CLINIC CONSULT

Pulmonology

# Tuberculosis

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# Contents

CHAPTER 1

# History of Tuberculosis

Tuberculosis (TB) is a disease of antiquity that has long been a major public health challenge in the world, particularly in the developing countries. Early descriptions of the disease date to the pre-Christian era. Consumption, phthisis, scrofula, Pott's disease, and white plague are all terms used to refer to TB throughout history. It is postulated that humans first acquired the disease in Africa about 5,000 years ago. It spreads to other humans along trade routes. It also spread to domesticated animals, such as goats and cows, in Africa. Seals and sea lions that bred on African beaches are believed to have acquired the disease and carried it across the Atlantic to South America. Hunters would have been the first humans to contract the disease there.

The term "phthisis" first appeared in Greek literature around 460 BC. Hippocrates identified the illness as the most common cause of illness in his time. Although Aristotle believed that the disease might be contagious, many of his contemporaries believed it to be hereditary. Galen, the most eminent Greek physician after Hippocrates, defined phthisis as the ulceration of the lungs, thorax, or throat, accompanied by a cough, fever, and consumption of the body by pus. The TB epidemic in Europe, probably started in the 17$^{th}$ century, lasted 200 years, and was known as the "Great White Plague". Its

incidence is thought to have peaked between the ends of 18th and 19th centuries. Over time, various cultures of the world gave the illness different names: *phthisis* (Greek), *consumption* (Latin), *yaksma* (India), and *chaky oncay* (Incan), each of which make reference to the "drying" or "consuming" aspects of the illness, cachexia. In the 19th century, TB's high mortality was referred to as the "romantic disease". The oldest example of spinal TB in the form of fossil bones dates back to about 8000 BC. Its evidenced in the mummified remains unearthed in Mesopotamia, Egypt and Central Asia, various Neolithic sites in Italy, Denmark, and countries in the Middle East. Europe become the epicenter for many TB epidemics starting in the 16th and 17th centuries due to population explosion and urbanization. European immigrants to the New World brought the disease with them.

Tuberculosis morbidity and mortality rates steadily dropped during the 20th century in the developed world as a result of better public health practices and widespread use of Bacillus Calmette-Guérin (BCG) vaccine, as well as the development of drugs in the 1950s. This downward trend ended and the numbers of new cases started increasing in the mid-1980s because of increased homelessness and poverty, and the emergence of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (HIV).

In 1865, Villemin, a French military physician, transmitted TB to laboratory rabbits by inoculating them with tuberculous tissue from a cadaver. He also demonstrated that environmental conditions greatly influenced the course of the disease. Dubos clearly rearticulated the role of environment. No specific class or strata in the society was immune to the disease. Death rate in the UK was 1% of the population by the 18th century due to TB and was known as "Captain of all these men of death" and "White Plague". Subsequently, the disease rose steadily for more than two centuries, but then it inexplicably went

into a long, slow decline. Subsequent epidemiology of the disease varies according to the country, in some the decline was maintained, while in some others the rise continued with a plateau and then a decline till about a decade ago when it showed another rising trend because of the HIV infection. Royal touch was a form of treatment practiced in early days. Scrofula was known as the "mal du roi" or the "King's Evil". René Laennec, died from the disease at the age of 45, after contracting TB while studying contagious patients and infected bodies. He invented the stethoscope and used to corroborate his auscultatory findings. Another French physician Louis used statistical methods to evaluate different aspects of the disease's progression, the efficacy of various therapies, and individuals' susceptibility. He divided pthisis into six types. Koch, brought out major changes by establishing the basic and fundamental cause of TB in 1882. He delivered a lecture at the Physiological Society at the Christie Hospital, Berlin, on the 24$^{th}$ of March 1882 under the title "*Die Atiologie Tuberkulose*" and named the causative organism as the tubercle bacillus, the *Mycobacterium tuberculosis*. X-rays was discovered by von Rontgen in 1895. Scientific research of TB in the 19$^{th}$ century was more concerned with the description, pathogenesis, and diagnosis of the disease. The concept of sanatorium treatment started around the middle of 19$^{th}$ century. In the 1930s, collapse therapy through artificial pneumothorax and thoracoplasty supplemented due to discouraging results of sanatorium treatment.

Calmette and Guérin in 1906 developed the "BCG" vaccine from attenuated bovine-strain. The vaccine was first used on humans in 1921 in France, however, it was not until after World War II that BCG received widespread acceptance in the United States, Great Britain, and Germany. Bacillus Calmette-Guérin immunization was first carried out in Paris in 1921, which suffered a major setback in 1930 when

240 children were inadvertently vaccinated with virulent bacilli and 73 of them died. By 1945, BCG vaccination was again in use after its usefulness was realized. Modern drug treatment started with discovery of streptomycin in 1943 from the actinomycete, *Streptomyces griseus*. It was used for the first time on 20th November 1944 in a young woman. More discovery of many more anti-TB drugs was made: para-aminosalicylate sodium (PAS; 1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethambutol (1962), rifampicin (1963), and more recently bedaquiline and others. From the use of monotherapy, the concept of combination therapy evolved, followed by domiciliary treatment and short-course chemotherapy.

### The Modern Era

The modern era of TB control started in the mid-1990s when the World Health Organization (WHO) and various countries in the world adopted the directly observed treatment, short-course (DOTS) strategy. World Health Organization declared TB, a global public health emergency in 1993 and publishes a global report on TB every year since 1997. Stop TB Strategy, was launched in 2006 as an enhancement of the DOTS therapy.

## HISTORY OF TUBERCULOSIS IN INDIA

The first references to TB in non-European civilization is found in the Vedas. The oldest of them (Rigveda, 1500 BC) calls the disease *yaksma*. The Atharvaveda calls it *balasa*. Atharvaveda gave the first description of scrofula. The *Sushruta Samhita* (600 BC) recommends treatment with breast milk, various meats, alcohol, and rest. The Yajurveda advises sufferers to move to higher altitudes.

## Tuberculosis Control in India

The first open air sanatorium was founded in 1906 in Tiluania, near Ajmer, followed by one in Almora. In 1909, the first nonmissionary sanatorium was built near Shimla. United Mission Tuberculosis Sanatorium was built in 1912 at Madanapalle. Frimodt Moller, the first medical superintendent, played a large role in India's fight against TB through the training of TB workers, conducting TB surveys (1939), and introduction of BCG vaccination (1948). The first TB dispensary was opened in Bombay in 1917, followed by Madras. Soon anti-TB societies were formed in Lucknow and Ajmer. Government worked closely with the nongovernmental organizations and support their activities. The Tuberculosis Association of India (TAI) was formed in February, 1939. The provinces and states which received money also started their TB associations. The Bengal Tuberculosis Association had been functioning from 1929. In 1946, there were only 6,000 beds available for the treatment of TB patients. The Bhore Committee recommended enhancement. As no drug or combination of drugs were effective against TB till the middle of 20$^{th}$ century, the main line of treatment was good food, open air, and dry climate. Till the advent of adequate chemotherapy, treatment took a second place to diagnosis and prognosis. In 1939, the TAI recommended the Organized Home Treatment Scheme as the best compromise under the prevailing circumstances. Bacillus Calmette-Guérin work started in 1948; and in 1949, it was extended to schools in almost all the states of India. Under the aegis of the International Tuberculosis Campaign, which had considerable experience in BCG work in many countries, it was introduced in India on a small scale in Madanapalle with Frimodt Moller in the lead. India started a mass BCG campaign in 1951.

A BCG vaccine production center in Guindy, Madras, was set up in 1948 with WHO and United Nations Children's Fund support. In 1953, Frimodt Moller reported remarkable results with the regimen streptomycin (SM) and isoniazid (INH), single and combined, in the treatment of pulmonary TB in Indian patients. In 1956, Sikand and Pamra presented a paper on the "effect of SM, PAS, and INH in 703 cases of pulmonary TB, diagnosed and treated during 1951–53" and found that domiciliary treatment results were encouraging. The government established a Tuberculosis Chemotherapy Center in 1956 (Tuberculosis Research Center, in Madras, Chennai, now renamed as the National Institute of Research in Tuberculosis). It demonstrated that the time-honored virtues of sanatorium treatment such as bed rest, well-balanced diet, and good accommodation were remarkably unimportant provided adequate chemotherapy was prescribed and taken. Further, there was no evidence that close family contacts of patients treated at home incurred an increased risk of contracting TB. Therefore, it would be appropriate to treat infectious patients in their own homes. This finding revolutionized TB treatment the world over. National Tuberculosis Institute at Bangalore was established in 1959 for program and training. Countrywide national sample survey was carried out between 1955 and 1958 by the Indian Council of Medical Research. After a period of twelve and half years, it was shown that BCG vaccination did not offer significant protection against TB of the lung, but could provide substantial protection against childhood forms of TB such as tubercular meningitis and miliary TB. Bacillus Calmette-Guérin vaccination policy was revised and it was recommended to be given at an early age, preferably before the end of the first year after birth by integrating under Universal Immunization Program.

## Evaluation of the National Tuberculosis Control Program

In 1992, the Government of India, together with the WHO and Swedish International Development Agency, reviewed the then national TB program and concluded that it suffered from managerial weakness, inadequate funding, over-reliance on X-ray, nonstandard treatment regimens, low rates of treatment completion, and lack of systematic information on treatment outcomes. As a result, a revised national tuberculosis control program was designed.

**KEY MESSAGE**

- Tuberculosis is a disease of antiquity that is known to exist for many centuries. It has devastated civilizations. The treatment and prevention attempts have failed earlier. Newer strategies in the form of TB control Programs are the new attempts to curtail the disease.

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CHAPTER 2

# Epidemiology

## INTRODUCTION

The word epidemiology comes from the Greek words *epi*, meaning "on or upon", *demos*, meaning "people", and *logos*, meaning "the study of". It is the study of how often diseases occur in different groups of people and why. It also investigates all the factors that determine the presence or absence of diseases and disorders. About one-third of the global population (nearly 2 billion) is infected with tuberculosis (TB) and 95% of deaths due to TB are in the developing world. It is the second leading cause of death from an infectious disease worldwide after human immunodeficiency virus (HIV). Tuberculosis caused an estimated 1.5 million deaths in 2013 out of an estimated 9.0 million people who developed TB. Of these deaths, 360,000 were HIV-positive.

## GLOBAL SCENE

Tuberculosis has been classically associated with poverty, overcrowding, and malnutrition. Mostly the young adults in their productive years are affected. Low income countries and deprived areas (particularly slums), within big cities in developed countries, present the highest TB incidences and TB

mortality rates. These are settings where immigration, important social inequalities, HIV infection, and drug or alcohol abuse may coexist, all factors strongly associated with TB.

Epidemiology of TB will vary from country to country and from region to region. The epidemiology will also change from time to time depending on the time points of the study (like yearly and so on) because of varying control measures. Many earlier studies from different parts of the world have given varying figures. World Health Organization publishes a global TB report every year since 1997 to provide a comprehensive and up-to-date information of the TB epidemic situation and progress made in prevention, diagnosis, and treatment of the disease at global, regional, and country levels based primarily on data reported by countries and territories.

The 2014 global TB report is the 19$^{th}$ in the series of annual reports, and has used data from 202 countries and territories, including 183 member states, accounting for over 99% of the estimated world values. There are also other sources of estimation of the burden of disease.

The burden of disease caused by TB is expressed by three parameters:

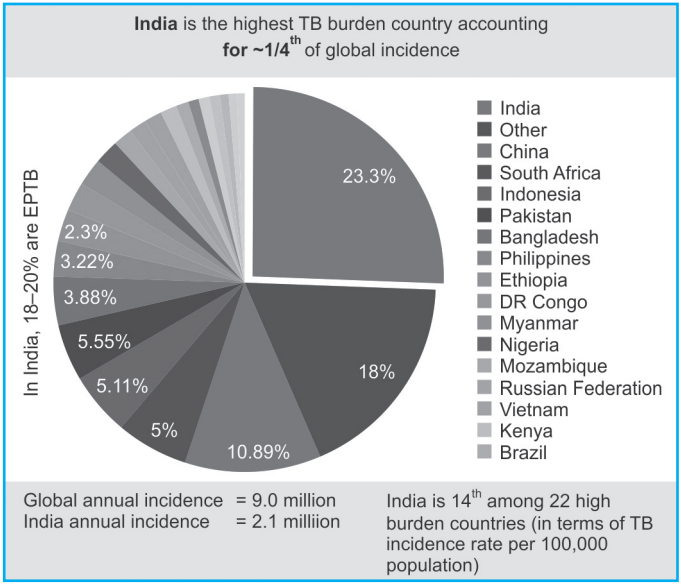
1. Incidence: number of new and relapse cases arising in a given time period, usually 1 year
2. Prevalence: number of cases at a given point in time
3. Mortality: number of deaths caused by TB in a given time period, usually 1 year.

## INCIDENCE

The 19$^{th}$ report of 2014 published in 2015, reported that, in 2013, there were an estimated 9.0 million (range, 8.6–9.4 million) incident cases (new and relapse cases) of TB,

equivalent to 126 cases per 100,000 population. The absolute number of incident cases is falling slowly at an average rate of 1.5% per year between 2000 and 2013 and 0.6% between 2012 and 2013. The incidence in the 22 high burden countries is shown in Table 2.1 and depicted in Figure 2.1. Table 2.2 shows the burden in the six WHO regions of the world.

More than half of the estimated number of cases in 2013 reported are from Asia (South East and Western Pacific regions; 56%) and the African Region (29%).




TB, tuberculosis, EPTB, extrapulmonary tuberculosis.

**Figure 2.1** Tuberculosis incidence cases in 2013 in the 22 high burden countries. ***(For color version, see Plate 1)***

*Source:* Global Tuberculosis Report 2014, World Health Organization.

**TABLE 2.1**

**Estimated burden of tuberculosis (incidence, prevalence, and mortality) in 2013 in 22 high burden countries. Best estimates and lower and upper ranges of the 95% uncertainty interval (numbers in thousands[a])**

| *Countries* | *Population* | *Prevalence* | | *Incidence* | | *Global burden (%)* | *HIV-positive incident TB cases* | | *Mortality[b]* | | *HIV-positive TB mortality* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| India[c] | 1,252,140 | 2,600 | 1,800–3,700 | 2,100 | 2,000–2,300 | 23.3 | 120 | 100–140 | 240 | 150–350 | 38 | 31–44 |
| China | 1,385,567 | 1,300 | 100–1,500 | 980 | 910–1,100 | 10.89 | 4.5 | 4.3–9.9 | 41 | 40–43 | 0.7 | 0.2–1.3 |
| Nigeria | 173,615 | 570 | 430–730 | 590 | 340–880 | 6.55 | 140 | 81–220 | 160 | 68–270 | 85 | 47–140 |
| Pakistan | 182,143 | 620 | 520–740 | 500 | 370–650 | 5.55 | 2.6 | 1.2–3.4 | 100 | 45–170 | 1 | 0.5–1.6 |
| Indonesia[d] | 249,866 | 680 | 340–1,100 | 460 | 410–520 | 5.11 | 15 | 8.7–20 | 64 | 36–93 | 3.9 | 2.2–6.2 |
| South Africa | 52,776 | 380 | 210–590 | 450 | 410–520 | 5.0 | 270 | 240–310 | 25 | 15–38 | 64 | 47–83 |
| Bangladesh[e] | 156,595 | 630 | 330–1,000 | 350 | 310–400 | 3.88 | 0.4 | 0.2–0.5 | 80 | 51–110 | 0.2 | 0.1–0.2 |
| Philippines | 98,394 | 430 | 380–490 | 290 | 260–330 | 3.22 | 0.3 | 0.2–0.3 | 27 | 25–29 | <0.1 | <0.1–<0.1 |
| DR Congo | 67,514 | 370 | 190–610 | 220 | 200–240 | 2.44 | 16 | 9.8–75 | 46 | 22–53 | 6.4 | 0.2–24 |

*Continued*

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