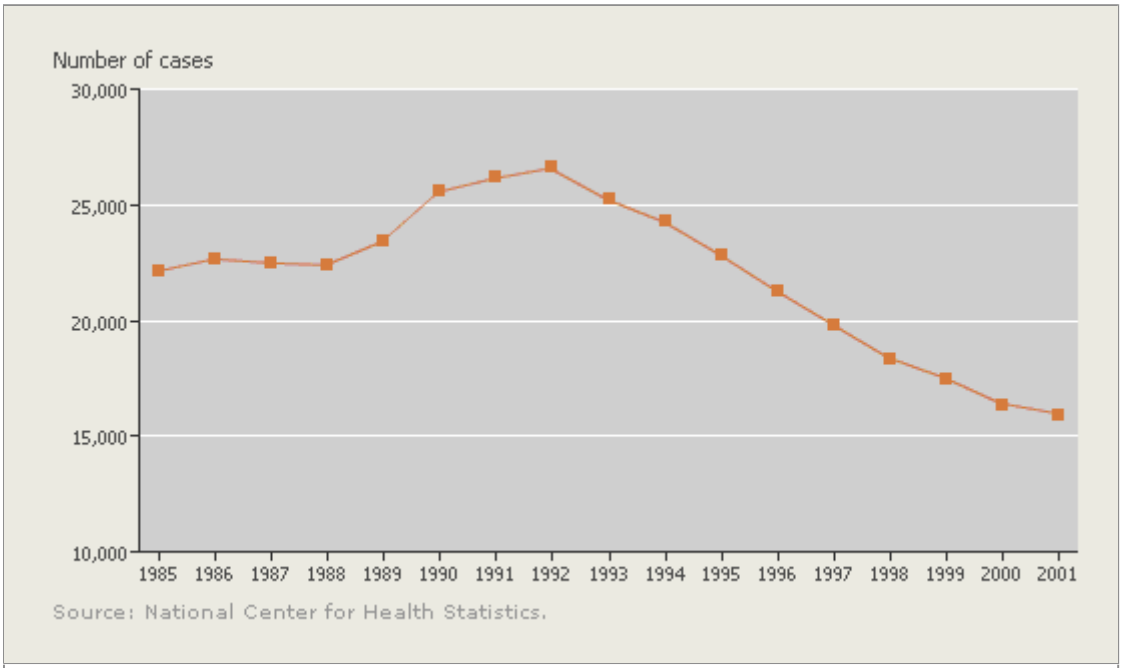
Tuberculosis

INTRODUCTION

Tuberculosis (TB), chronic or acute bacterial infection that primarily attacks the lungs, but which may also affect the kidneys, bones, lymph nodes, and brain. The disease is caused by *Mycobacterium tuberculosis,* a rod-shaped bacterium. Symptoms of TB include coughing, chest pain, shortness of breath, loss of appetite, weight loss, fever, chills, and fatigue. Children and people with weakened immune systems are the most susceptible to TB. Half of all untreated TB cases are fatal.



Incidence of Tuberculosis, United States

This graph illustrates the number of new cases of tuberculosis in the United States since 1985. Many researchers attribute the sharp increase in the early 1990s to the spread of acquired immunodeficiency syndrome (AIDS). People with AIDS have weakened immune systems and are particularly susceptible to contagious diseases such as tuberculosis. Poorly supervised treatment of tuberculosis also led to an increase in drug-resistant strains of the bacteria that cause tuberculosis, furthering the spread of the disease. Renewed emphasis on control and prevention has brought the incidence of tuberculosis to record low levels.

In 1993 the World Health Organization (WHO) declared TB to be a global emergency, the first such designation ever made by that organization. According to WHO, one individual becomes infected with TB every second, and every year 8 million people contract the disease. Tuberculosis causes 2 million deaths a year. WHO predicts that between 2000 and 2020, nearly 1 billion people will become infected with the TB bacteria and 35 million people will die from the disease.

TRANSMISSION AND INFECTION

TB is transmitted from person to person, usually by inhaling bacteria-carrying air droplets. When a person sick with TB coughs, sneezes, or speaks, small particles that carry two to three bacteria surrounded by a layer of moisture are released in the air. When another person inhales these particles, the bacteria may lodge in that person's lungs and multiply.

A less common route of transmission is through the skin. Pathologists and laboratory technicians who handle TB specimens may contract the disease through skin wounds. TB has also been reported in people who have received tattoos and people who have been circumcised with unsterilized instruments.

A person may become infected with TB bacteria and not develop the disease. His or her immune system may destroy the bacteria completely. In fact, only 5 to 10 percent of those infected with TB actually become sick. If a person does contract the infection, disease can develop in two stages: primary and secondary.

A Primary TB

In primary TB, a person has become infected with the TB bacteria but often is not aware of it, since this stage of the disease does not produce noticeable symptoms. Primary TB is not contagious in this early stage. Macrophages, immune cells that detect and destroy foreign matter, ingest the TB bacteria and transport them to the lymph nodes where they may be inhibited, destroyed, or they may multiply.

If the bacteria multiply, active primary tuberculosis will develop. Symptoms include coughing, night sweats, weight loss, and fever. A chest X ray may show shadows in the lung or fluid collection between the lung and its lining. If the bacteria are inhibited, rather than destroyed, the immune cells and the bacteria form a mass known as a granuloma or tubercle. In effect, the immune cells form a wall around inactive bacteria. As long as the immune system remains strong, the TB bacteria remain walled off and inactive. The tubercle gradually collects calcium deposits to form what is known as a Ghon focus. These initial tubercles in the lung usually heal, leaving permanent scars that appear as shadows in chest X rays. At this initial stage of TB, the disease does not progress, but bacteria may remain dormant in the body for many years. If the immune system becomes weakened, the tubercle opens, releasing the bacteria, and the infection may develop into secondary TB.

B Secondary TB

In secondary TB, the formerly dormant bacteria multiply and destroy tissue in the lungs. They also may spread to the rest of the body via the bloodstream. Fluid or air may collect between the lungs and the lining of the lungs, while tubercles continue to develop in the lung, progressively destroying lung tissue. Coughing of blood or phlegm may occur. At this secondary stage, carriers of TB can infect others.

III DIAGNOSIS OF INFECTION AND DISEASE

Photo Researchers, Inc./CNRI

Tuberculosis in the Lungs

Lung tissue calcification, resulting from pulmonary tuberculosis, appears as yellow patches within the chest area of this human X ray. When airborne phlegm contaminated with the bacillus *Mycobacterium tuberculosis* is inhaled, nodular lesions, called tubercles, may form in the lungs and spread through the nearest lymph node.

Diagnosis of TB requires two separate methods. Tuberculin skin testing is a method of screening for exposure to TB infection. A person who was infected with TB will have developed a hypersensitivity to the TB bacteria even if they did not develop the disease. A purified protein derived from the bacteria is injected into the skin. The skin area is inspected 48 to 72 hours later for a bump. A positive test implies that TB infection has occurred. Skin tests are not 100 percent accurate and they do not always indicate the presence of active disease.

Diagnosis of TB disease is established by the identification of the bacteria in sputum (matter coughed up from the lungs) or other body fluids and tissues in conjunction with an abnormal chest X ray and the presence of TB symptoms. Once TB has been diagnosed, further testing is required to determine which drugs would be most appropriate to treat the particular strain of TB bacteria.

Detecting the presence or the strain of the TB bacterium was once a time-consuming process that would often delay therapy. Today, the use of genetic engineering techniques greatly reduces the time required for diagnosis. A new technique is the polymerase chain reaction (PCR), which can rapidly duplicate a tiny amount of bacterial hereditary material from a small sample of infected sputum.

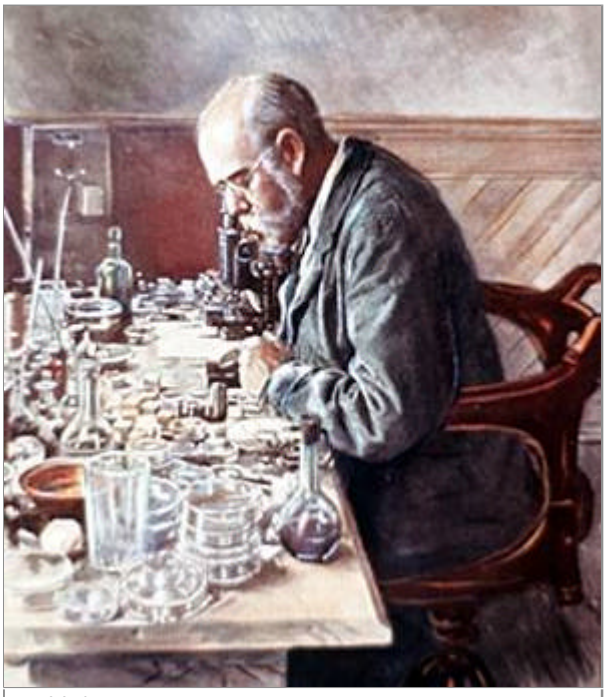
IV TREATMENT AND PREVENTION

General preventive measures can be taken to reduce the spread of TB in public places. Ventilation

systems lessen the chance of infection by dispersing the bacteria. Ultraviolet lighting also reduces, but does not eliminate, the threat of infection by killing TB bacteria in confined spaces. Vaccines, such as the bacillus Calmette Guerin (BCG) vaccine, prepared from bacteria that have been weakened, are another preventive measure. The BCG vaccine is most effective in preventing childhood cases of TB.

With the advent of effective antibiotics for TB, drug therapy has become the cornerstone of treatment. Single-drug treatment often causes bacterial resistance to drugs. Therefore, all recommended therapies include multiple drugs given for at least 6 months, often for as long as 9 to 12 months. Adjustments to the treatments are made based on susceptibility of the bacterial strain. A combination of antibiotics, including isoniazid, rifampin, streptomycin, pyrazinamide, and ethambutol, is usually prescribed. In 1998, scientists successfully decoded the entire gene sequence, or genome, of the tuberculosis bacteria. This advance is likely to lead to the development of new methods for treatment and prevention of TB.

V HISTORY



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Robert Koch

A color illustration depicts German scientist Robert Koch at work in his laboratory. Considered the founder of modern medical bacteriology, Koch isolated the bacillus that causes tuberculosis in 1882. He won the Nobel Prize for physiology or medicine in 1905.

TB has existed since at least 2000 BC, as shown by tubercles found in mummified bodies. References to TB can be found in the writings of ancient Babylonia, Egypt, and China. The term tuberculosis was first used in 1839, and it is derived from the Latin word *tubercula,* meaning small lump, referring to the small scars seen in tissues of infected individuals. TB reappeared in Europe and the United States in epidemic form in the 19th century.

Significant research into the causes and cure of TB began in earnest in the early 19th century. French physician Gaspard Bayle described the damage caused by TB in 900 autopsies. René-Théophile-Hyacinthe Laënnec, also a French physician, described the evolution of the disease from the initial tubercle through its final stages. J. A. Villemin, a French army doctor, showed that TB could be transmitted from humans to animals.

The American physician Edward Trudeau was affected by the disease twice, in 1873 and 1876. When he thought he was dying, he traveled to Saranac Lake in the Adirondack Mountains of New York to spend his final days. When he found his symptoms eventually cured, he attributed his healing to the fresh air of the mountains. In 1885 Trudeau built the first American sanatorium. It later became a model for the many sanatoriums that became the mainstay of TB treatment in the late 19th century and early 20th century. By 1930 the United States had 600 sanatoriums with a total of 84,000 beds. Trudeau also established the Trudeau Laboratory, which during the following 50 years, was responsible for training most physicians versed in the treatment of TB.

Early in the 19th century TB was considered a refined disease, one that affected artistic, morally superior individuals. But as the epidemic continued and claimed a larger circle of people, often the poor and disadvantaged, the victims themselves were blamed, and in the absence of scientific knowledge, TB was attributed to a person's lifestyle.

Scientific pursuit of the true nature of TB continued. In 1882 German physician Robert Koch discovered the bacteria that caused TB. Using simple but precise observations and experiments, Koch demonstrated the presence of the bacteria and how it was transmitted.

In Paris, French bacteriologists Albert Calmette and Camille Guerin worked with a virulent strain of bovine (cow) tubercle bacillus at the Pasteur Institute. In 1924 they prepared the BCG vaccine in hopes of protecting the world against tuberculosis. It was administered to a newborn child who was at high risk of developing TB. The vaccine was successful, and the child never contracted the disease. In 1944 American microbiologist Selman Waksman isolated streptomycin from a fungus, *Streptomyces lavendula,* heralding the beginning of modern antibiotic therapy for TB.

The success of drug therapy and the declining rates of disease incidence and mortality over the next 30 years instilled a sense of confidence in public health officials that TB could be conquered. As antibiotic therapy became the primary treatment, mortality rates from TB decreased significantly. Deaths from TB in the United States dropped from 188 per 100,000 in 1904 to about 1 per 100,000 in 1980. From 1953 to 1984, the average annual decline in cases was about 5 percent per year. As a result, funding for public health programs in the United States, including those for the prevention and treatment of TB, was drastically curtailed in the 1980s.

VI CURRENT PREVALENCE OF TB

As the incidence of TB continued to decline in the early 1980s, most medical experts expected that the disease would be completely eliminated in industrialized nations by the year 2010. But by the mid-1980s, the number of TB cases began to increase—between 1985 and 1991, the number of reported cases in the United States increased 20 percent. Worldwide the incidence also skyrocketed in this

period, and by the year 2000, the TB bacteria had infected more than one-third of the world's population.

Multiple factors contribute to the global increase in TB. Infection with the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS), is the single greatest risk for progression of TB infection to disease. People with HIV have weakened immune systems that increase their susceptibility to TB, and in these people, TB often progresses rapidly from the primary to the secondary stage. The increase of TB incidence is highest in Africa and Asia, areas with the highest number of people infected with HIV.

A second factor contributing to TB resurgence is the failure of patients to complete the full six to nine months of antibiotic therapy required to cure the disease. Many people stop taking antibiotics when they begin to feel healthier, but successful treatment of TB requires therapy beyond the period of obvious symptoms. When patients fail to follow the prescribed treatment, they may become actively infectious, spreading the disease to others. An infected person may infect as many as 10 to 15 other people in a single year. Failure to complete the full round of treatment also can cause the emergence of TB bacterial strains with acquired drug resistance, further complicating treatment by increasing the length and cost of therapy.

The emergence of strains of bacteria that are resistant to multiple drug therapy is a serious problem, particularly because no ready drug treatment is available to combat newly emerging strains. To improve compliance, the WHO strongly recommends that all countries, especially those in Africa and Asia, adopt a program called directly observed treatment, short-course (DOTS). DOTS requires health workers to monitor patients to make sure that they follow the complete course of treatment. The success rate and the cost effectiveness of this program have been proven around the world. Epidemics in New York City, Tanzania, Peru, and China in the early 1990s were brought under control using DOTS.

Migration, international air travel, and tourism also have contributed to the global spread of TB. The extreme difficulty of screening immigrants and travelers for TB allows the disease to cross international borders easily. The substantial increase in homelessness, and the related circumstances of poverty, crowding, and malnutrition, also contributed to the increased incidence of TB in the United States and other industrialized countries during the early 1990s.

While industrialized nations with good public health systems have been able to control the recent TB resurgence, curbing the spread of TB on a global scale will require ongoing international efforts. In the future, combating TB throughout the world will require advances in molecular biology, research into the genetics of TB in order to understand drug resistance, and the continuous development of new drugs, as well as the prospect of synthesizing additional vaccines.

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