system responds

↓

Phagocytes engulf too many bacteria

↓

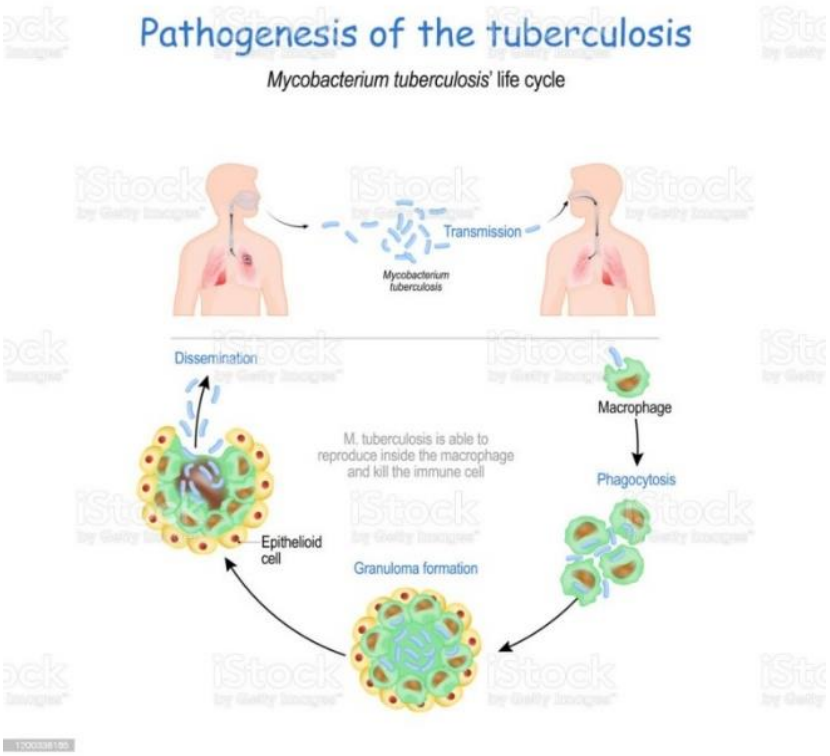
Tuberculosis lymphocytes bacilli spread in normal tissues

↓

Accumulation of exudate in alveoli

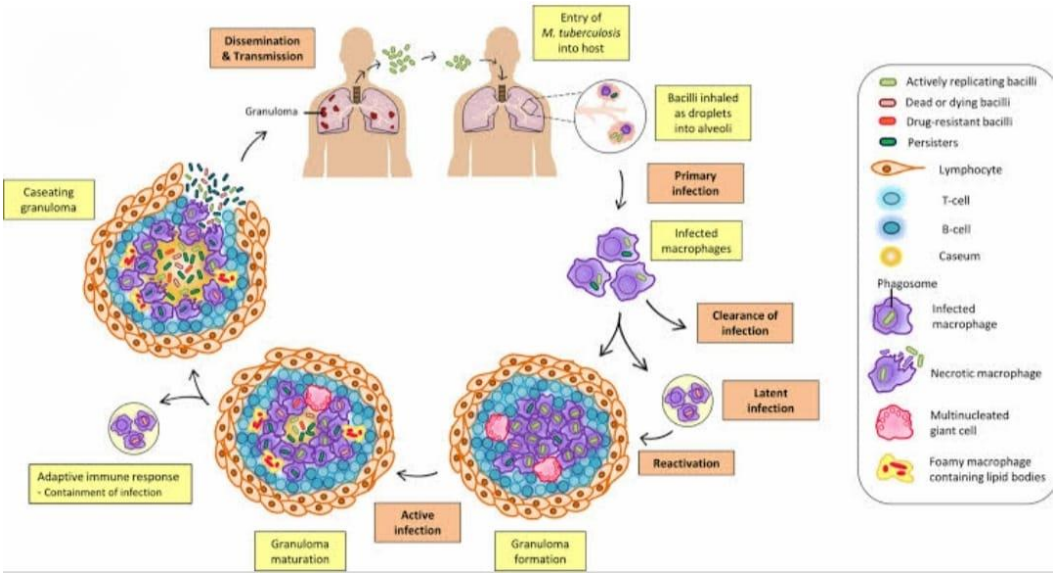
↓

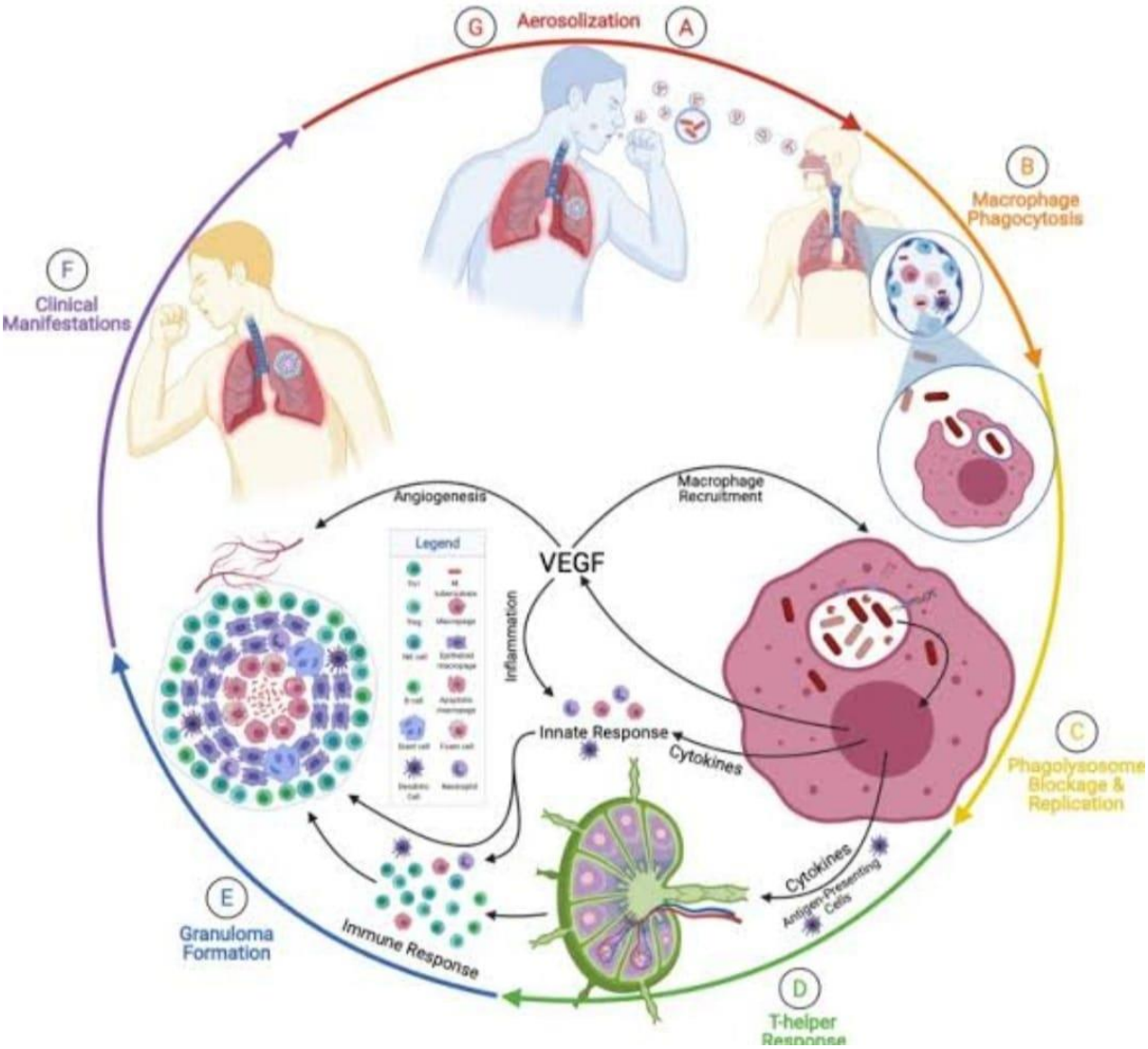
Bronchopneumonia [13,14]



PATHOPHYSIOLOGY:

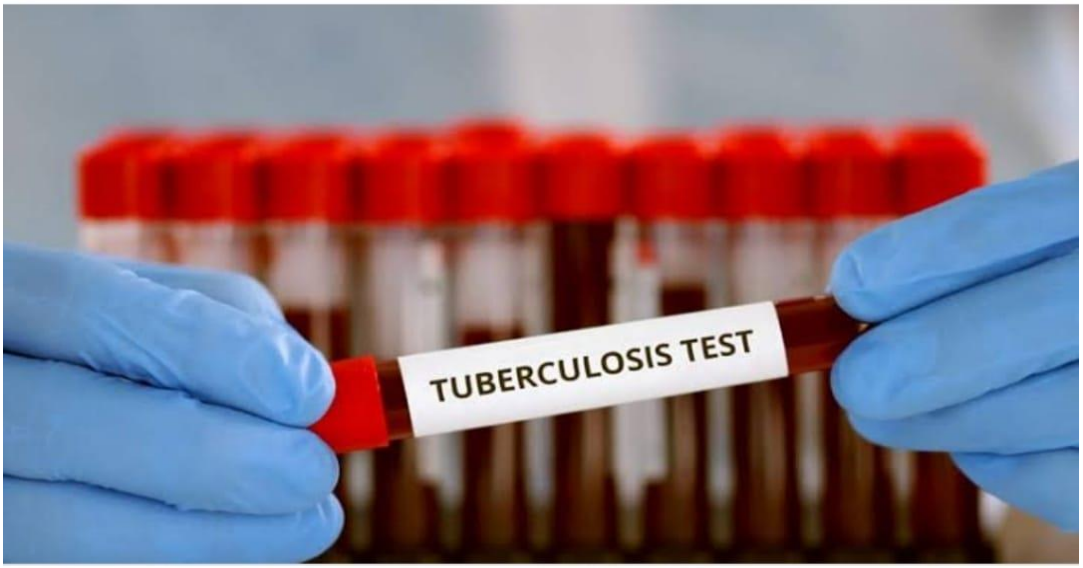
The basic lesion is tubercle. It consists of a localized collection of epitheloid cells surrounded by a zone of lymphocytes and fibroblasts. A few giant cells and bacilli are present at the Centre. Later, the adjacent tubercles combine together to produce bigger lesions. Necrosis that occurs at the Centre of the lesion is known as caseation. The lungs are common site of primary infection that occurs in the form of a small pneumonia patch commonly known as Ghon's focus. It usually situated at the periphery of one of the lower lobes but may be situated in any other part of the lung.[15,16,17]The primary lesion along with associated lymphagitis and hilar lymphadenopathy constitutes a triad commonly known as primary complex. Sometimes the primary infection fails to heal but instead, pursues an active course and produces the overt disease, the so called progressive primary tuberculosis. This happens only when the general vitality is low and the balance between allergy and immunity conferred is disturbed. Even when the primary lesion has healed completely, reinfection either with a massive dose of tubercular bacilli or with a virulent strain of the organism is always possible. Such an infection is likely to overpower immunity conferred by the primary infection. The secondary pulmonary lesion caused by reinfection (Assmann's focus) is usually situated either at the apex of the upper lobe or the apical segment of the lower lobe. A secondary lesion is free to spread anywhere, locally or distantly as in the case of progressive primary tuberculosis. [15,16,17]

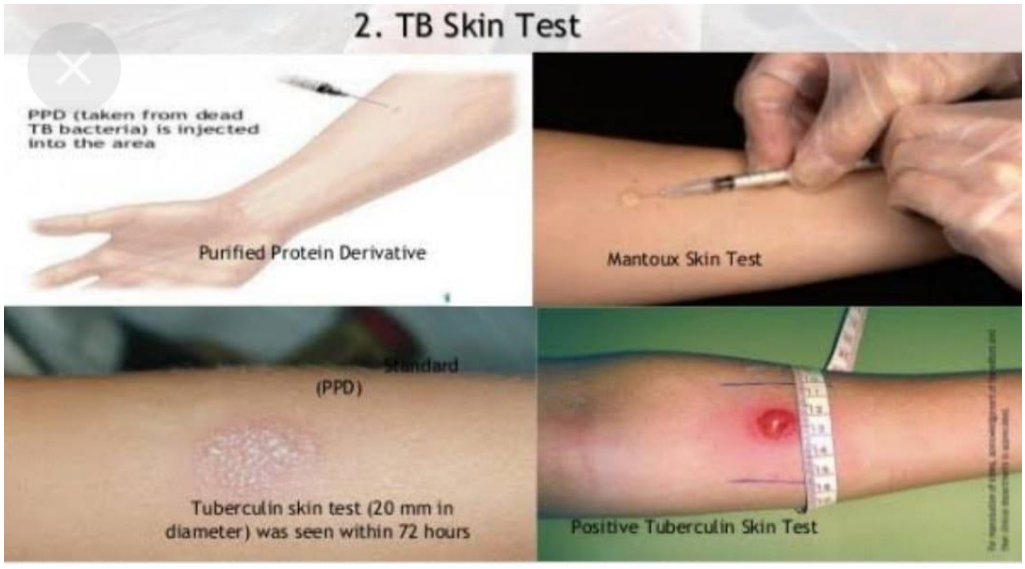

Dissemination & Transmission
Entry of M. tuberculosis into host
Granuloma
Bacilli inhaled as droplets into alveoli
Primary infection
Infected macrophages
Clearance of infection
Latent infection
Reactivation
Caseating granuloma
Adaptive immune response - Containment of infection
Active infection
Granuloma maturation
Granuloma formation
Actively replicating bacilli
Dead or dying bacilli
Drug-resistant bacilli
Persisters
Lymphocyte
T-cell
B-cell
Caseum
Phagosome
Infected macrophage
Necrotic macrophage
Multinucleated giant cell
Foamy macrophage containing lipid bodies


G
Aerosolization
A
B
Macrophage Phagocytosis
F
Clinical Manifestations
Angiogenesis
Macrophage Recruitment
Legend
VEGF
Inflammation
Innate Response
Cytokines
C
Phagolysosome Blockage & Replication
Cytokines
Antigen-Presenting Cells
E
Granuloma Formation
Immune Response
D
T-helper Response

SCREENING:

- Confirmatory and Diagnostic Tests
- A chest x-ray is indicated to rule out or rule in the presence of active disease in all screening test positive cases.
- Acid Fast Staining-Ziehl-Nielsen culture
- Nuclear Amplification and Gene-Based Tests: These represent a new generation of diagnostic tools for tuberculosis. These tests enable identification of the bacteria or bacteria particles making use of DNA-based molecular techniques. Examples are GeneXpert and DR-MTB.
- The new molecular-based techniques are faster and enable rapid diagnosis with high precision. Confirmation of TB could be made in hours rather than the days or weeks it takes to wait for a standard culture. This is very important, especially among immunocompromised hosts where there is a high rate of false-negative results. Some molecular-based tests such as GeneXpert and DR-MTB also allow for the identification of multidrug resistant tuberculosis.[18,19]





DIRECTLY OBSERVED THERAPY (DOT):

DOT is a component of case management that helps ensure patients adhere to therapy. It is the method whereby a trained health-care worker or another trained designated person watches a patient swallow each dose of anti-TB drugs and documents it. DOT is the preferred core management strategy recommended by CDC for treatment of TB disease and, if resources allow, for latent tuberculosis infection (LTBI) treatment. DOT can reduce the development of drug resistance, treatment failure, or relapse after the end of treatment. Good case management, which includes establishing a relationship with the patient and addressing barriers to adherence, facilitates successful DOT. [20]

It is important that DOT be carried out at times and in locations that are as convenient as possible for the individual patient. Therapy may be directly observed in a medical office or clinic setting, but can also be observed by an outreach worker in the field (e.g., patient's home, place of employment, school, or other mutually agreed-upon place). In some situations, staff of correctional facilities or drug treatment programs, home health-care workers, maternal and child health staff, or designated community members may provide DOT. In general, family members should not be the providers of DOT.[21]

Table 1. DOTS therapy for tuberculosis treatment.

Category	Clinical symptoms of patient	Regimen	Duration in months
Category I	Red New Sputum Smear, Positive New Sputum Smear, Negative New Extra Pulmonary	2 (HRZE)3, 4 (HR)3	6
Category II	Blue Sputum Positive relapse, Sputum Positive failure, Sputum Positive treatment after default	2 HRZES)3, 1 (HRZE)3, 5 (HRE)3	8
Category III	Green Sputum Negative, extra pulmonary, not Seriously ill	2 (HRZ)3, 4 (HR)3	6

DIAGNOSIS:

The detection of LTBI has to be distinguished from the diagnosis of active TB. Indirect procedures such as the interferon-gamma release assays (IGRA) are the modern standard for diagnosis of LTBI in adults. These assays detect the secretion of interferon-gamma (IFN-γ) by T lymphocytes, which are stimulated by means of relatively TB-specific antigens. Prior bacilli Calmette–Guerin (BCG) vaccination usually does not lead to false-positive results. IGRA are used principally to investigate the persons who have been in contact with an index patient who has contagious pulmonary TB. Another indication is testing for LTBI in advance of administration of drugs to achieve immunosuppression (see "Preventive treatment" below). IGRA are not suitable for diagnosis of clinically manifest TB, because they do not distinguish between latent TB and active disease [22]

The principal techniques for diagnosis of active TB are direct microscopic demonstration of the pathogen, culture, and nucleic acid amplification tests (NAAT; generally polymerase chain reaction [PCR]–based procedures). The sample for testing should be obtained before the commencement of treatment, and investigation for M. tuberculosis should be specified on the request form, as it does not always form part of the routine program. Open pulmonary tuberculosis can be excluded if microscopy fails to detect acid-fast rods in samples of sputum collected on three separate days. Demonstration of M. tuberculosis in culture also demonstrates infectivity but TB diagnosis by culture takes several weeks to become positive. Microscopy of samples of sputum, bronchial secretion, or bronchoalveolar lavage (BAL) fluid is

economical, quick, and represents a marker for the patient's infectiousness[23] However, its sensitivity is very variable (20% to 80%) and differs among investigators the specificity of microscopy is also limited, because it cannot distinguish M. tuberculosis from nontuberculous mycobacteria (NTM). At least several days' culture are required for a positive result when fluorescence-based detection systems are used, while the growth of visible colonies on solid culture media can take up to 8 weeks. Culture nevertheless remains the gold standard of TB diagnosis and is of central importance for resistance testing. NAAT-based methods are characterized by their swiftness, relatively good sensitivity, and very high specificity.[24] Moreover, many PCR-based methods permit conclusions regarding resistance to the commonly used substances to be drawn directly from sputum or other PCR-positive materials, thus enabling early detection of monoresistant or multiresistant TB. However, comprehensive testing of resistance to all available substances, e.g., via whole-genome sequencing of the strain concerned, requires culture. If extra pulmonary TB is suspected, aspirates, biopsy samples, or body fluids (urine, sperm, stool, cerebrospinal fluid) must also is investigated using the methods described above. It is essential to include TB among the differential diagnoses and send material not just for histopathology but also for microbiological examination.[25]

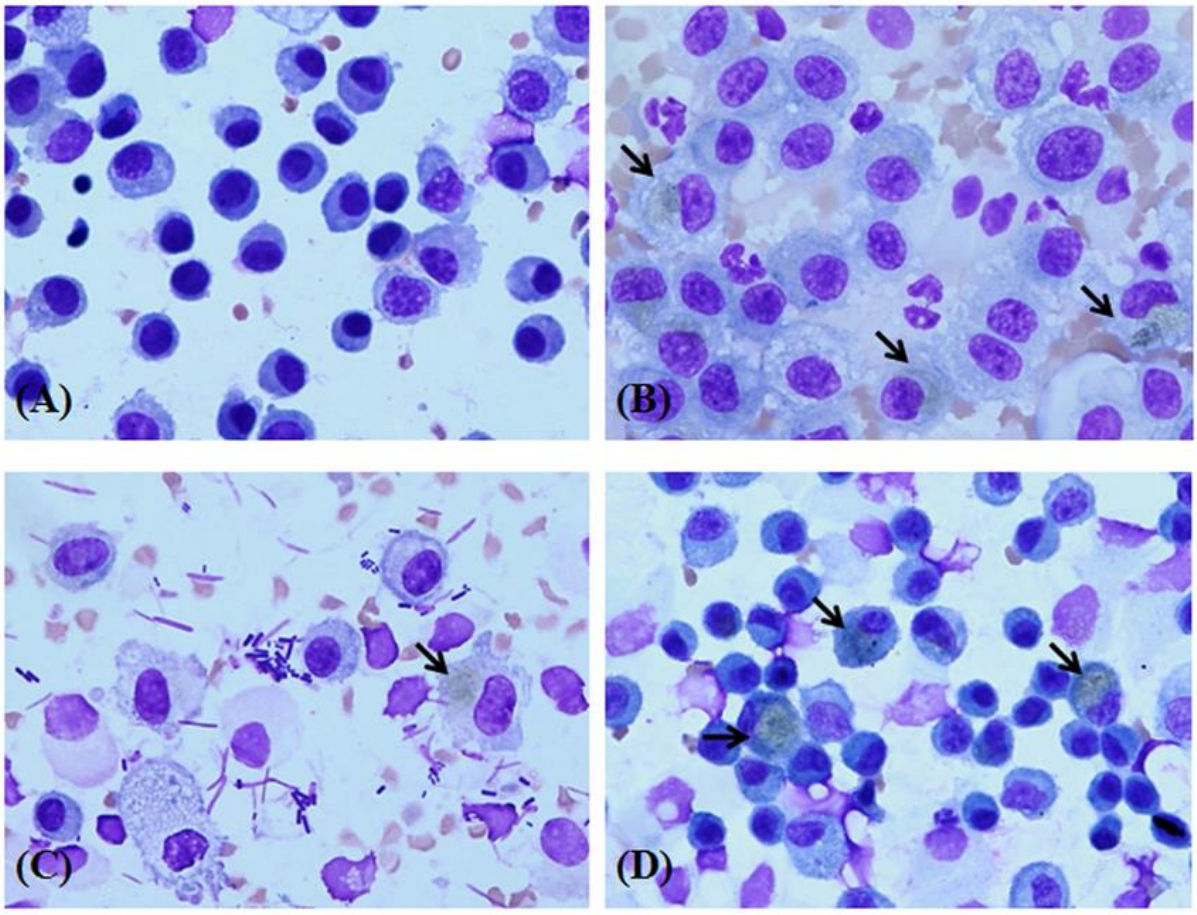
DIFFERENTIAL DIAGNOSIS:

Tuberculosis is a great mimic and should be considered in the differential diagnosis of several systemic disorders. The following is a non-exhaustive list of conditions to be strongly considered when evaluating the possibility of pulmonary tuberculosis

- Pneumonia
- Malignancy
- Non-tuberculosis mycobacterium
- Fungal infection
- Histoplasmosis
- Sarcoidosis

X_Ray Chest commonly used diaognosis

SPUTUM COLLECTION



BRONCHIAL ALVEOLAR LAVAGE [BAL]

TREATMENT:

The major goals of treatment for TB disease are to

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

MONITORING PLAN:

For each patient with newly diagnosed TB disease, a specific treatment and monitoring plan should be developed in collaboration with the local TB control program within 1 week of the presumptive diagnosis. This plan should include:

- Description of the TB treatment regimen;
- Methods of assessing and ensuring adherence to the TB treatment regimen;
- Methods to monitor for adverse reactions;
- Methods for evaluating treatment response.

SELF ADMINISTRATION THERAPY:

Patients on self-administered therapy should be asked routinely about adherence at follow-up visits. Pill counts should be performed consistently, and urine or blood tests can be used periodically to check for the presence of urine drug metabolites or appropriate blood serum level of the drugs. In addition, the response to treatment should be monitored closely for all patients. If culture results have not become negative after 2 months of treatment, the patient should be re-evaluated and DOT should be considered for the remainder of treatment.[26]

PATIENT EDUCATION:

Educating patients about TB disease helps ensure their successful completion of therapy. Health-care providers must take the time to explain clearly to patients what medication should be taken, how much, how often, and when. Patients should be clearly informed about possible adverse reactions to the medications they are taking and when to seek necessary medical attention. Providing patients with the knowledge they need regarding the consequences of not taking their medicine correctly is very important. In addition, patients should be educated about infection control measures and potential need for isolation.

HIV testing and counselling is recommended for all patients with TB disease in all health-care settings. The patient must first be notified that testing will be performed. The patient has the right to decline HIV testing and counselling (opt-out screening) [27]

CLASSIFICATION OF TUBERCULAR AGENTS:

The anti-tubercular drugs are classified as first line, second line and third line drugs based on their efficacy, side effects, toxicity, availability and cost. The first-line anti tubercular drugs is,

• Streptomycin,

• Rifampicin,

• Ethambutol,

• Isoniazid

• Pyrazinamide.

Tuberculosis can be cured by using first line drugs with the success rate of up to 95%. If the treatment fails because of the bacterial resistance or intolerance to one or more drugs, second line drugs are used.

There are six classes of second line drugs used for the treatment of TB.

• Amino glycosides: eg amikacin, kanamycin

• Polypeptides: eg capreomycin, viomycin

• Fluor quinolones: eg ciprofloxacin, gatifloxacin, moxifloxacin

• Thioamides: e.g. ethionamide, prothionamide

• Isoxazolidinone: eg cycloserine

• Salicylic acid: e.g. p-amino salicylic acid

Second line drugs are less effective, more toxic and more expensive than the first line agents. Other drugs which are not very effective and not included in the WHO list are called third line drugs. These drugs include Rifabutin, macrolides (clarithromycin), linezolid, thioacetazone, thioridazine, arginine etc.[28]

CLASSIFICATION OF NEW DRUGS:

The World Health Organisation (WHO) has recently updated the classification of new antituberculosis drugs. Previous World Health Organisation (WHO) guidelines classified anti-TB drugs into five main groups, based on safety and effectiveness considerations. This classification originated in 2006, updated in 2008, 2011 and, finally, in 2016 based on new evidence, mainly from the former group 5 drugs. WHO categorisation of second-line antituberculosis drugs recommended for the treatment of rifampicin resistant and multidrug-resistant tuberculosis

Group A:

- Fluoroquinolones
- Levofloxacin
- Moxifloxacin
- Gatifloxacin

Group B: second-line injectable agents

- Amikacin
- Capreomycin
- Kanamycin
- Streptomycin

Group C: other core second-line agents

- Ethionamide/prothionamide
- Cycloserine/terizidone
- Linezolid
- Clofazimine

Group D: add-on agents (not part of the core multidrug-resistant tuberculosis regimen) D1

- Pyrazinamide
- Ethambutol[28]

DRUGS USED IN TREATMENT OF TUBERCULOSIS

Drug	Oral	Injectable†
First-line	Isoniazid Rifamycins: Rifampin, rifapentine, rifabutin Ethambutol Pyrazinamide	Streptomycin
Second-line	Fluoroquinolones: Ofloxacin, levofloxacin, moxifloxacin Thioamides: Ethionamide, prothionamide Para-aminosalycylic acid Serine analogs: Cycloserine, terizidone, thicetazone	Aminoglycosides: Amikacin, kanamycin Capreomycin
Third-line‡	Linezolid Amoxicillin–clavulanate Clarithromycin Clofazimine	Carbapenems: Imipenem, meropene

FUTURE IMPLANTS OF TUBERCULOSIS:

In recent years, a renewed focus on anti-TB medications has generated promising research into new agents. Several new classes of anti-TB medications are currently under development; some with novel mechanisms of action. These drugs offer the possibility of shortened regimens and more effective treatment for MDR-TB. TABLE 4 provides a brief overview of some investigational therapies.

Table 4. Investigational Therapies for the Treatment of Tuberculosis

Drug	Class	Area of Primary Research	New Chemical Entity	Notes
PA-824[a]	Nitroimidazopyran	DS-TB, MDR-TB	Yes	Not metabolized by CYP450
Sutezolid	Oxazolidinone	DS-TB	Yes	—
SQ-109	Ethylenediamine	DS-TB, MDR-TB	Yes	—
AZD5847	Oxazolidinone	DS-TB	Yes	—
Delamanid	Nitroimidazopyran	MDR-TB	Yes	—
Bedaquiline	Diarylquinoline	DS-TB	No	Approved in 2012 for MDR-TB
Linezolid	Oxazolidinone	MDR-TB, XDR-TB	No	Use previously limited due to adverse events including myelosuppression, peripheral neuropathy, optic neuropathy
Moxifloxacin[a]	Fluoroquinolone	DS-TB	No	Little interaction with CYP450 system

[a] Combination of PA-824, moxifloxacin, and pyrazinamide (PaMZ regimen) killed TB faster than current standard of care; combination currently undergoing additional studies.
DS-TB: drug-sensitive tuberculosis; MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant TB.
Source: References 16, 17.

TOXIC EFFECTS:

1) Isoniazid- Asymptomatic elevation of aminotransferases
(10-20%), clinical hepatitis (0.6%), peripheral neurotoxicity, hypersensitivity.

1) Isoniazid- Asymptomatic elevation of aminotransferases

2) Rifampin- Pruritus, nausea & vomiting, flulike symptoms, hepatotoxicity, orange discoloration of bodily fluid.

3) Rifabutin- Neutropenia, uveitis (0.01%), polyarthralgias, hepatotoxicity (1%))

4) Rifapentine- Similar to Rifampin

5) Pyrazinamide- Hepatotoxicity (1%), nausea & vomiting, polyarthralgias (40%), acute gouty arthritis, rash and photosensitive dermatitis

6) Ethambutol- Retro bulbar neuritis (18%). [(29)]

SIGNS AND SYMPTOMS:

In inactive TB there is not any clear visible symptoms; once the infection becomes active, the symptoms appear gradually overtime (may be after many weeks). Lungs are the organs most commonly affected by the disease; though kidneys, lymph nodes, bones, joints and other organs can also be infected. The following symptoms are seen commonly in patients suffering from the TB:

- Coughing(that lasts longer than two weeks with green, yellow, or bloody sputum)
- Weight loss
- Fatigue or Malaise
- Fever
- Night sweats
- Chills
- Anorexia
- Chest pain
- Shortness of breathe
- Loss of appetite

Only when the disease spreads beyond the chest and the lungs, the additional symptoms may be noted, e.g. swollen glands at the sides of the neck or under the arms signified the TB. TB has been spread to the lymph nodes; pain or swelling in the hip or knee indicates the spread of infection to the bones and joints; pain in abdomen, pain or discomfort while urinating, and blood in the urine suggests the spread of infection to the Genitourinary system. [(30)]

PROGNOSIS:

The majority of patients with a diagnosis of TB have a good outcome. This is mainly because of effective treatment. Without treatment mortality rate for tuberculosis is more than 50%.The following group of patients is more susceptible to worse outcomes or death following TB infection:

1. Extremes of age, elderly, infants, and young children
2. Delay in receiving treatment
3. Radiologic evidence of extensive spread.
4. Severe respiratory compromise requiring mechanical ventilation
5. Immunosuppression
6. Multidrug Resistance (MDR) Tuberculosis [(31)]

COMPLICATIONS:

Most patients have a relatively benign course. Complications are more frequently seen in patients with the risk factors mentioned above. Some of the complications associated with tuberculosis are:

1. Extensive lung destruction
2. Damage to cervical sympathetic ganglia leading to Horner's syndrome.
3. Acute respiratory distress syndrome
4. Milliary spread (disseminated tuberculosis) including TB meningitis.
5. Empyema
6. Pneumothorax
7. Systemic amyloidosis [(32)]

CONCLUSION:

Tuberculosis remains one of the most deadly infectious diseases and has claimed millions of lives for many years. While significant progress has been made towards controlling the global burden of TB over the past decade, more efforts are still needed. Emerging issues such as multi drug-resistance threatens to revert the progress made regarding TB care and control. The knowledge base for TB remains a rapidly expanding area and global guidelines are continually being refined for instance to incorporate new anti-tubercular drugs to tackle issues of resistance. Health professionals, policy makers, patients and the general public need to keep up-to-date with current trends in TB management and control. This will be essential for efficient adoption of global guidelines to country-level situation, particularly taking into consideration issues such as disease burden, health system structures and available resources.

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