Tuberculosis:

One-third of the world's population is thought to have been infected with *M. tuberculosis*, with new infections occurring in about ١٪ of the population each year. In ٢٠٠٧, an estimated ١٣,٧ million chronic cases were active globally, while in ٢٠١٠, an estimated ٨,٨ million new cases and ١,٥ million associated deaths occurred, mostly in developing countries. The absolute number of tuberculosis cases has been decreasing since ٢٠٠٦, and new cases have decreased since ٢٠٠٢. The rate of tuberculosis in different areas varies across the globe; about ٨٠٪ of the population in many Asian and African countries tests positive in tuberculin tests, while only ٥–١٠٪ of the United States population tests positive. More people in the developing world contract tuberculosis because of a poor immune system, largely due to high rates of HIV infection and the corresponding development of AIDS.

The classic symptoms of active TB infection are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. Infection of other organs causes a wide range of symptoms. Diagnosis of active TB relies on radiology (chest X-rays), as well as microscopic examination and microbiological culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) and/or blood tests. Treatment is difficult and requires administration of multiple antibiotics over a long period of time. Social contacts are also screened and treated if necessary. Antibiotic resistance is a growing problem in multiple drug-resistant tuberculosis (MDR-TB) infections. Prevention relies on screening programs and vaccination with the bacillus Calmette-Guérin vaccine.

Tuberculosis, MTB, or TB (short for *tubercle bacillus*), in the past also called phthisis, phthisis pulmonary or consumption, is a widespread, and in many cases fatal, infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis*. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air. Most infections do not have symptoms, known as latent tuberculosis. About one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than ٥٠٪ of those so infected.

Signs and symptoms:

The main symptoms of variants and stages of tuberculosis are given, with many symptoms overlapping with other variants, while others are more (but not entirely) specific for certain variants. Multiple variants may be present simultaneously.

Tuberculosis may infect any part of the body, but most commonly occurs in the lungs as Extrapulmonary TB occurs when tuberculosis develops outside of the lungs, although extrapulmonary TB may coexist with pulmonary TB, as well. General signs and symptoms include fever, chills, night sweats, loss of appetite, weight loss, and fatigue. Significant nail clubbing may also occur.

Pulmonary:

If a tuberculosis infection does become active, it most commonly involves the lungs (in about ٩٠٪ of cases). Symptoms may include chest pain and a prolonged cough producing sputum.

About ٢٥٪ of people may not have any symptoms. Occasionally, people may cough up blood in small amounts, and in very rare cases, the infection may erode into the pulmonary artery, resulting in massive bleeding .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 entirely clear. It may be due either to better air flow, or to poor lymph drainage within the upper lungs.

Extrapulmonary:

In ١٥–٢٠٪ of active cases, the infection spreads outside the lungs, causing other kinds of TB. These are collectively denoted as "extrapulmonary tuberculosis". Extrapulmonary TB occurs more commonly in immunosuppressed persons and young children. In those with HIV, this occurs in more than ٥٠٪ of cases. Notable extrapulmonary infection sites include the pleura. 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. When it spreads to the bones, it is also known as "osseous tuberculosis". A form of osteomyelitis. Sometimes, bursting of a tubercular abscess through skin results in tuberculous ulcer. An ulcer originating from nearby infected lymph node is painless, slowly enlarging and has an appearance of "wash leather". A potentially more serious, widespread form of TB is called "disseminated" TB, commonly known as miliary tuberculosis. Miliary TB makes up about ١٠٪ of extrapulmonary cases.

Causes:

The main cause of TB is *Mycobacterium tuberculosis*, a small, aerobic, nonmotile bacillus. The high lipid content of this pathogen accounts for many of its unique clinical characteristics. It divides every ١٦ to ٢٠ hours, which is an extremely slow rate compared with other bacteria, which usually divide in less than an hour. Mycobacteria have an outer membrane lipid bilayer. 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.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.

Scientists can identify MTB under a regular (light) microscope. Since MTB retains certain stains even after being treated with acidic solution, it is classified as an acid-fast bacillus (AFB). The most common acid-fast staining techniques are the Ziehl–Neelsen stain, which dyes AFBs a bright red that stands out clearly against a blue background, and the auramine-rhodamine stain followed by fluorescence microscopy. The *M. tuberculosis* complex (MTBC) includes four other TB-causing mycobacteria: *M. bovis*, *M. africanum*, *M. canetti*, and *M. microti*. *M. africanum* is not widespread, but it is a significant cause of tuberculosis in parts of Africa. *M. bovis* was once a common cause of tuberculosis, but the introduction of pasteurized milk has largely eliminated this as a public health problem in developed countries. *M. canetti* is rare and seems to be limited to the Horn of Africa, although a few cases have been seen in African emigrants. *M. microti* is also rare and is mostly seen in immunodeficient people, although the prevalence of this pathogen has possibly been significantly underestimated. 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 pulmonary diseases that resemble TB.

Risk factors:

A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; ١٣٪ of all people with TB are infected by the virus. This is a particular problem in sub-Saharan Africa, where rates of HIV are high. Of people without HIV who are infected with tuberculosis, about ٥–١٠٪ develops active disease during their lifetimes; in contrast, ٣٠٪ of those confected with HIV develop the active disease. Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty. Those at high risk thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather edictally underprivileged and resource-poor communities, high-risk ethnic minorities, children in close contact with high-risk category patients, and health-care providers serving these patients. Chronic lung disease is another significant risk factor. Silicosis increases the risk about ٣٠-fold.Those who smoke cigarettes have nearly twice the risk of TB compared to nonsmokers. Other disease states can also increase the risk of developing tuberculosis. These include alcoholism and diabetes mellitus. Certain medications, such as corticosteroids and infliximab (an anti-αTNF monoclonal antibody), are becoming increasingly important risk factors, especially in the developed world. Also a genetic susceptibility element exists, for which the overall importance remains undefined.

Transmission:

When people with active pulmonary TB cough, sneeze, speak, sing, or spit, they expel infectious aerosol droplets ٠٫٥ to ٥٫٠ µm in diameter. A single sneeze can release up to ٤٠٬٠٠٠ droplets.[٤٠] Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very small (the inhalation of fewer than ١٠ bacteria may cause an infection). People with prolonged, frequent, or close contact with people with TB are at particularly high risk of becoming infected, with an estimated ٢٢٪ infection rate. A person with active but untreated tuberculosis may infect ١٠–١٥ (or more) other people per year. Transmission should only occur from people with active TB – those with latent infection are not thought to be contagious. The probability of transmission from one person to another depends upon several factors, including the number of infectious droplets expelled by the carrier, the effectiveness of ventilation, the duration of exposure, the virulence of the *M. tuberculosis* strain, the level of immunity in the uninfected person, and others. The cascade of person-to-person spread can be circumvented by effectively segregating those with active ("overt") TB and putting them on anti-TB drug regimens. After about two weeks of effective treatment, subjects with nonresistant active infections generally do not remain contagious to others. If someone does become infected, it typically takes three to four weeks before the newly infected person becomes infectious enough to transmit the disease to others.

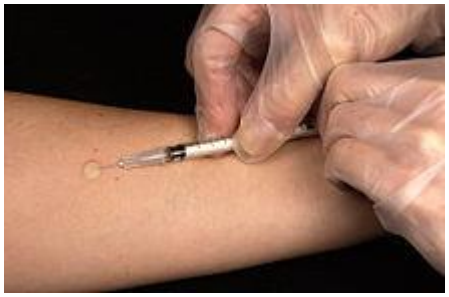
Diagnosis:

Active tuberculosis

Diagnosing active tuberculosis based merely on signs and symptoms is difficult, as is diagnosing the disease in those who are immunosuppressed. A diagnosis of TB should, however, be considered in those with signs of lung disease or constitutional symptoms lasting

longer than two weeks. A chest X-ray and multiple sputum cultures for acid-fast bacilli are typically part of the initial evaluation. Interferon-γ release assays and tuberculin skin tests are of little use in the developing world. IGRA have similar limitations in those with HIV. A definitive diagnosis of TB is made by identifying *M. tuberculosis* in a clinical sample (e.g. sputum, pus, or a tissue biopsy). However, the difficult culture process for this slow-growing organism can take two to six weeks for blood or sputum culture. Thus, treatment is often begun before cultures are confirmed. Nucleic acid amplification tests and adenosine deaminase testing may allow rapid diagnosis of TB. These tests, however, are not routinely recommended, as they rarely alter how a person is treated. Blood tests to detect antibodies are not specific or sensitive, so they are not recommended.

Latent tuberculosis


Mantoux tuberculin skin test

The Mantoux tuberculin skin test is often used to screen people at high risk for TB. Those who have been previously immunized may have a false-positive test result. The test may be falsely negative in those with sarcoidosis, Hodgkin's lymphoma, malnutrition, or most notably, in those who truly do have active tuberculosis. Interferon gamma release assays (IGRAs), on a blood sample, are recommended in those who are positive to the Mantoux test. These are not affected by immunization or most environmental mycobacteria, so they generate fewer false-positive results. However, they are affected by *M. szulgai*, *M. marinum*, and *M. kansasii*. IGRAs may increase sensitivity when used in addition to the skin test, but may be less sensitive than the skin test when used alone.

Prevention:

Tuberculosis prevention and control efforts primarily rely on the vaccination of infants and the detection and appropriate treatment of active cases. The World Health Organization has achieved some success with improved treatment regimens, and a small decrease in case numbers.

Vaccines:

The only available vaccine as of ٢٠١١ is bacillus Calmette-Guérin (BCG). In children it decreases the risk of getting the infection by ٢٠٪ and the risk of infection turning into disease by nearly ٦٠٪.It is the most widely used vaccine worldwide, with more than ٩٠٪ of all children being vaccinated. The immunity it induces decreases after about ten years. As tuberculosis is uncommon in most of Canada, the United Kingdom, and the United States, BCG is only administered to people at high risk. Part of the reasoning arguing against the use of the vaccine is that it makes the tuberculin skin test falsely positive, so of no use in screening. A number of new vaccines are currently in development.

Management:

Treatment of TB uses antibiotics to kill the bacteria. Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which hinders the entry of drugs and makes many antibiotics ineffective. The two antibiotics most commonly used are isoniazid and rifampicin, and treatments can be prolonged, taking several months. Latent TB treatment usually employs a single antibiotic, while active TB disease is best treated with combinations of several antibiotics to reduce the risk of the bacteria developing antibiotic resistance. People with latent infections are also treated to prevent them from progressing to active TB disease later in life. Directly observed therapy, i.e. having a health care provider watch the person take their medications, is recommended by the WHO in an effort to reduce the number of people not appropriately taking antibiotics. The evidence to support this practice over people simply taking their medications independently is poor. Methods to remind people of the importance of treatment do, however, appear effective.

New onset:

The recommended treatment of new-onset pulmonary tuberculosis, as of ٢٠١٠, is six months of a combination of antibiotics containing rifampicin, isoniazid, pyrazinamide, and ethambutol for the first ٢ months, and only rifampicin and isoniazid for the last ٤ months.Where resistance to isoniazid is high, ethambutol may be added for the last ٤ months as an alternative.

Recurrent disease:

If tuberculosis recurs, testing to determine to which antibiotics it is sensitive is important before determining treatment. If multiple drug-resistant TB is detected, treatment with at least four effective antibiotics for ١٨ to ٢٤ months is recommended.

Medication resistance:

Primary resistance occurs when a person becomes infected with a resistant strain of TB. A person with fully susceptible TB may develop secondary resistance during therapy because of inadequate treatment, not taking the prescribed regimen appropriately or using low-quality medication. Drug-resistant TB is a serious public health issue in many developing countries, as its treatment is longer and requires more expensive drugs. MDR-TB is defined as resistance to the two most effective first-line TB drugs: rifampicin and isoniazid. Extensively drug-resistant TB is also resistant to three or more of the six classes of second-line drugs. Totally drug-resistant TB is resistant to all currently used drugs. It was first observed in ٢٠٠٣ in Italy, but not widely reported until ٢٠١٢, and has also been found in Iran and India. Bedaquiline is tentatively supported for use in multiple drug-resistant TB. XDR-TB is a term sometimes used to define *extensively resistant* TB, and constitutes one in ten cases of MDR-TB. Cases of XDR TB have been identified in more than ٩٠٪ of countries.

Research:

The BCG vaccine has limitations, and research to develop new TB vaccines is ongoing. A number of potential candidates are currently in phase I and II clinical trials. Two main approaches are being used to attempt to improve the efficacy of available vaccines. One approach involves adding a subunit vaccine to BCG, while the other strategy is attempting to

create new and better live vaccines. MVA٨٥A, an example of a subunit vaccine, currently in trials in South Africa, is based on a genetically modified vaccinia virus. Vaccines are hoped to play a significant role in treatment of both latent and active disease. To encourage further discovery, researchers and policymakers are promoting new economic models of vaccine development, including prizes, tax incentives, and advance market commitments. A number of groups, including the Stop TB Partnership, the South African Tuberculosis Vaccine Initiative, and the Aeras Global TB Vaccine Foundation, are involved with research. Among these, the Aeras Global TB Vaccine Foundation received a gift of more than $٢٨٠ million (US) from the Bill and Melinda Gates Foundation to develop and license an improved vaccine against tuberculosis for use in high burden countries. A number of medications are being studied for multi drug resistant tuberculosis including: bedaquiline and delamanid. Bedaquiline received U.S. FDA approval in late ٢٠١٢. The safety and effectiveness of these new agents are still uncertain, because they are based on the results of a relatively small studies. However, existing data suggest that patients taking bedaquiline in addition to standard TB therapy are five times more likely to die than those without the new drug, which has resulted in medical journal articles raising health policy questions about why the FDA approved the drug and whether financial ties to the company making bedaquiline influenced physicians' support for its use .

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