

# A Review on Tuberculosis [TB], its Control and Management

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**Abstract:** Tuberculosis (TB) is a human disease caused by *Mycobacterium tuberculosis*. It mainly affects the lungs, making pulmonary disease the most common presentation. Other commonly affected organ systems include the respiratory system, the gastrointestinal (GI) system, the lymphoreticular system, the skin, the central nervous system, the musculoskeletal system, the reproductive system, and the liver. In the past few decades, there has been a concerted global effort to eradicate tuberculosis. Despite the gains in tuberculosis control and the decline in both new cases and mortality, it still accounts for a huge burden of morbidity and mortality worldwide. This activity reviews the evaluation and management of tuberculosis and highlights the role of interprofessional team members in collaborating to provide well-coordinated care and enhance outcomes for affected patients.

**Keywords:** *Mycobacterium*, Gastrointestinal system, Lymphoreticular system, Musculoskeletal.

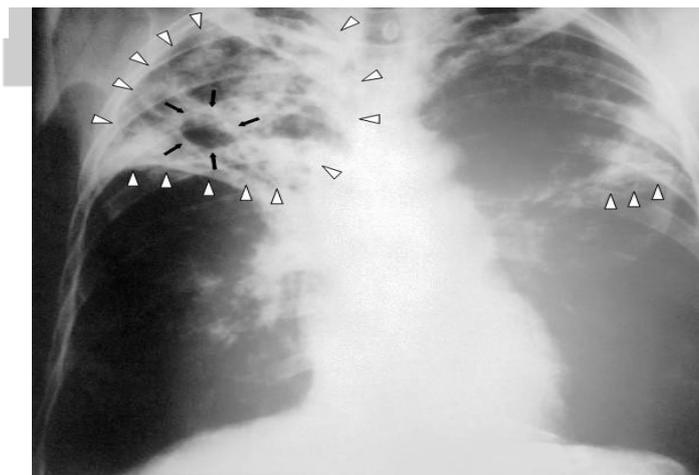
## Introduction:

Tuberculosis (TB) is an ancient human disease caused by *Mycobacterium tuberculosis* which mainly affects the lungs, making pulmonary disease the most common presentation (K Zaman, 2010) <sup>[1]</sup> However, TB is a multi-systemic disease with a protean presentation. The organ system most commonly affected include the respiratory system, the gastrointestinal (GI) system, the lymphoreticular system, the skin, the central nervous system, the musculoskeletal system, the reproductive system, and the liver <sup>[2,3]</sup>.

Despite the gains in tuberculosis control and the decline in both new cases and mortality, TB still accounts for a huge burden of morbidity and mortality worldwide. The bulk of the global burden of new infection and tuberculosis death is borne by developing countries with 6 countries, India, Indonesia, China, Nigeria, Pakistan, and South Africa, accounting for 60% of TB death in 2015, (WHO, 2017) <sup>[4]</sup>.

Tuberculosis remains a significant cause of both illness and death in developed countries especially among individuals with a suppressed immune system <sup>[5, 6]</sup>. People with HIV are particularly vulnerable to death due to tuberculosis. Tuberculosis accounted for 35% of global mortality in individuals with HIV/AIDS in 2015. (W.H.O, 2017). Children are also vulnerable, and tuberculosis was responsible for one million illnesses in children in 2015 according to the WHO.

In the past few decades, there has been a concerted global effort to eradicate TB. These efforts had yielded some positive dividends especially since 2000 when the World Health Organization (WHO, 2017) estimated that that global incidence rate for tuberculosis has fallen by 1.5% every year. Furthermore, mortality arising from tuberculosis has significantly and steadily declined. The World Health Organization (WHO, 2016) reports a 22% drop in global TB mortality from 2000 through 2015.



Tuberculosis is spread from one person to the next through the air when people who have active TB in their lungs cough, spit, speak, or sneeze <sup>[7,10]</sup>. People with latent TB do not spread the disease. Active infection occurs more often in people with HIV/AIDS and in those who smoke. Diagnosis of active TB is based on chest X-rays, as well as microscopic examination and culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) or blood tests. <sup>[11]</sup>



## HISTORY OF TUBERCULOSIS

### Geographic Distribution

Tuberculosis is present globally<sup>[9]</sup>. However; developing countries account 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 unacceptably high burden of tuberculosis.

In more advanced countries, high burden tuberculosis is seen among recent arrivals from tuberculosis-endemic zones, health care workers, and HIV-positive individuals. 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. Drugs in this category include infliximab, adalimumab, etanercept, and golimumab. Patients using any of these medications should be monitored for tuberculosis before and during the period of drug treatment.

### Etiology

*M. tuberculosis* causes tuberculosis. *M. tuberculosis* is an alcohol and acid-fast bacillus. It is part of a group of organisms classified as the *M. tuberculosis* complex. Other members of this group are, *Mycobacterium africanum*, *Mycobacterium bevis*, and *Mycobacterium microti*<sup>[9]</sup>. Most other mycobacterium organisms are classified as non-tuberculous or atypical mycobacterium organisms.

*M. tuberculosis* is a non-spore forming, non-motile, obligate-aerobic, facultative, catalase negative, intracellular bacteria. The organism is neither gram-positive nor gram-negative because of very poor reaction with the Gram stain. Weakly positive cells can sometimes be demonstrated on Gram stain, a phenomenon known as "ghost cells."

The organism has several unique features compared to other bacteria such as the presence of several lipids in the cell wall including mycolic acid, cord factor, and Wax-D. The high lipid content of the cell wall is thought to contribute the following properties of *M. tuberculosis* infection:

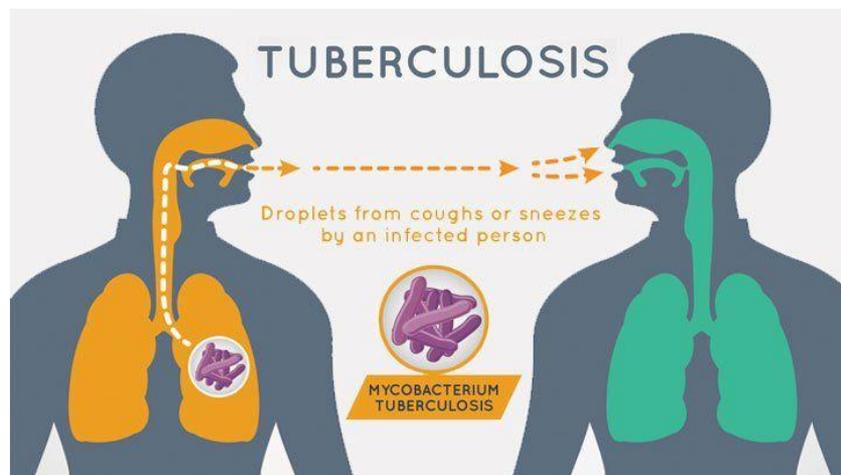
- Resistance to several antibiotics
- Difficulty staining with Gram stain and several other stains
- Ability to survive under extreme conditions such as extreme acidity or alkalinity, low oxygen situation and intracellular survival (within the macrophage)

The Ziehl-Neelsen stain is one of the most commonly used stains to diagnose T.B. The sample is initially stained with carbol fuchsin (pink color stain), decolorized with acid-alcohol and then counter-stained with another stain (usually, blue colored methylene blue). A positive sample would retain the pink color of the original carbol fuchsin, hence the designation, alcohol and acid-fast bacillus (AAFB).

### Tuberculosis Risk Factors

You could be more likely to get TB if:

- A friend, co-worker, or family member has active TB.
- You live in or have travelled to an area where TB is common, like Russia, Africa, Eastern Europe, Asia, Latin America, and the Caribbean.
- You're part of a group in which TB is more likely to spread, or you work or live with someone who is. This includes homeless people, people who have HIV, people in jail or prison, and people who inject drugs into their veins.
- You work or live in a hospital or nursing home.
- You're a health care worker for patients at high risk of TB.
- You're a smoker.



A healthy immune system fights the TB bacteria. But you might not be able to fend off active TB disease if you have:

- HIV or AIDS
- Diabetes
- Severe kidney disease
- Head and neck cancers
- Cancer treatments such as chemotherapy
- Low body weight and poor nutrition
- Medications for organ transplants
- Certain drugs to treat rheumatoid arthritis, Crohn's disease, and psoriasis

Babies and young children also have higher chances of getting it because their immune systems aren't fully formed.

#### Tuberculosis Transmission

When someone who has TB coughs, sneezes, talks, laughs, or sings, they release tiny droplets that contain the germs. If you breathe in these germs, you can get it.

TB isn't easy to catch. You usually have to spend a long time around someone who has a lot of the bacteria in their lungs. You're most likely to catch it from co-workers, friends, and family members.

Tuberculosis germs don't thrive on surfaces. You can't get it from shaking hands with someone who has it or by sharing their food or drink.

#### Other Major Risk Factors

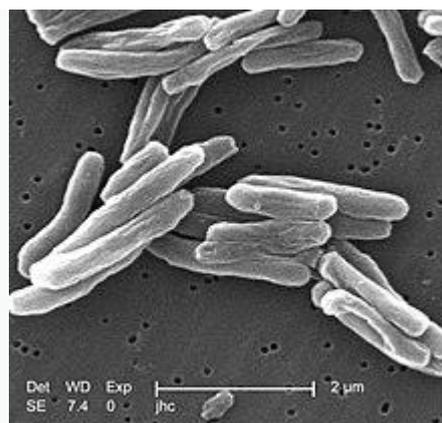
- Socio-economic factors: Poverty, malnutrition, wars
- Immunosuppression: HIV/AIDS, chronic immunosuppressive therapy (steroids, monoclonal antibodies against tumor necrotic factor), a poorly developed immune system (children, primary immunodeficiency disorders)
- Occupational: Mining, construction workers, pneumoconiosis (silicosis)

#### Tuberculosis Causes

Tuberculosis is caused by bacteria that spread through the air, just like a cold or the flu. You can get TB only if you come into contact with people who have it.

Mycobacteria

Main article: Mycobacterium tuberculosis



### Scanning electron micrograph of *M. tuberculosis*

The main cause of TB is *Mycobacterium tuberculosis* (MTB), a small, aerobic, nonmotile bacillus. The high lipid content of this pathogen accounts for many of its unique clinical characteristics.<sup>[23]</sup> It divides every 16 to 20 hours, which is an extremely slow rate compared with other bacteria, which usually divide in less than an hour.<sup>[24]</sup> Mycobacteria have an outer membrane lipid bilayer.<sup>[25]</sup> If a Gram stain is performed, MTB either stains very weakly "Gram-positive" or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall.<sup>[26]</sup> MTB can withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of a host organism, but *M. tuberculosis* can be cultured in the laboratory.<sup>[27]</sup>

Using histological stains on expectorated samples from phlegm (also called "sputum"), scientists can identify MTB under a microscope. Since MTB retains certain stains even after being treated with acidic solution, it is classified as an acid-fast bacillus.<sup>[14,26]</sup> The most common acid-fast staining techniques are the Ziehl–Neelsen stain<sup>[28]</sup> and the Kinyoun stain, which dye acid-fast bacilli a bright red that stands out against a blue background.<sup>[29]</sup> Auramine-rhodamine staining<sup>[30]</sup> and fluorescence microscopy<sup>[31]</sup> are also used.

The *M. tuberculosis* complex (MTBC) includes four other TB-causing mycobacteria: *M. bovis*, *M. africanum*, *M. canetti*, and *M. microti*.<sup>[32]</sup> *M. africanum* is not widespread, but it is a significant cause of tuberculosis in parts of Africa.<sup>[33,34]</sup> *M. bovis* was once a common cause of tuberculosis, but the introduction of pasteurized milk has almost completely eliminated this as a public health problem in developed countries.<sup>[14,35]</sup> *M. canetti* is rare and seems to be limited to the Horn of Africa, although a few cases have been seen in African emigrants.<sup>[36,37]</sup> *M. microti* is also rare and is seen almost only in immunodeficient people, although its prevalence may be significantly underestimated.<sup>[38]</sup>

Other known pathogenic mycobacteria include *M. leprae*, *M. avium*, and *M. kansasii*. The latter two species are classified as "nontuberculous mycobacteria" (NTM). NTM cause neither TB nor leprosy, but they do cause lung diseases that resemble TB.<sup>[39]</sup>

### 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-tuberculous 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.

#### XDR-TB

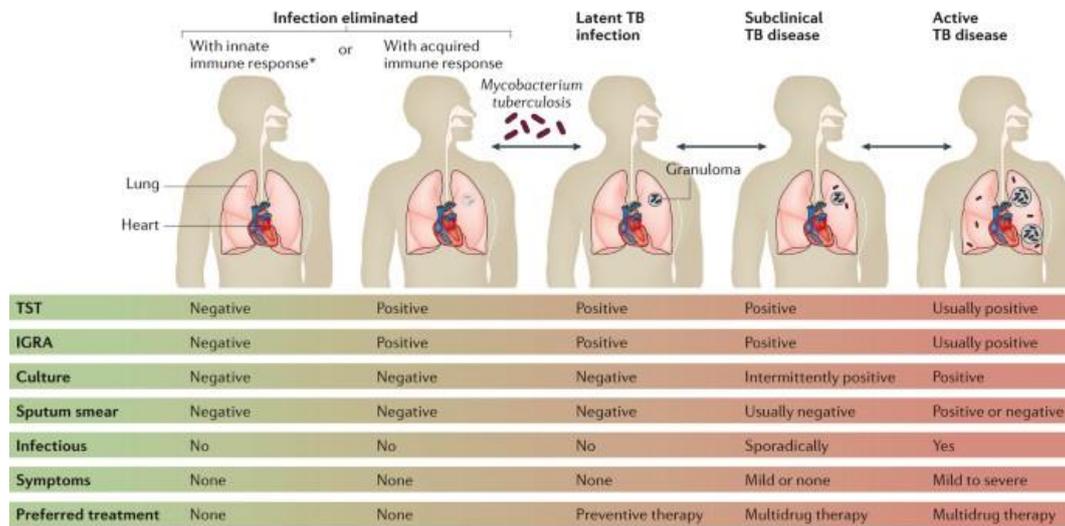
- This is a more severe type of MDR-TB. Diagnosis requires resistance to at least four anti-tuberculous medications including resistance to Rifampicin, Isoniazid, and resistance to any two of the newer anti-tuberculous medications. The newer medications implicated in XDR-TB are the fluoroquinolones (Levofloxacin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

### TYPES OF TUBERCLULOSIS

A TB infection doesn't always mean you'll get sick. There are two forms of the disease:

- **Latent TB.** You have the germs in your body, but your immune system keeps them from spreading. You don't have any symptoms, and you're not contagious. But the infection is still alive and can one day become active. If you're at high risk for re-activation -- for instance, if you have HIV, you had an infection in the past 2 years, your chest X-ray is unusual, or your immune system is weakened -- your doctor will give you medications to prevent active TB.
- **Active TB.** The germs multiply and make you sick. You can spread the disease to others. Ninety percent of active cases in adults come from a latent TB infection.

A latent or active TB infection can also be **drug-resistant**, meaning certain medications don't work against the bacteria.



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## Tuberculosis Signs and Symptoms

Latent TB doesn't have symptoms. A skin or blood test can tell if you have it;



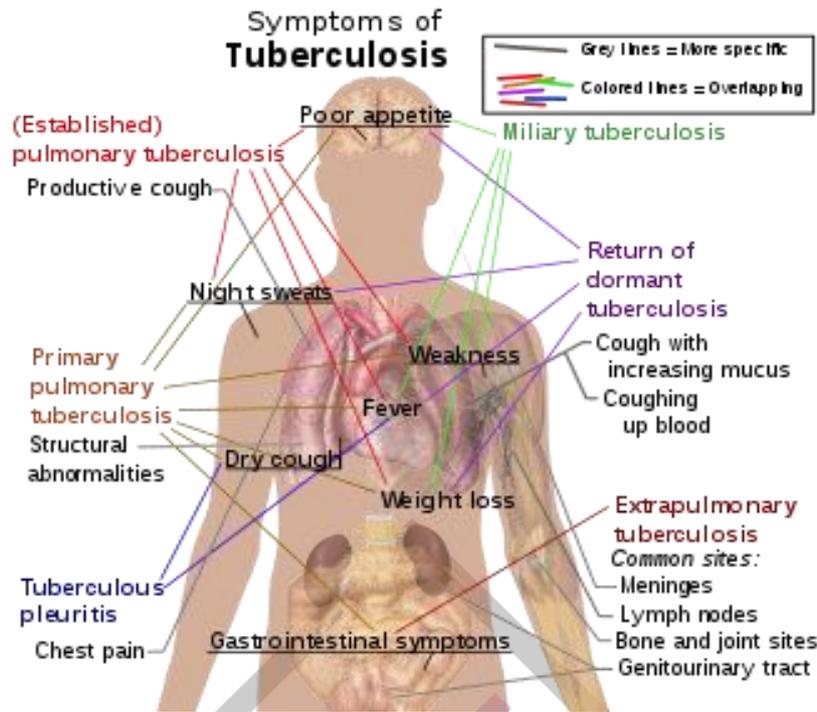
- A cough that lasts more than 3 weeks
- Chest pain
- Coughing up blood
- Feeling tired all the time
- Night sweats
- Chills
- Fever
- Loss of appetite
- Weight loss

## Pulmonary

If a tuberculosis infection does become active, it most commonly involves the lungs (in about 90% of cases).<sup>[35,37]</sup> Symptoms may include chest pain and a prolonged cough producing sputum. About 25% of people may not have any symptoms (i.e. they remain "asymptomatic").<sup>[35]</sup> Occasionally, people may cough up blood in small amounts, and in very rare cases, the infection may erode into the pulmonary artery or a Rasmussen's aneurysm, resulting in massive bleeding.<sup>[33,19]</sup> Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs. The upper lung lobes are more frequently affected by tuberculosis than the lower ones. The reason for this difference is not clear.<sup>[38]</sup> It may be due to either better air flow,<sup>[38]</sup> or poor lymph drainage within the upper lungs:

## Extrapulmonary

In 15–20% of active cases, the infection spreads outside the lungs, causing other kinds of TB.<sup>[39]</sup> These are collectively denoted as "extrapulmonary tuberculosis". Extrapulmonary TB occurs more commonly in people with a weakened immune system and young children. In those with HIV, this occurs in more than 50% of cases.<sup>[40]</sup> Notable extrapulmonary infection sites include the pleura (in tuberculous pleurisy), the central nervous system (in tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (in urogenital tuberculosis), and the bones and joints (in Pott disease of the spine), among others. A potentially more serious, widespread form of TB is called "disseminated tuberculosis", it is also known as miliary tuberculosis.<sup>[33]</sup> Miliary TB currently makes up about 10% of extrapulmonary cases.<sup>[41]</sup>



If you have any of these symptoms, see your doctor to get tested. Get medical help right away if you have chest pain.

**Tuberculosis Tests and Diagnosis**

There are two common tests for tuberculosis:

**Skin test**

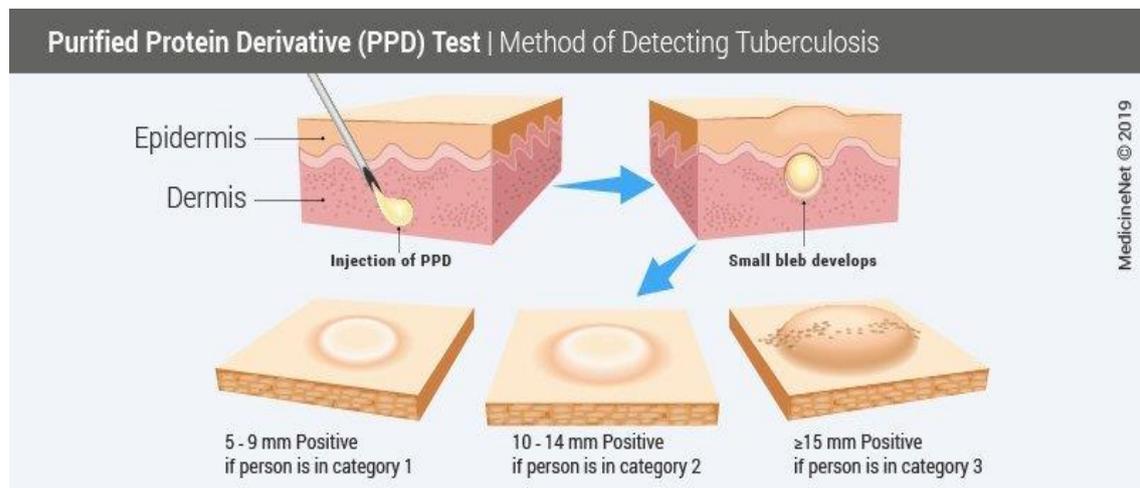
Your doctor can use a purified protein derivative (PPD) skin test to determine if you're infected with the TB bacteria.

For this test, your doctor will inject 0.1 milliliter of PPD (a small amount of protein) under the top layer of your skin. Between two and three days later, you must return to your doctor's office to have the results read. If there is a welt on your skin over 5 millimeters (mm) in size where the PPD was injected, you may be TB-positive. This test will tell you whether you have a TB infection; it doesn't tell you whether you have active TB disease.

Reactions between 5 to 15 mm in size can be considered positive depending on risk factors, health, and medical history. All reactions over 15 mm are considered positive regardless of risk factors.

However, the test isn't perfect. Some people don't respond to the test even if they have TB, and others respond to the test and don't have TB. People who've recently received the TB vaccine may test positive but not have TB infection.

This is also known as the Mantoux tuberculin skin test. A technician injects a small amount of fluid into the skin of your lower arm. After 2 or 3 days, they'll check for swelling in your arm. If your results are positive, you probably have TB bacteria. But you could also get a false positive. If you've gotten a tuberculosis vaccine called bacillus Calmette-Guerin (BCG), the test could say that you have TB when you really don't. The results can also be false negative, saying that you don't have TB when you really do, if you have a very new infection. You might get this test more than once



### Blood test

You doctor can use a blood test to follow up on TB skin results. The blood test may also be preferred over the skin test with certain health conditions or for specific groups of people. The two TB blood tests currently approved in the United States are QuantiFERON and T-Spot. Blood test results are reported as positive, negative, or indeterminate. Like the skin test, the blood test can't indicate whether or not you have active TB disease.

These tests, also called interferon-gamma release assays (IGRAs), measure the response when TB proteins are mixed with a small amount of your blood.

Those tests don't tell you if your infection is latent or active. If you get a positive skin or blood test, your doctor will learn which type you have with:



### CHEST X-RAY

If your skin test or blood test is positive, you will likely be sent for a chest X-ray, which looks for certain small spots in your lungs. These spots are a sign of TB infection and indicate that your body is trying to isolate the TB bacteria. If your chest X-ray is negative, you likely have latent TB. It is also possible your test results were incorrect and other testing may be necessary.

If the test indicates you have active TB disease, you will begin treatment for active TB. Otherwise, you will likely need to be treated for latent TB to prevent the bacteria from reactivating and making you and others sick in the future.

- A chest X-ray or CT scan to look for changes in your lungs
- Acid-fast bacillus (AFB) tests for TB bacteria in your sputum, the mucus that comes up when you cough

### OTHER TESTS

Your doctor may also order tests on your sputum or mucus, extracted from deep inside your lungs, to check for TB bacteria. If your sputum tests positive, this means you can infect others with the TB bacteria and should wear a special mask until after you've started treatment and your sputum tests negative for TB.

Other tests such as a CT scan of the chest, bronchoscopy, or lung biopsies may be required if other test results remain unclear.

## Treatment of tuberculosis

Many bacterial infections are treated with antibiotics for a week or two, but TB is different. People diagnosed with active TB disease generally have to take a combination of medications for six to nine months. The full treatment course must be completed. Otherwise, it's highly likely a TB infection could come back. If TB does recur, it may be resistant to previous medications and be much more difficult to treat.

Your doctor may prescribe multiple medications because some TB strains are resistant to certain drug types. The most common combinations of medications for active TB disease include:

### Treatment / Management

#### First-line Medications, Group 1

DRUGS NAME	Adults/children	Dosage[mg/kg]	Days
• Isoniazid	Adults(max)	5mg/kg(300mg)	Daily
	Adults(max)	15mg/kg(900mg)	Once, twice, three times weekly.
	Children(max)	10-15mg/kg(300mg)	Daily
	Children(max)	20-30mg/kg(900)	Twice weekly
• Rifampicin	Adults(max)	10mg/kg(600mg)	Once daily twice weekly, or three times weekly.
	Children(max)	10-20mg/kg(600mg)	Once daily or twice weekly.
• Rifabutine	Adults(max)	5mg/kg(300mg)	Daily, twice, or three times weekly.
	Children(max)	unknown	-
• Rifapentine	Adults(max)	10mg/kg(600)	Once weekly(continuation phase of treatment)
	Children	Not approved for children	-
• Pyrazinamide	Adult	20-25mg/kg	Per day

• Ethambutol	Adults(max)	15-20mg/kg	Per day
	Children(max)	15-20mg/kg	Per day(2.5g)
		50mg/kg	Twice weekly (2.5g)

#### Isoniazid -

Tablets (50 mg, 100 mg, 300 mg); syrup (50 mg/5 ml); aqueous solution (100 mg/ml) for IV or IM injection.

Preparations.

#### Rifampicin -

Capsules (150 mg, 300 mg)

Preparations.

#### Rifabutin-

Capsules (150 mg) for oral administration.

Preparations:

#### Rifapentine -

Tablet (150 mg, film-coated).

Preparation.

#### Pyrazinamide -

Tablets (500 mg).

Preparations.

#### Ethambutol -

The drug can be used safely in older children but should be used with caution in children in whom visual acuity cannot be monitored (generally less than 5 years of age) (66). In younger children, EMB can be used if there is a concern with resistance to INH or RIF. Preparations. Tablets (100 mg, 400 mg) for oral administration.

Isoniazid and Rifampicin follow a 4-drug regimen (usually including Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide) for 2 months or six months. Vitamin B6 is always given with Isoniazid to prevent neural damage (neuropathies).

Several other antimicrobials are effective against tuberculosis including the following categories:

### **Second-Line Anti-tuberculosis Drugs, Group 2**

Injectables aminoglycosides and injectable polypeptides

#### **Injectable aminoglycosides**

- Amikacin
- Kanamycin
- Streptomycin

#### **Injectable polypeptides**

- Capreomycin
- Viomycin

### **Second-Line Anti-Tuberculosis Drugs, Group 3, Oral and Injectable Fluoroquinolones**

#### **Fluoroquinolones**

- Levofloxacin
- Moxifloxacin
- Ofloxacin
- Gatifloxacin

### **Second-Line Anti-tuberculosis Drugs, Group 4**

- Para-aminosalicylic acid
- Cycloserine
- Terizidone
- Ethionamide
- Prothionamide
- Thioacetazone
- Linezolid

These particular medications can affect your liver, so people taking TB medications should be aware of liver-injury symptoms, such as:

- appetite loss
- dark urine
- fever lasting longer than three days
- unexplained nausea or vomiting
- jaundice, or yellowing of the skin
- abdominal pain

Notify your doctor immediately if you experience any of these symptoms. You should also have your liver function checked with frequent blood tests while taking these medications.

#### **Medication and Side Effects of TB**

**Like any medication, TB drugs can have side effects.**

Common isoniazid side effects include:

- Numbness and tingling in your hands and feet
- Upset stomach, nausea, and vomiting
- Loss of appetite
- Weakness

Ethambutol side effects may include:

- Chills
- Painful or swollen joints
- Belly pain, nausea, and vomiting
- Loss of appetite
- Headache
- Confusion

Some pyrazinamide side effects include:

- Lack of energy
- Nausea and vomiting
- Loss of appetite
- Muscle or joint pain

Common rifampin side effects include:

- Skin rash
- Upset stomach, nausea, and vomiting
- Diarrhea
- Loss of appetite
- Inflamed pancreas

### Prevention of Tuberculosis

Most people in high-risk regions around the world receive TB vaccinations as children. The vaccine is called Bacillus Calmette-Guerin, or BCG, and protects against only some TB strains. The vaccine isn't commonly given in the United States.

Having the TB bacteria doesn't necessarily mean you'll have symptoms of active TB. If you do have the infection and don't show symptoms, you likely have latent TB. Your doctor may recommend a shorter course of antibiotics to keep it from developing into active TB disease. Common medications for latent TB include isoniazid, rifampin, and rifapentine, which may need to be taken for three to nine months, depending on the medications and combinations used.

People who've been diagnosed with active TB should avoid crowds until they are no longer contagious. According to WHO Trusted Source, people with active TB can infect 10 to 15 people through close contact per year if they don't take precautions.

People who are infected with active TB should also wear a surgical mask, known as a respirator, to keep TB particles from spreading through the air.

It's best that a person with active TB avoid contact with others and continuing wearing a mask until instructed otherwise by their doctor.

### Tuberculosis Complications

Tuberculosis infection can cause complications such as:

- Joint damage
- Lung damage
- Infection or damage of your bones, spinal cord, brain, or lymph nodes
- Liver or kidney problems
- Inflammation of the tissues around your heart

#### Tuberculosis Prevention

To help stop the spread of TB:

- If you have a latent infection, take all of your medication so it doesn't become active and contagious.
- If you have active TB, limit your contact with other people. Cover your mouth when you laugh, sneeze, or cough. Wear a surgical mask when you're around other people during the first weeks of treatment.
- If you're travelling to a place where TB is common, avoid spending a lot of time in crowded places with sick people.

## CONCLUSIONS

As is evident from the above discussion, we have come a long way in our fight against this deadly disease, but as the famous English poet Robert Frost said, "... miles to go before I sleep", we still have miles to go before we will make this planet TB free. WHO with its "STOP TB" strategy has given a vision to eliminate TB as a public health problem from the face of this earth by 2050. In order to intensify our fight against this deadly disease, we need to further strengthen our surveillance programs to accurately estimate the burden of all kinds of TB (childhood, HIV/TB, MDR-TB). There is dire need to regulate the rational use of first- and second-line anti-TB drugs. They should absolutely not be sold as over the counter drugs. In India and in other developing countries, local governments should put in and encourage wholehearted efforts for local manufacturing of anti-TB drugs, thus resulting in more efficient monitoring of their manufacturing and quality control standards. Monitoring the quality of products available in the marketplace should involve identifying products that are defective because of poor manufacturing practices; deteriorated because of inadequate distribution and storage; and adulterated, tampered or counterfeit because of vested interests. Many studies have documented the circulation of counterfeit and substandard medicines, especially antimalarials, in developing countries. If counterfeit drugs belonging to this category are circulating in the markets, then there is every reason to assume that the counterfeit anti-TB drugs are also available in these markets.

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