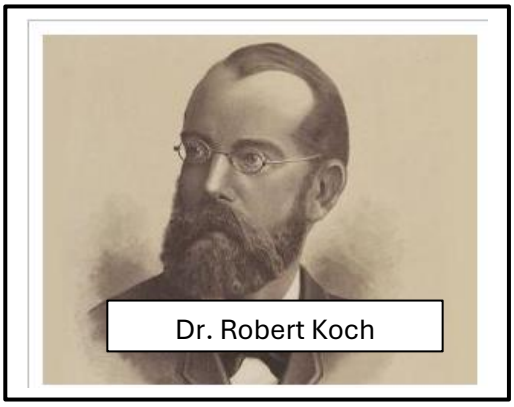
Tuberculosis

Introduction

Definition and Overview

It's a serious infectious disease that affects the lungs caused by a sort of bacteria that can spread from one person to another with illness coughs, sneezing, or signs. An infected person can put tiny droplets mixed with germs causing this disease in the air so that another person can breathe them and inhale germs in his lungs. This disease spreads easily in places where people gather or in crowds. People with immune system deficiency or illnesses such as HIV/AIDS are more likely to be infected easily. Every year, 10 M people fall ill with (TB). Despite being a preventable or curable disease, 1.5 M people die from TB each year making it the world's top infectious disease. Most of the death cases are present in low and middle-income countries while it is present in all world nations.

Historical context


Dr. Robert Koch

This infectious disease is one of the ancient diseases that killed people 9000 years ago. It was rediscovered on March 24, 1882, by Dr. Robert Koch announced the discovery of mycobacterium tuberculosis which is the bacteria that causes (TB). By the following century, March 24 was designated World TB Day to educate people about TB precautions and dangers. In the 1700s, TB was called the white plague due to the paleness of patients. Also, it was discovered on the sculptured monuments of the Middle Ages that scrofula, a disease affecting the cervical lymph nodes was described as a new clinical form of TB. In the ancient Egyptian civilization, there wasn't any evidence of TB in Egyptian papyri. On the other hand, dating back to 3300 and 2300 years ago, there were similar diseases similar in symptoms to TB in China and India respectively. Recently, in 1865 TB was demonstrated by Jean-Antonine who was a French surgeon at the Army Medical School.

Epidemiology

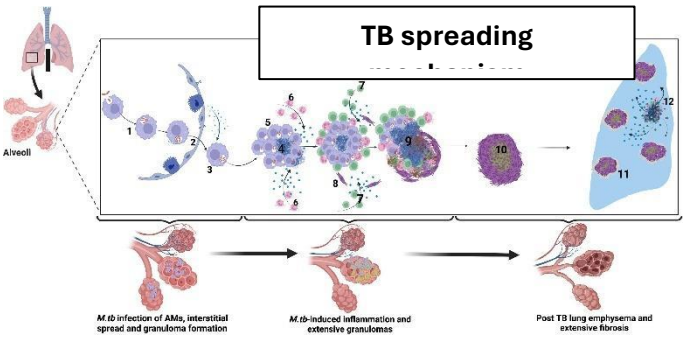
According to WHO, TB is the second leading infectious killer after COVID-19 causing an estimated 10.6 M new cases and 1.5 M deaths worldwide in 2022. Over 80% of TB cases as mentioned before are from low and medium-income countries, especially in Asia, and Africa, some Asian countries such as Bangladesh, and the Western Pacific. TB is one of the airborne diseases, this property makes it easy to be transmitted from one person to another in any way

from touching surfaces to inhaling the droplets released from sneezing the infected person in the air including the mycobacteria stuck in the lungs and reproduce causing the incidences. After the bacterial entrance in both lungs, it begins its journey by related and designated steps:

Alveolar macrophages and cilia in lungs engulf (TB) in alveolar space, these macrophages migrate from alveolar space into the interstitium in an IL-1R-dependent manner

Consequently, TB exploits its presence in alveolar microphages and uses its DNA for replication, after replication it induces the infected microphage apoptosis and expression of host lytic proteins in an ESX-1-dependent manner.

Macrophages continue engulfing infected cells with TB until they form granulomas within the lungs (sacs contain TB bacteria). Following this step, T-cells of (M. TB) bacteria begin to secrete (**cytokine TGF*β***) which induces the rapture of granulomas of TB making it spread within the lungs



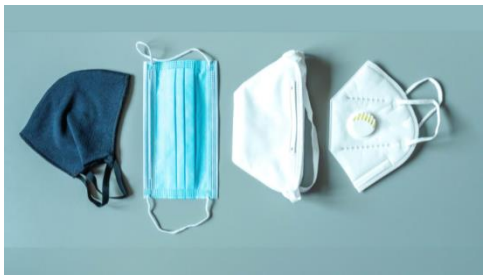
Additionally, some people with immune system disorders and infections may suffer from multiple including exposure to **COPD** besides **TB** which worsens the cases more and more.

Etiology

Causes and Risk factors

Previously, we have talked about the leading reason behind the infection of Tb which was the mycobacteria tuberculosis and its pathway in the lungs and respiratory system. Furthermore, some ways related to the culture and knowledge of residents help in spreading the disease in the country.

Hugs and kisses with your relatives may be one of the main reasons for disease infections spreading



Neglecting wearing masks in crowded and closed spaces although it includes the highest risks and makes people more exposed to respiratory diseases.

Coping with normal flu cases without precautions is also one of the wrong cultures for some people and insufficient awareness about risks they may face.

Previous TB infections are more exposed to being infected once again if they didn't receive the exact treatment or vaccinations.

Smoking needless to say that is one of the contributing factors in the weakness of respiratory system tracts and immune system also it elevates the person's probability of being infected than non-smokers.

Genetic and environmental influences

Genetic factors haven't a direct effect on the probability of infection while two factors may affect some people easing their infection which is an immune disorder known as (**HLA**) Human Leukocyte Antigen which is a main factor in engulfing the bacterial bodies and strange bodies enter human's body. This disorder may lead to the misrecognition of TB bacterial cells in the body worsening the case. **Vitamin D Receptor (VDR)** Polymorphisms in the VDR gene can affect the immune response to TB. Family history can be considered as one of the genetic factors while it is a part of the last two factors.

Clinical features

Signs and symptoms

Signs and symptoms are split into two kinds:

Common symptoms
Golden symptoms

Beginning with **common symptoms** which are common with all people as a flu case including:

- **Cough**: this kind of cough may continue for more than three weeks.
- **Hemoptysis**: Coughing up blood or sputum-containing blood.
- **Fever:** it is not a normal fever in contrast, it is disconnected waves of fever and most of the time happens at night.

- **Fatigue and loss of weight:** these two factors are sequences of fever at night for the next day.

Golden symptoms

Experiencing this disease for more than 1 century in the new millennium most specialists and doctors say that the high indicative of TB infection is a persistent cough lasting more than three weeks, especially if it is accompanied by other symptoms like hemoptysis (coughing up blood), night sweats, weight loss, and fever. This symptom is critical for prompting further diagnostic evaluation, such as a chest X-ray and sputum examination.

Disease stages and progression

Infection with TB requires some stages to say that someone is fully infected with this disease and each stage is worse than the previous one and requires more care and medications.

Exposure: this is the initial stage where a person meets someone who has active TB. At this moment, a healthy person may inhale TB bacteria from the infected person although he isn't infected yet.

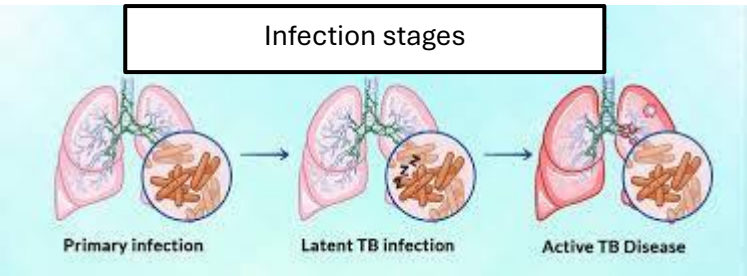
Latent TB infection: After exposure, the bacteria can become dormant in the body or may become active at any time. This depends on the immune system's activity and strength in the body of the exposed person. In this stage and the previous one, there aren't any apparent TB symptoms in this person, and he can't infect another person as well.

Active TB: This stage occurs when TB overcomes the immune system barrier and begins to multiply making their granulomas. As soon as bacteria finish their multiplication T-cells gained by TB induce the granulomas to be ruptured spreading TB bacteria in all parts of the respiratory system and the active stage begins. At this stage, an infected person can transmit TB to any other person in one of the ways that has been mentioned before.

As a person reaches the active TB stage, symptoms begin to appear on him. Most cases require from 7 to 8 weeks to have symptoms of TB. If the patient neglects his illness as long as he will suffer with the development of his case. The consequences of neglecting may lead to death.

Complications

Some potential complications may result from neglecting TB symptoms or the wrong diagnosis of doctors:



- Joint damage
- Lung damage
- Infection and damage in patient bones
- Liver and kidney problems
- Inflammation around tissues of patient's heart

Reaching this stage makes the patient's case worse and makes his probability of death higher.

Diagnosis

Diagnostic criteria
Diagnostic test procedure

This stage is disease discovery and certainty is required in this stage to overcome disease results and reduce their severity. We can split them down into 3 steps:

- **Clinical evaluation:**

When the patient comes to the doctor with a cough for 3 weeks or more with bloody mucous cough, fatigue night sweats, and weight loss.

Immediately doctor moves to the next stage which is:

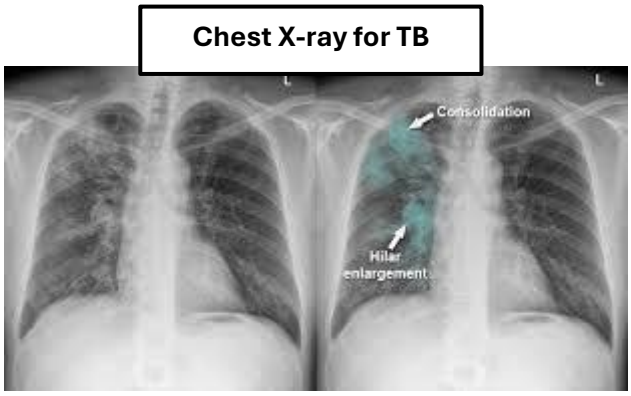
- **Laboratory tests:**

Sputum Smear Microscopy: Examination of sputum samples under a microscope after staining with acid-fast bacilli (AFB) stains (e.g., Ziehl-Neelsen stain). This test detects the presence of TB bacteria in the sputum. Sputum Culture: Culturing sputum samples on specialized media to grow and identify "**Mycobacterium tuberculosis**". This is the gold standard for diagnosing TB and can confirm the presence of the bacteria and determine drug susceptibility. Cultures can take several weeks to yield results.

Moving to the third stage of diagnosis which is:

- **Imaging studies**

Chest X-ray: The primary imaging tool to evaluate lung involvement. Chest X-rays can show abnormalities such as infiltrations, cavities, and pleural effusion indicative of TB.



However, X-rays alone cannot confirm TB diagnosis. This is the most widespread way of Imaging studies besides CT scans of the lungs.

Differential diagnosis

Tuberculosis (TB) can present with a variety of symptoms that overlap with many other diseases. Additionally, they must be considered to differentiate between TB and other common respiratory diseases so as not to make wrong diagnoses leading to devastating results.

1- Bacterial Pneumonia: Acute or chronic bacterial lung infections caused by organisms like *Streptococcus pneumoniae*, *Hemophilus influenzae*, or *Staphylococcus aureus*.

- **Symptoms**: Fever, cough, chest pain, sputum production
- **Diagnosis**: Sputum culture, chest X-ray

2- Viral Pneumonia: Lung infection caused by viruses such as influenza, respiratory syncytial virus (RSV), or COVID-19

- **Symptoms**: Fever, cough, shortness of breath, myalgia.
- **Diagnosis**: Viral PCR tests, chest X-ray.

3- Chronic Obstructive Pulmonary Disease (COPD) Exacerbation: Worsening of COPD symptoms, often due to infection or other triggers.

- **Symptoms**: Chronic cough, wheezing, shortness of breath, increased sputum.
- **Diagnosis**: Pulmonary function tests, chest X-ray.

4- Bronchiectasis: Permanent enlargement of parts of the airways of the lung.

- **Symptoms**: Chronic cough, large amounts of sputum, recurrent infections.
- **Diagnosis**: Chest CT scan.

5- **Fungal Infections**: Infections like histoplasmosis, coccidioidomycosis, or aspergillosis.

- **Symptoms**: Fever, cough, night sweats, weight loss.
- **Diagnosis**: Fungal cultures, serology, chest X-ray.

Pathophysiology

Mechanism of disease development

The development of **TB** is indeed integrated with the immune system's effectiveness and strength that's why we can find two persons of the same age and in the same place who have the same disease (TB) In contrast, the severity of TB and its development varies in both. This development is owed to genetic mutations and mal-functional organelles within the system itself. In detail, Let's talk about the mechanism of incidence of **TB.** Diabetes patients are the target people who have immune deficiency due to problems in phagocytosis which impairs the ability of:

- **macrophages** and **neutrophils** to engulf and destroy Mycobacteria Tuberculosis this leads to reduced capacity to contain the initial infection
- **Chemotaxis**: the migration of immune cells to the site of infection is less effective in diabetics, delaying the immune response to TB bacteria.

- **Reduction of Cytokines:** Diabetes affects the production of cytokines like TNF-α, IL-1, and IL-6 which are crucial for the immune response against TB as a strange body (Bacteria).

- **Reduction of T-cells:** T lymphocytes are affected by diabetes particularly CD4+ T cells, which play a crucial role in activating macrophages to kill TB bacteria. A reduced T-cells response means that the immune system is less effective at controlling TB infection.
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Cellular and molecular changes

We have discussed the cellular changes that occur during the infection and the evolution of TB within the patient's body from the macrophages to the T-cells.

Now, we are going to discuss the chemical and molecular changes that occur as a person is infected with **TB:**

- **Reactive nitrogen and oxygen species**:

Activated macrophages produce reactive nitrogen species (Nitric oxide) and reactive oxygen species to kill TB bacteria. However, TB has a mechanism to resist these molecules thus, it

becomes mal-functional. This is partially considered a chemical change within the body due to the neglecting of these chemical's function

Impact on Body systems

Besides affecting the respiratory and immune systems **TB** affects most of the body systems consequently and each one depends on the other one which may lead to damaging some of the dependent systems.

- **Nervous system**: TB meningitis is a serious complication that can cause inflammation of the meninges, the membranes that surround the brain and spinal cord. Symptoms can include headache, fever, stiff neck, and confusion.

- **Skeletal system:** TB can infect bones and joints, causing pain and swelling. This is most common in the spine and hips.

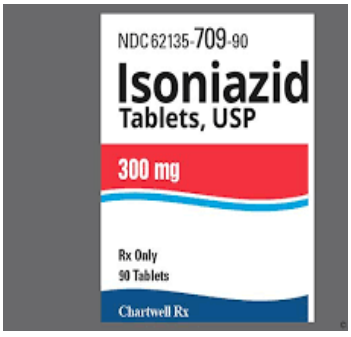
- **Urinary system:** TB can affect the kidneys and bladder, causing pain, blood in the urine, and difficulty urinating.

- **Genital system:** TB can affect the reproductive organs in both men and women. This can lead to infertility

Management and treatment

Medical and surgical treatments

Pharmacological therapies



Let's begin with **medical treatments** which are the medicines which are prescribed by doctors with specific therapies for each person and it's forbidden to use the same therapy on another person without asking doctors to avoid problems, noticing that not all cases are similar.

- **Isoniazid (INH)**: A bactericidal drug that inhibits the synthesis of mycolic acids, essential components of the mycobacterial cell wall.

- Rifampicin (RIF): A bactericidal antibiotic that inhibits DNA-dependent RNA polymerase in mycobacteria.

These are the most effective medicines provided for people who suffer from TB or even if it was and early infection.

For **surgical treatments**:

Surgical interventions are considered when medical therapy alone is insufficient, particularly in cases of drug-resistant TB, complications, or localized disease that can be surgically managed.

1- Pulmonary Surgery:

- **Lobectomy or Pneumonectomy**: Removal of a lobe or entire lung in cases of localized disease, cavitary lesions, or drug-resistant TB.
- **Segmentectomy or Wedge Resection**: Removal of a segment or wedge of lung tissue containing TB lesions.

2- Pleural Procedures:

- **Thoracentesis**: Aspiration of pleural fluid for diagnostic or therapeutic purposes in TB pleuritis.
- **Pleurectomy or Decortication**: Surgical removal of the pleura or fibrous tissue to relieve trapped lung or chronic empyema.

3- Lymph Node Excision:

- **Lymphadenectomy**: Surgical removal of TB-infected lymph nodes that are causing obstruction, fistulae, or abscesses.

4- Spinal Surgery:

- **Decompression and Stabilization**: Surgical intervention to relieve spinal cord compression and stabilize the spine in cases of Pott's disease (spinal TB).

Lifestyle and dietary modifications

A person's lifestyle is an adequate way to enhance his illness case and well it elevates the pointers of healing, although some other habits can be serious to people's lives without his conscious. Here are some lifestyle tips to overcome the infection of TB and elevate the healing progression:

1- Rest and Recovery:

Adequate Sleep: Ensure sufficient rest and maintain a regular sleep schedule to help the body recover and strengthen the immune system.
Avoid Overexertion: Limit strenuous activities, especially during the intensive phase of treatment, to conserve energy.

2- Avoid Alcohol and Tobacco:

- **No Alcohol**: Avoid alcohol as it can interfere with TB medications, particularly isoniazid and rifampicin, and increase the risk of liver damage.
- **Quit Smoking**: Smoking can worsen lung damage and impair the immune response.

3- Stress Management:

- **Reduce Stress**: Engage in relaxation techniques such as deep breathing exercises, meditation, or gentle activities like yoga to reduce stress, which can weaken the immune system.

4- Infection Control:

- **Good Hygiene**: Practice good personal hygiene, such as covering the mouth when coughing or sneezing, to reduce the spread of TB bacteria.
- **Ventilation**: Ensure living spaces are well-ventilated to reduce the concentration of airborne TB bacteria.
- **Isolation When Necessary**: In the initial stages of active TB, minimize contact with others to prevent transmission.

Prevention and Control

Primary, secondary, and tertiary prevention strategies

Primary prevention is summarized within some pioneering points to prevent the incidences that lead to worsening the case and decreasing the healing rates.

1- Vaccination:

BCG Vaccine: The Bacillus Calmette-Guérin (BCG) vaccine is used in many countries to protect against TB, particularly severe forms such as TB meningitis and disseminated TB in children. Its effectiveness in preventing pulmonary TB in adults is less well-established.

2- Health Education:

- **Public Awareness**: Educate communities about TB, its transmission, and preventive measures. This includes promoting good respiratory hygiene, such as covering coughs and sneezes, and the importance of regular health check-ups.

3- Control of Risk Factors:

- **Addressing Social Determinants**: Improve living conditions, nutrition, and access to healthcare to reduce the risk of TB infection. This includes reducing overcrowding and improving ventilation in housing.

Second prevention is the stage following the infection stage and it is demonstrated in the ways of coping with the disease and how to resist its spreading at the same time.

1- **Early Diagnosis and Treatment**:

- **Prompt Medical Care**: Encourage early diagnosis and treatment of TB to reduce the duration of infectiousness and prevent complications. This involves using diagnostic tools such as sputum smear microscopy, culture, and molecular tests

2- **Latent TB Infection (LTBI) Treatment**:

- **Preventive Therapy**: Provide preventive treatment for individuals with latent TB infection, particularly those at high risk of developing active TB, such as those with compromised immune systems.

3- **Infection Control Measures**:

- **Isolation**: Isolate individuals with active TB, especially in healthcare settings, to prevent the spread of TB bacteria to others.
- **Respiratory Protection**: Use appropriate personal protective equipment (PPE) and implement infection control measures in healthcare facilities.

Public Health interventions

WHO has made several efforts to control TB and prevent it from becoming an epidemic once again. One of them is their intention to have 0 TB deaths by 2030, A world free of TB deaths. Moreover, they intend to cut deaths by 90% and new cases by 80% additionally, ensuring that no family is burdened with catastrophic costs due to TB by 2030. The organization began in 1997 by making international reports annually.

Vaccination and Screening Programs

WHO began with newborns and children due to their high percentage of exposure to the disease owing to their weak immunity. One of the effective vaccinations for children against this disease is the "**Bacillus Calmette-Guérin (BCG) Vaccine"** (**BCG**). The organization noticed that TB spread among children and newborns within poor and medium-income countries. This vaccination had excellent results with children, and it was highly effective, on the other hand, they found that it wasn't effective with most adults as a result, they dedicated it to high-risk cases of adults with different therapies based on the complications of the case.

This vaccine was safe for most people without facing any side effects, but generally, any vaccination may exclude some people from this role. Consequently, they found that some people face

Reddish of their skin temporarily
Small Bump or Nodule: A small bump or nodule often forms at the injection site within 2-3

weeks and can persist for several weeks.These are light side effects not serious to their lives.

Prognosis

Disease outcomes and Survival rates

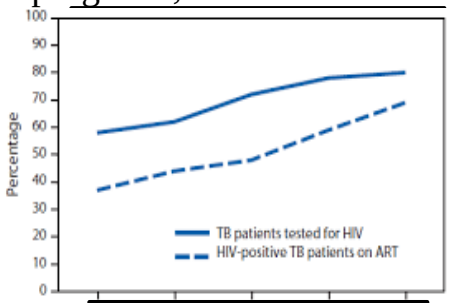
The outcomes and survival rates of tuberculosis (TB) vary significantly based on several factors, including the type of TB (pulmonary or extrapulmonary), the patient's overall health, the presence of drug resistance, timely diagnosis, and the effectiveness of treatment. Here's an overview of the general outcomes and survival rates for TB:

1- Successful Treatment:

- **Cure and Treatment Completion**: The most favorable outcome is a complete cure or treatment completion, which means the patient has completed the prescribed course of antibiotics and is free of TB.

- **Success Rates**: In most countries with effective TB control programs, the treatment success rate for drug-susceptible TB is around 85-90%.

2- Immunity efficiency: this factor is considered one of the most important items of multiples of survival rates, according to WHO HIV is indeed related to TB infection and this is demonstrated in the next table



HIV & TB relation

Factors Influencing Prognosis

We have mentioned before about the strong relation between the immune system and the infection of TB especially, HIV infections because it is one of the threats to the immune system's strength besides, some other factors influence the exposure of this disease rather than the immunity

Age: **Children and Elderly,** these age groups are at higher risk for severe TB and complications. Children are more susceptible to TB meningitis and miliary TB, while the elderly may have comorbidities that affect prognosis.

Geographical Location:

- **High-Burden Areas**: Living in areas with high TB prevalence increases the risk of exposure and infection, and these regions may have limited healthcare resources.

Current research and Future directions

Recent advanced discoveries

Recent advancements in tuberculosis (TB) research have focused on improving diagnostics, treatments, vaccines, and understanding the disease's molecular and immunological mechanisms. Here are some of the most notable recent discoveries and advancements related to TB:

1- GeneXpert MTB/RIF Ultra:

Improved Sensitivity: The GeneXpert MTB/RIF Ultra is an enhanced version of the widely used GeneXpert MTB/RIF test. It offers improved sensitivity for detecting Mycobacterium tuberculosis, especially in patients with low bacterial loads and in pediatric cases.

Rapid Detection: It also provides rapid detection of rifampicin resistance, which is a key indicator of multidrug-resistant TB (MDR-TB).

2- Blood-Based Biomarkers:

- **Non-Sputum Tests**: Research is ongoing to identify blood-based biomarkers that can diagnose TB without the need for sputum samples. This is particularly useful for diagnosing TB in children and individuals who cannot produce sputum.
- **Predictive Value**: These biomarkers are also being studied for their potential to predict treatment response and relapse.

3- New Drug Regimens:

- **Bedaquiline and Delamanid**: These newer anti-TB drugs have shown promise in treating MDR-TB and extensively drug-resistant TB (XDR-TB). They are included in combination regimens to shorten treatment duration and improve outcomes.
- **Shortened Regimens**: Trials of shorter, all-oral regimens for drug-resistant TB, such as the BPaL regimen (Bedaquiline, Pretomanid, and Linezolid), have shown success in reducing treatment duration from years to months.

Ongoing Clinical trials
Future research need

Ongoing clinical trials for tuberculosis (TB) focus on various aspects such as new drug development, vaccine efficacy, diagnostic methods, and treatment strategies. Here are some notable ongoing clinical trials:

Drug Development and Treatment Regimens

- **BPaL Regimen (Bedaquiline, Pretomanid, Linezolid)**:
- **Trial Focus**: Evaluating the efficacy and safety of the BPaL regimen for treating extensively drug-resistant TB (XDR-TB) and multidrug-resistant TB (MDR-TB).
- **Significance**: This regimen aims to shorten the treatment duration and improve outcomes for patients with drug-resistant TB.
- **New Drug Combinations**:
- **Trials**: Several trials are investigating combinations of new and existing TB drugs to find shorter, more effective treatment regimens. Examples include combinations involving Bedaquiline, Delamanid, Pretomanid, and Linezolid.

Study case

Case Overview

Objective: To assess the efficacy and safety of a new 4-month all-oral TB treatment regimen in patients with drug-sensitive TB.

Location: Russia

Participants: 150 adults with newly diagnosed drug-sensitive pulmonary TB

Case Details

Patient Profile**:**

- Name: Ahmed Mohamed
- Age: 32
- Occupation: Farmer

- Background: Ahmed lives in a rural area of Russia. He has recently been diagnosed with drug-sensitive pulmonary TB after experiencing persistent cough, fever, and weight loss. He is generally healthy but has limited access to healthcare facilities due to his remote location.

The Study:

- Study Design: Ahmed is enrolled in a clinical trial evaluating a new 4-month treatment regimen that combines Bedaquiline, Linezolid, and Rifapentine. This regimen is compared to the standard 6-month treatment regimen that includes Isoniazid, Rifampin, Ethambutol, and Pyrazinamide.

- **Initial Steps**:

Consent and Enrollment: Ahmed provides informed consent to participate in the trial. He undergoes initial health assessments to confirm eligibility.

Randomization: Ahmed is randomly assigned to receive the new 4-month regimen.

Treatment Commencement: He starts the new treatment regimen and is provided with medication and instructions for adherence.

During the Trial:

- **Monitoring and Support**:

Regular Visits: Ahmed visits the local clinic every two weeks for monitoring. Healthcare workers track his progress, manage side effects, and ensure adherence to the treatment.

Adherence Support: He receives counseling and support to help him adhere to the medication regimen. Mobile health tools are used to remind him of his medication schedule.