

## Review on Tuberculosis

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### I. Introduction

Tuberculosis (TB) is a potentially serious infectious disease that mainly affects the lungs. The bacteria that cause tuberculosis are spread from person to person through tiny droplets released into the air via coughs and sneezes.

Once rare in developed countries, tuberculosis infections began increasing in 1985, partly because of the emergence of HIV, the virus that causes AIDS. HIV weakens a person's immune system, so it can't fight the TB germs. In the United States, because of stronger control programs, tuberculosis began to decrease again in 1993. But it remains a concern.

Many tuberculosis strains resist the drugs most used to treat the disease. People with active tuberculosis must take many types of medications for months to get rid of the infection and prevent antibiotic.

### Symptoms

Although your body can harbor the bacteria that cause tuberculosis, your immune system usually can prevent you from becoming sick. For this reason, doctors make a distinction between:

- **Latent TB.** You have a TB infection, but the bacteria in your body are inactive and cause no symptoms. Latent TB, also called inactive TB or TB infection, isn't contagious. Latent TB can turn into active TB, so treatment is important.
- **Active TB.** Also called TB disease, this condition makes you sick and, in most cases, can spread to others. It can occur weeks or years after infection with the TB bacteria.

Signs and symptoms of active TB include:

- Coughing for three or more weeks
- Coughing up blood or mucus
- Chest pain, or pain with breathing or coughing
- Unintentional weight loss
- Fatigue
- Fever
- Night sweats
- Chills
- Loss of appetite

### Causes

Tuberculosis is caused by bacteria that spread from person to person through microscopic droplets released into the air. This can happen when someone with the untreated, active form of tuberculosis coughs, speaks, sneezes, spits, laughs or sings.

Although tuberculosis is contagious, it's not easy to catch. You're much more likely to get tuberculosis from someone you live or work with than from a stranger. Most people with active TB who've had appropriate drug treatment for at least two weeks are no longer contagious.

### HIV and TB

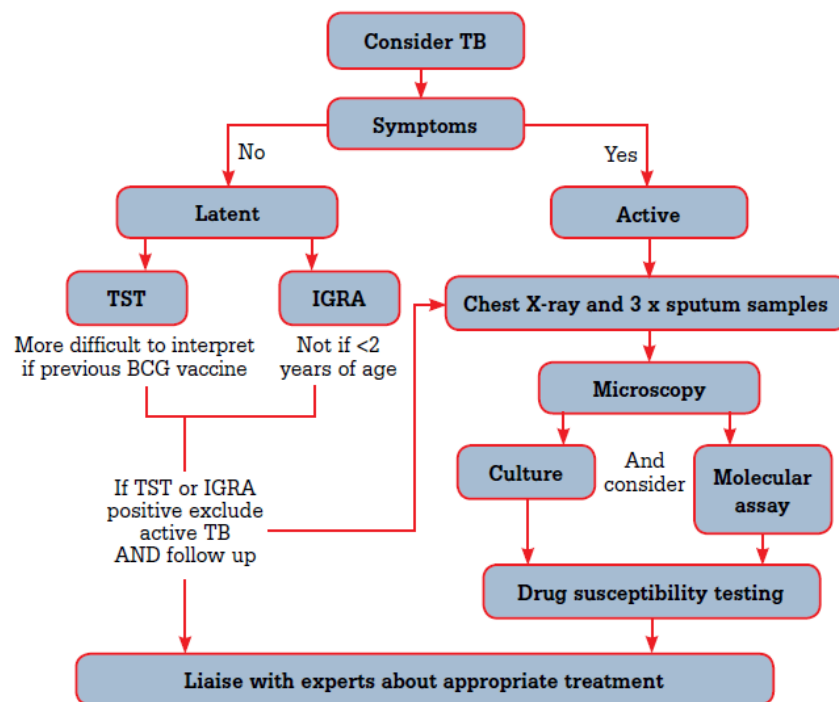
Since the 1980s, tuberculosis cases have increased dramatically because of the spread of HIV, the virus that causes AIDS. HIV suppresses the immune system, making it difficult for the body to control TB bacteria. As a result, people with HIV are much more likely to get TB and to progress from latent to active disease than are people who aren't HIV positive.

### Drug-resistant TB

Tuberculosis also remains a major killer because of the increase in drug-resistant strains. Over time, some TB germs have developed the ability to survive despite medications. This is partly because people don't take their drugs as directed or don't complete the course of treatment.

Drug-resistant strains of tuberculosis emerge when an antibiotic fails to kill all of the bacteria it targets. The surviving bacteria become resistant to that drug and often other antibiotics as well. Some TB bacteria have developed resistance to the most commonly used treatments, such as isoniazid and rifampin (Rifadin, Rimactane).

Some TB strains have also developed resistance to drugs less commonly used in TB treatment, such as the antibiotics known as fluoroquinolones, and injectable medications including amikacin and capreomycin (Capastat). These medications are often used to treat infections that are resistant to the more commonly used drugs



### Risk factors

Anyone can get tuberculosis, but certain factors can increase your risk, including:

#### Weakened immune system

A healthy immune system often successfully fights TB bacteria. However, several conditions and medications can weaken your immune system, including:

- HIV/AIDS
- Diabetes
- Severe kidney disease
- Certain cancers
- Cancer treatment, such as chemotherapy
- Drugs to prevent rejection of transplanted organs
- Some drugs used to treat rheumatoid arthritis, Crohn's disease and psoriasis
- Malnutrition or low body weight
- Very young or advanced age

#### Other factors

- **Using substances.** IV drugs or excessive alcohol use weakens your immune system and makes you more vulnerable to tuberculosis.
- **Using tobacco.** Tobacco use greatly increases the risk of getting TB and dying of it.

- **Working in health care.** Regular contact with people who are ill increases your chances of exposure to TB bacteria. Wearing a mask and frequent hand-washing greatly reduce your risk.
- **Living or working in a residential care facility.** People who live or work in prisons, homeless shelters, psychiatric hospitals or nursing homes are all at a higher risk of tuberculosis due to overcrowding and poor ventilation.
- **Living with someone infected with TB.** Close contact with someone who has TB increases your risk.

### Complications

Without treatment, tuberculosis can be fatal. Untreated active disease typically affects your lungs, but it can affect other parts of your body, as well.

Tuberculosis complications include:

- **Spinal pain.** Back pain and stiffness are common complications of tuberculosis.
- **Joint damage.** Arthritis that results from tuberculosis (tuberculous arthritis) usually affects the hips and knees.
- **Swelling of the membranes that cover your brain (meningitis).** This can cause a lasting or intermittent headache that occurs for weeks and possible mental changes.
- **Liver or kidney problems.** Your liver and kidneys help filter waste and impurities from your bloodstream. Tuberculosis in these organs can impair their functions.
- **Heart disorders.** Rarely, tuberculosis can infect the tissues that surround your heart, causing inflammation and fluid collections that might interfere with your heart's ability to pump effectively. This condition, called cardiac tamponade, can be fatal.

### Prevention

If you test positive for latent TB infection, your doctor might advise you to take medications to reduce your risk of developing active tuberculosis. Only active TB is contagious.

#### Protect your family and friends

If you have active TB, it generally takes a few weeks of treatment with TB medications before you're not contagious anymore. Follow these tips to help keep your friends and family from getting sick:

- **Stay home.** Don't go to work or school or sleep in a room with other people during the first few weeks of treatment.
- **Ventilate the room.** Tuberculosis germs spread more easily in small closed spaces where air doesn't move. If it's not too cold outdoors, open the windows and use a fan to blow indoor air outside.
- **Cover your mouth.** Use a tissue to cover your mouth anytime you laugh, sneeze or cough. Put the dirty tissue in a bag, seal it and throw it away.
- **Wear a face mask.** Wearing a face mask when you're around other people during the first three weeks of treatment may help lessen the risk of transmission.

### Diagnosis

During the physical exam, your doctor will check your lymph nodes for swelling and use a stethoscope to listen to the sounds your lungs make when you breathe.

The most commonly used diagnostic tool for tuberculosis is a skin test, though blood tests are becoming more commonplace. A small amount of a substance called tuberculin is injected just below the skin on the inside of your forearm. You should feel only a slight needle prick.

Within 48 to 72 hours, a health care professional will check your arm for swelling at the injection site. A hard, raised red bump means you're likely to have TB infection. The size of the bump determines whether the test results are significant.

#### Results can be wrong

The TB skin test isn't perfect. Sometimes, it suggests that people have TB when they don't. It can also indicate that people don't have TB when they do.

You can have a false-positive result if you've been vaccinated recently with the bacille Calmette-Guerin (BCG) vaccine. This tuberculosis vaccine is seldom used in the United States but is widely used in countries with high TB infection rates.

False-negative results also can occur.

#### Blood tests

Blood tests can confirm or rule out latent or active tuberculosis. These tests measure your immune system's reaction to TB bacteria.

These tests require only one office visit. A blood test might be useful if you're at high risk of TB infection but have a negative response to the skin test, or if you've recently received the BCG vaccine.

### Imaging tests

If you've had a positive skin test, your doctor is likely to order a chest X-ray or a CT scan. This might show white spots in your lungs where your immune system has walled off TB bacteria, or it might reveal changes in your lungs caused by active tuberculosis.

### Sputum tests

If your chest X-ray shows signs of tuberculosis, your doctor might take samples of your sputum — the mucus that comes up when you cough. The samples are tested for TB bacteria.

Sputum samples can also be used to test for drug-resistant strains of TB. This helps your doctor choose the medications that are most likely to work. Getting results of these tests can take four to eight weeks.

- Chest X-rays

#### Treatment

If you have latent TB, your doctor might recommend treatment with medication if you're at high risk of developing active TB. For active tuberculosis, you must take antibiotics for at least six to nine months.

The exact drugs and length of treatment depend on your age, overall health, possible drug resistance and where the infection is in your body.

### Most common TB drugs

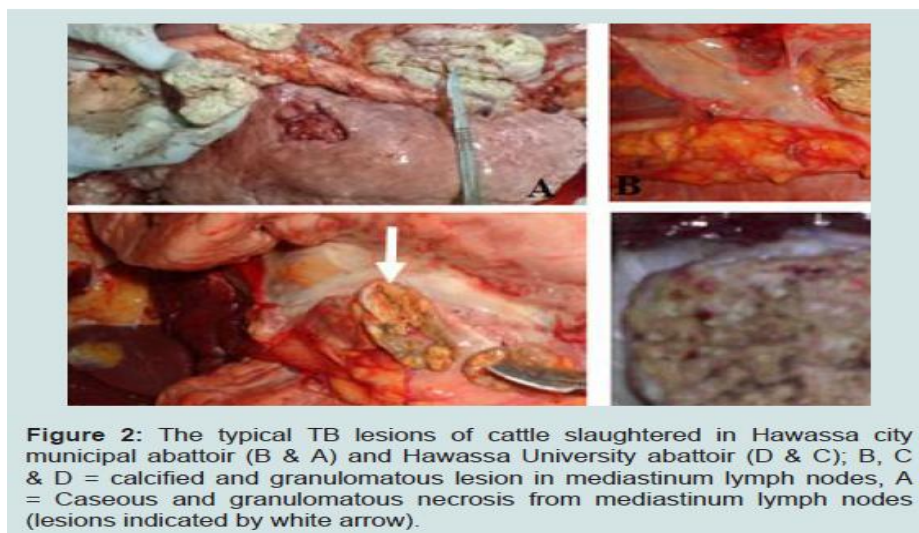
If you have latent tuberculosis, you might need to take only one or two types of TB drugs. Active tuberculosis, particularly if it's a drug-resistant strain, will require several drugs at once. The most common medications used to treat tuberculosis include:

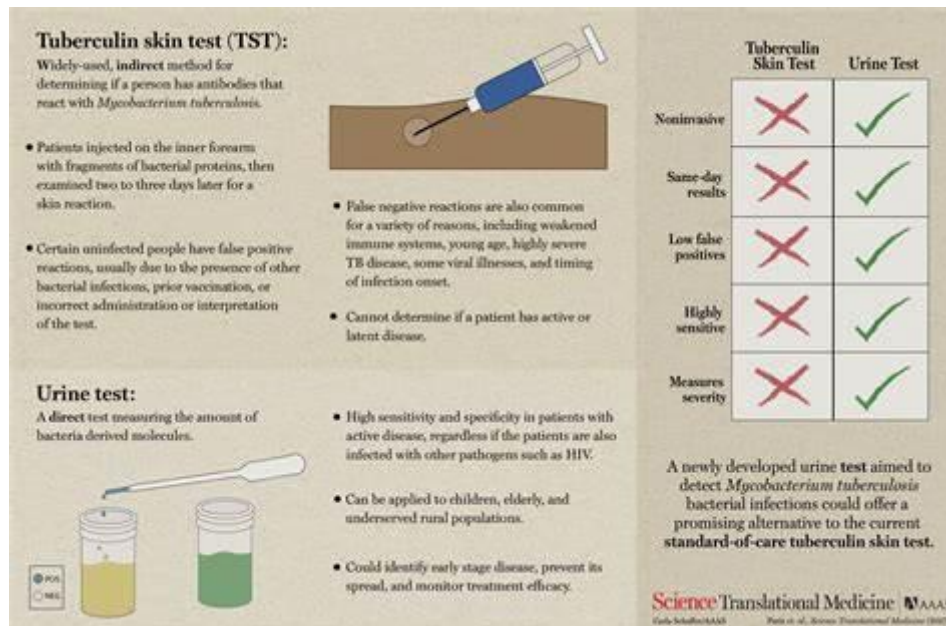
- Isoniazid
- Rifampin (Rifadin, Rimactane)
- Ethambutol (Myambutol)
- Pyrazinamide

If you have drug-resistant TB, a combination of antibiotics called fluoroquinolones and injectable medications, such as amikacin or capreomycin (Capastat), are generally used for 20 to 30 months. Some types of TB are developing resistance to these medications as well.

Some drugs might be added to therapy to counter drug resistance, including:

- Bedaquiline (Sirturo)
- Linezolid (Zyvox)





This figure represent test for tuberculosis on the skin. This test is widely used to determine if a person has an antibody that react with mycobacterium tuberculosis.

## II. LITERATURE REVIEW

Tuberculosis (TB), which is caused by bacteria of the *Mycobacterium tuberculosis* complex, is one of the oldest diseases known to affect humans and a major cause of death worldwide. Tuberculosis continues to be a huge peril disease against the human population and according to WHO, tuberculosis is a major killer of the human population after HIV/AIDS. Tuberculosis is highly prevalent among the low socioeconomic section of the population and marginalized sections of the community. In India, National strategic plan (2017-2025) has a national goal of elimination of tuberculosis by 2025. It requires increased awareness and understanding of Tuberculosis. In this review article history, taxonomy, epidemiology, histology, immunology, pathogenesis and clinical features of both pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB) has been discussed. A great length of detailed information regarding diagnostic modalities has been explained along with diagnostic algorithm for PTB and EPTB. Treatment regimen for sensitive, drug resistant and extensive drug resistant tuberculosis has been summarized along with newer drugs recommended for multi drug resistant tuberculosis. This review article has been written after extensive literature study in view of better understanding and to increase awareness regarding tuberculosis, as a sincere effort that will help eliminate tuberculosis off the face of the earth in near future. As a consequence of the emergence of drug resistant tuberculosis (TB) and various immuno-compromised states, there is a re-emergence of many forgotten extrapulmonary manifestations of TB including oral TB, which must be taken into consideration while diagnosing oral lesions. The present article discusses the geographical burden, temporal evolution, demographic variables, clinical presentation and treatment of oral TB. The occurrence is most commonly secondary to pulmonary TB but oral symptoms may precede systemic symptoms. The most common presentation is ulceration (71%) and histopathological specimens demonstrate the characteristic epithelioid and langhans cells. In a unique case, presented here, an ulcerative tuberculous gingival lesion demonstrated dense plasma cell infiltration histologically and closely mimicked plasma cell gingivitis which made the diagnosis challenging Tuberculosis (TB) updates and guidelines have been published rapidly in last few years. The WHO and RNTCP have recommended suggestions that have changed the diagnostics and therapeutics paradigm in 2019. The rapid nature of these changes need to be appraised at the pulmonologist end. We conducted a google survey to study these gaps and subsequently review TB in 2019 focusing on the gaps in the survey. We narrate a short review covering the important diagnostic and therapeutic aspects in brief. We discuss the results of our google survey to address the knowledge gaps. Diagnosis, principles and rationale of therapy and treatment of drug sensitive and drug resistant tuberculosis including the shorter regimen and regrouping of drugs are important considerations of our review. Tuberculosis is a health concern worldwide. The anti-tubercular drugs (particularly rifampicin) used for its management offers side effects like acute kidney injury. Creatinine, which is recognised as an important biomarker for the renal function, is commonly estimated with Jaffe's reaction (alkaline picrate reaction). However, interference of Jaffe's reaction with non-creatinine chromogens has been reported. In this context, we have checked the possibility of interference by Rifampicin and Isoniazid at therapeutic concentration with the Jaffe's reaction. Through in-silico study, we have studied the reaction prediction of picric acid with other

chemicals/reactant (i.e. Rifampicin, Isoniazid and non-creatinine chromogens) in terms of confidence value. It is observed that the confidence value of reaction prediction between picric acid and INH and Rifampicin is much more than the same of pyruvic acid (non-creatinine chromogen). Further, we have checked the absorbance value of Jaffe's reaction mixture in aqueous media in the presence of both the drugs at 520nm. It is observed that the absorbance of alkaline picric acid increases with an increase in drug concentration. However, the increasing trend of absorbance is much more in the case of rifampicin compared to INH. It appears from our result rifampicin, and isoniazid has the potential to behave as non-creatinine chromogen and can give false positive creatinine results in Jaffe's reaction. Thus, it can cause misdiagnosis in patients consuming these drugs. We recommend study in the biological matrix for further validation of the result

### III. DISCUSSION AND CONCLUSION

#### DISCUSSION

Tuberculosis (TB) is a potentially serious infectious disease that mainly affects the lungs. The bacteria that cause tuberculosis are spread from person to person through tiny droplets released into the air via coughs and sneezes.

Once rare in developed countries, tuberculosis infections began increasing in 1985, partly because of the emergence of HIV, the virus that causes AIDS. HIV weakens a person's immune system, so it can't fight the TB germs. In the United States, because of stronger control programs, tuberculosis began to decrease again in 1993. But it remains a concern.

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Anti-TB medicines have been used for decades and strains that are resistant to one or more of the medicines have been documented in every country surveyed. Drug resistance emerges when anti-TB medicines are used inappropriately, through incorrect prescription by health care providers, poor quality drugs, and patients stopping treatment prematurely.

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the 2 most effective first-line anti-TB drugs. MDR-TB is treatable and curable by using second-line drugs. However, second-line treatment options are limited and require extensive chemotherapy (up to 2 years of treatment) with medicines that are expensive and toxic.

In some cases, more severe drug resistance can develop. TB caused by bacteria that do not respond to the most effective second-line anti-TB drugs can leave patients without any further treatment options.

MDR-TB remains a public health crisis and a health security threat. Only about one in three people with drug resistant TB accessed treatment in 2020.

Worldwide in 2018, the treatment success rate of MDR/RR TB patients was 59%. In 2020, WHO recommended a new shorter (9-11 months) and fully-oral regimen for patients with MDR-TB. This research has shown that patients find it easier to complete the regimen, compared with the longer regimens that last up to 20 months. Resistance to fluoroquinolones should be excluded prior to the initiation of treatment with this regimen.

In accordance with WHO guidelines, detection of MDR/RR-TB requires bacteriological confirmation of TB and testing for drug resistance using rapid molecular tests, culture methods or sequencing technologies. Treatment requires a course of second-line drugs for at least 9 months and up to 20 months, supported by counselling and monitoring for adverse events. WHO recommends expanded access to all-oral regimens.

By the end of 2020, 65 countries started using shorter MDR-TB treatment regimens and 109 had started using bedaquiline, in an effort to improve the effectiveness of MDR-TB treatment. WHO's End TB Strategy target of "No TB patients and their households facing catastrophic costs as a result of TB disease", monitored by countries and WHO since WHA67.1 End TB Strategy was adopted in 2015, shows that the world did not reach the milestone of 0% by 2020.

According to the results of 23 national surveys on costs faced by TB patients and their families, the percentage facing catastrophic costs\* ranged from 13% to 92% and the pooled average, weighted for each country's number of notified cases, was 47% (95% CI: 33–61%).

US\$ 13 billion are needed annually for TB prevention, diagnosis, treatment and care to achieve global targets agreed on UN high level-TB meeting. Investments in TB prevention, diagnosis and care for tuberculosis in low- and middle-income countries (LMICs) accounting for 98% of reported TB cases, fall far short of what is needed. Less than half (41%) of the global TB funding target is available, leaving a US\$ 7.7 funding gap in 2020 to achieve global targets. TB funding is back to the level of 2016 with an 8.7% drop in TB spending

between 2019 and 2020 (from US\$ 5.8 billion to US\$ 5.3 billion). Of the US\$5.3 billion funding for tuberculosis available in 2020, 81% was from domestic sources, with the BRICS countries (Brazil, Russian Federation, India, China and South Africa) accounting for US\$2.8 billion (65% of total domestic funding). Over the past decade, US\$ 0.9 billion were invested annually in tuberculosis by international donors, 76% of which accounted by the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), the largest contribution. The United States (US) Government is the largest contributor of funding to the Global Fund and also the largest bilateral donor; overall, it contributes close to 50% of international donor funding for TB. Provisional data for TB funding in 2021 suggests that allocations for 2021 will remain inadequate. Increases in both domestic and international funding for TB are urgently required. For research and development, according to the Treatment Action Group, only US\$ 0.9 billion were available in 2019 of the US\$2 billion required per year to accelerate the development of new tools. At least an extra US\$ 1.1 billion per year is needed to accelerate the development of new tools.

On 26 September 2018, the United Nations (UN) held its first- ever high-level meeting on TB, elevating discussion about the status of the TB epidemic and how to end it to the level of heads of state and government. It followed the first global ministerial conference on TB hosted by WHO and the Russian government in November 2017. The outcome was a political declaration agreed by all UN Member States, in which existing commitments to the SDGs and WHO's End TB Strategy were reaffirmed, and new ones added.

SDG Target 3.3 includes ending the TB epidemic by 2030. The End TB Strategy defines milestones (for 2020 and 2025) and targets (for 2030 and 2035) for reductions in TB cases and deaths. The targets for 2030 are a 90% reduction in the number of TB deaths and an 80% reduction in the TB incidence rate (new cases per 100 000 population per year) compared with levels in 2015. The milestones for 2020 are a 35% reduction in the number of TB deaths and a 20% reduction in the TB incidence rate. The strategy also includes a 2020 milestone that no TB patients and their households face catastrophic costs as a result of TB disease.

#### IV. CONCLUSION

According to the sex, the results showed increased in male patients more than female patients. Most of the patients had family history of TB. Clinical feature in the study patients were night sweat, persistent cough and chest pain.

As delve in the review it is clearly shown that there must be a great strategy to deal with the rise of tuberculosis as it has been stated by the WHO that The political declaration of the UN high-level meeting included four new global targets: treat 40 million people for TB disease in the 5-year period 2018–2022; reach at least 30 million people with TB preventive treatment for a latent TB infection in the 5-year period 2018–2022; mobilize at least US\$ 13 billion annually for universal access to TB diagnosis, treatment and care by 2022; mobilize at least US\$ 2 billion annually for TB research. As requested in the political declaration:

WHO finalized and published a Multisectoral Accountability Framework for TB (MAF-TB) in 2019. WHO is supporting countries to adapt and use the framework to translate commitments into actions and to monitor, report, and review progress, with the engagement of high-level leadership, all relevant sectors, civil society and other stakeholders. In 2020, a progress report of the UN Secretary-General to the General Assembly was developed and released with the support of WHO. Examples of **high-level leadership on multisectoral accountability** include Presidential or Head of State End TB initiatives and formalized mechanisms for the engagement and accountability of stakeholders in India, Indonesia, Pakistan, Philippines and Viet Nam as well as national campaigns to drive progress such as the Race to End TB. WHO is working closely with countries, partners and civil society in scaling up the TB response. Six core functions are being pursued by WHO to contribute to achieving the targets of the UN high-level meeting political declaration, SDGs, End TB Strategy and WHO strategic priorities:

Providing global leadership to end TB through strategy development, political and multisectoral engagement, strengthening review and accountability, advocacy, and partnerships, including with civil society; Shaping the TB research and innovation agenda and stimulating the generation, translation and dissemination of knowledge;

Setting norms and standards on TB prevention and care and promoting and facilitating their implementation; Developing and promoting ethical and evidence-based policy options for TB prevention and care; Ensuring the provision of specialized technical support to Member States and partners jointly with WHO regional and country offices, catalyzing change, and building sustainable capacity; Monitoring and reporting on the status of the TB epidemic and progress in financing and implementation of the response at global, regional and country levels.

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