Tuberculosis (TB) is debatably the most infectious disease with highest rate of causality throughout human history. The Ottoman Empire also had the profound effect of the disease; however, following the establishment of the Republic of Turkey in 1923 effective TB control programs were implemented at times jointly with the WHO. From 1949 onwards, significant reduction in disease incidence and death rates in Turkey was recorded due to the significant efforts of the state and civil established Tuberculosis Associations. These successful Turkish control programs as well as the history of TB and the current global challenges related to the re-emergence of this deadly disease will be communicated in this article.

Tuberculosis was named Phthisis by Ancient Greek physicians. Although its meaning is unclear, it might have originated from ‘spitting’ (saliva) or ‘exhaustion’ (consumed) in Greek. For centuries, Anatolians have called it ‘verem’ (TB), ‘ince ağın’ (subtle pain), ‘ince hastalik’ (thinning disease), or ‘kuru hastalik’ (dry illness). It is important to note this name has a unique definition in various languages: ‘fading, weakened, exhausted’.

Currently, each of the human-infecting strains of Mycobacterium tuberculosis complex (MTBC) derives from a different common ancestor forming six major lineages. Lineages 5 and 6, which include M. africanum strains, are encountered in Western Africa. However, other lineages display significant variation in their distribution. The strains of lineage 1 within the EAI [East African-Indian] spoligotype cluster are accepted as the ‘ancient’ M. tuberculosis strains. They are frequently encountered in India and on the shores of Indian Ocean. Ancestral strains of M. tuberculosis spread via migration from India evolving into ‘modern’ lineages 2 (Beijing), 3 CAS (Central Asian Indian) and 4 (X, Haarlem, LAM [Latin-American Mediterranean]). In Turkey, the latest evolved lineage 4 has been most dominant. Current evidence might suggest migratory movements over the past 35,000–89,000 years from Africa spread four main lineages into Eurasia, while the remaining two phylogenetically ‘ancient’ lineages stayed in Africa. These lineages were later spread to the Sub-Indian continent and from there into Europe, sub-Saharan Africa and America, following a wave of reverse Homo sapiens migrations and conquests. Analysis of known mutation rates of the M. tuberculosis reveals that the differences among strains started to appear 250–1000 years ago. Tuberculosis was initially documented over 5000 years ago in Ancient Egypt; characteristic Pott deformations of TB were detected in mummies, and even represented in Ancient Egyptian art. Recently, DNA of M. tuberculosis was amplified from mummy tissues providing confirmatory evidence. There are documents dating back 3500 years in India, and 2300 years in China and archaeological evidence from the Andes also confirm the existence of pre-Columbian tuberculosis. In preserved mummies of Peru, bone tuberculosis was detected, as well as the pathogen DNA in mummy tissues. It was fully defined by Hippocrates (b. 460 B.C.), while its infectious nature was first identified by Clarissimus Galenus of Pergamon (131 A.D.). Human-to-human transmission, on the other hand, was mentioned by Ibn-i Sina (Avicenna, Bakhara 980–1038 A.D.) in his book El-kanun fi’ tibb (Canon medicinae).

In medieval times, Europeans lived in small farming communities of 200–300 people and tuberculosis was not widespread. The Middle Ages saw the lymphadenitis form of tuberculosis named Scurfula as most dominant. Villagers, who suffered from Scurfula, believed they could regain their health with the king’s touch so it came to be known as ‘the King’s Evil’. Scurfula was not the most severe form and recovering patients attributed their fortune to the king’s divine power. In 1720, Benjamin Marten described the lesions caused as ‘wonderfully minute living creatures’ in A New Theory of Consumptions: More Especially a Phthisis or Consumption of the Lungs, and proposed the contagium vivum fluidum theory, which provided an explanation based on the Germ Theory. Marten was the first to describe its cause as ‘animicula’. Following a series of autopsies, Laennec (1819) concluded that lesions, which appear in various forms in a number of locations in the body, were the result of a single...
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disease. Schönlein defined TB as a proper disease and used the term *Tuberculosis* for the first time (1839). Despite all these observations, the common belief in 19th-Century Northern Europe remained that it was hereditary, whereas in Southern Europe it was believed to be contagious. Although seen in mediaeval Europe, TB became widespread only after large-scale urbanisation in the second half of 17th Century. John Bunyan, in his book *The Life and Death of Mr. Badman* of 1680, defined TB as ‘The Captain among these Men of Death’. In London, in 1600s, 1000–1250/100,000 persons had TB. At the time of Industrial Revolution in 1780, TB reached its peak and 1120/100,000 died as a result of it. Although casualties had a steady decrease by 19th Century, between the years 1831 and 1835 some 567/100,000 lost their lives in London due to TB. One fourth of the European population had TB, which was spread through migration of infected people into North and South America, Africa and the Pacific Islands. Also in the Ottoman Court, TB was common and Sultan Mahmut II (1785–1839) as well as his mother and son died of it. Ottoman records appear as late as the reign of Sultan Abdülhamid II in 1901; however, it was evident that TB was a major problem throughout Ottoman Empire in the 18th and 19th Centuries. In 19th-Century England, the pale face of TB patients was perceived as beautiful in literary circles, so it was associated with the birth of a new era called Romanticism. Alexander Dumas (fils) wrote *The Lady of the Camellias* in 1848 and the consumptive heroine ‘Marguerite Gautier’ deeply influenced Turkish literature initiating a sentimental approach to TB.

TB’s infectious nature was experimentally proved by J.A. Villemain, who published his findings in *Etudes sur la Tuberculose*. Robert Koch, 14 years later, described the causative agent in his speech titled *Die Aetiologie der Tuberkulose* (Berlin Physiology Society, 24 March 1882). He not only defined the infectious agent but also laid the foundations for the Koch-Henle postulate linking the infectious agent to the formation of the disease, still in use today. Koch also (10th International Conference of Medicine in Berlin, 1890) claimed the discovery of an inhibitory agent, which stopped the growth of tubercle bacillus both in tube and in animal models.

Koch’s discovery (although the tuberculin has not the curative effect he had initially hoped for) and similar developments in Europe were closely followed during the reign of Sultan Abdülhamid II, but the administration of tuberculin at the German Hospital in Istanbul turned ineffective. Upon this outcome, an Ottoman delegation was sent to Berlin and in a report published by this delegation in the ‘Gazette Médicale d’Orient’ (1891), it was stressed that the use of Koch’s compound throughout the empire was subject to permission from the Sultan. Koch’s tuberculin, first tested (for detection of latent TB infections) in 1907 by von Pirquet, was actually a pioneering step towards the intra-cutaneous administration of PPD (purified protein derivative) also used today. This first attempt was followed by Mantoux’s intra-cutaneous injection in 1908. In the 1930s, Seibert developed the standardised PPD used today and five units of PPD-S was subsequently used globally for detection of latent TB infections. In the Ottoman Empire, the first tuberculin production and application commenced at Bakteriyolojihane-i Şahane between 1910–1913.

Following the discovery of the tubercle bacillus, public health authorities made significant attempts to prevent its spread in North America and Europe. The focus of early measures was to prevent spitting, which was also the case in Ottoman Empire and upon orders of Sultan Abdülhamid II, a comprehensive report was produced by Cemiyeti-i Tibbiye-i Şahane. In hospitals and prisons, TB sufferers were isolated and allocated a spitting bowl each. Spitting was strictly forbidden in military barracks and schools, and special TB wards were established in hospitals as a preventative measure. Until the discovery of antibiotics, the establishment of sanatoria was the only effective strategy for treatment, and the first one opened in 1859 in Görbersdorf. Their curative effect has been unclear as the results obtained in New York sanatoria were similar to those spontaneous cases without sanatoria experience. The first children’s sanatorium Hamidiye Efsal Hastane-i Âlisi was opened in 1905 in Ottoman Empire. Efforts to establish these residences continued in the Republican era, and the most prominent sanatorium opened in 1925 on Heybeliada (Princes’ Islands, Istanbul) located among pine trees for clean air (Figure 1).

It closed down in 2005 but left its mark during its years of service not only due to the treatment but also due to the training provided to equip the patients. In Turkey, both at Ottoman times, and after the establishment of the Turkish Republic, the fight against TB was conducted via cooperation of the state and civil established *Tuberculosis Associations*. Dr. Besim Omer Pasha was a pioneering figure, who had a ticket to travel on the Titanic in 1912 but missed it only to become the founder and the first president of the association (Veremle Mücadele Osmanlıl cemiyyeti) established on 8 June 1918. With its offices around the country, the association survived thanks to donations from the public, private businesses, town councils and the sale of memorabilia. In the USA, from 1947, mobile X-ray teams screened large numbers of Americans to keep the disease under control; however, as incidence rates went down, the 1960s saw mobile assistance replaced by special TB clinics. In Turkey, pilot screens were conducted in the 1960s by similar mobile teams, and from 1966–1976 the entire population, even remote villages were screened for TB presence. In 1997, it was declared that TB had been in decline but mobile teams continued to screen high-risk areas such as prisons and correction facilities. In the pre-
antibiotic era, pulmonary collapse treatment was used to close the cavities caused by the disease. Surgically induced pulmonary collapse treatment started in the late 19th Century and became widely administered in the early 20th Century. The first successful pneumothorax treatment was conducted by Ramadge in London in 1834, and resulted in the recovery of the patient. This was also adopted in Turkey and the results were published in 1922. The first vaccine was developed by Albert Calmette and Camille Guérin at Pasteur Institute, Lille using the strain *Mycobacterium bovis* subcultured 230 times to achieve a low virulence vaccine strain. In 1919, the *Bacillus Calmette-Guérin* (BCG) vaccine strain was developed and orally administered to a 3-day-old baby for the first time (1921). Wallgren developed intra-dermal application of the vaccine in 1927, and BCG vaccine was approved for human use by UN in 1928. BCG was first applied orally in 1926 in Turkey. The vaccine was also produced at Refik Saydam Foundation (RSHM) (Figure 2) until 1998 and was first administered intradermally by Dr Tevfik Salim Sağlam in 1948.

The fight against TB gained further momentum in Turkey starting from 1949 and by the 1950s international agreements with WHO and UNICEF made BCG an integral part of the control programs. There were 10 major vaccine campaigns in Turkey between 1952–1985 jointly conducted with WHO and UNICEF and seven of these were conducted by Dr Hamdi Aşcan. During his time, public screening campaigns were run by travelling teams and 90% of the population was successfully vaccinated in cities, towns and villages. From 1997 onwards, the vaccine commenced to be administered to two-month-old babies as well as to primary school children bringing an end to large-scale public-screening campaigns subsequently.

While the success rate of BCG vaccine has always been an issue for debate, extensive studies have found it to be between 0–80%. Currently, WHO recommends vaccine administration only to newborns and it is routinely administered to 2-month-old babies in Turkey. The first effective antibiotic streptomycin was discovered in 1944 and led to significant improvements in the condition of a female patient within a few months of its application. This was followed by the orally administered mycobactericidal drug isoniazid in 1952 rendering the disease treatable. Subsequent effective antibiotics such as pyrazinamide (1954), ethambutol (1962), and rifampicin (1966) brought standard therapy time down to 6 months which resulted in the closure of sanatoria. With wide-scale applications of effective treatment, prevention and control of TB entered a new phase, and was extended to cover voluntary requests from infected patients for new treatments.

Streptomycin administration started in Turkey at Çamlıca Sanatorium (1947). At Heybeliada Sanatorium isoniazid treatment occurred first in 1955 and was followed by combined rifampicin, isoniazid, pyrazinamide and ethambutol therapy following the WHO’s recommendations in 1969. From the mid-19th Century onwards, TB waves weakened in Europe and North America, and in Britain, between the years 1860 and 1900 the death rate was reduced 42% (348/100,000 to 202/100,000). Increased food production (better nutrition) and infection-spread prevention measures might have played a significant role in this...
reduction. There were also claims related to development of TB-resistant human populations as part of natural selection, contributing to reduced rates to some extent. By 1901, the first record-keeping year in Ottoman Empire, the death rate from TB was 264/100,000 in Istanbul, which was 30% higher than that in England. During WWI, an increase was observed (351/100,000 in 1918 and 268/100,000 in 1922); however, in the Republican era, this number was reduced to 187/100,000 (1939). Despite the misery and difficult conditions of the Balkans, WWI and Turkish Independence War the death rate in Istanbul was reduced 29% within 38 years of initial record keeping. By 1949, out of a population of 20 million, the number of consumptive people stood around 300,000 and the death rate was 218/100,000. An increase between the years 1939–1949 may be attributed to a reduction in food supply and production (although Turkey did not participate in WWII), increased urbanisation and record-keeping efficiency. Similar increases were also observed in Europe during and after war years. Deaths from TB per 100,000 people were 204 (1950), 55 (1960), 8.8 (1980), and 1.8 (2000) and incidence rates per 100,000 172 (1965), 52.2 (1980), 40 (2002), 28 (2010) and 19.4 (2012). From 1949 onwards, significant reduction in deaths rates and incidence rates in Turkey was recorded. Between the years 1949 and 1965, reported incidence rates went down by 88%, and between 1949–1960 death statistics showed a 75% decrease. Natural selection of individuals insusceptible the disease, fewer infections due to BCG vaccination, improved nutrition due to food-aid and also introduction of chemotherapy from 1940s have all contributed to this reduction. In 2010, the TB patient number reported was 15,183 in Turkey out of the total population of 73,722,988. The reported mortality rate from the TB in Turkey was 0.72 in every 100,000 in 2011.

Styblo and co-workers reported a decrease in TB incidences in Europe (1978) and in parts of Africa; however, the emergence of AIDS in 1980s altered the incidence again for 20 years. Strict control measures were subsequently introduced to monitor patients, especially, Directly Observed Treatment Short Course (DOTS) created new hopes for eradication in Africa, with a significant decrease from 2005. Turkey also implemented these strategies and jointly with WHO, DOTS started in 2002 in pilot regions to be later applied nationwide (2006). Despite these strategies, we are still far from the WHO 2050 target of one case in a million. Currently, the infection rate with multidrug resistant TB (MDR-TB) in sub-Saharan Africa and former Soviet Union (FSU) countries is extremely concerning. In Turkey, surveys conducted in 2012 indicate that only 2% of the patients are MDR-TB; however, detection of MDR-Beijing strain spreading via FSU countries is recorded frequently. As human travel increases, full international cooperation is
required for eradication. The history of tuberculosis suggests that the current wave will pass, even in the face of AIDS, although many will lie dead in its wake. Our challenge is to lower its crest and hasten its passing.3

References

Biography
Prof. Cengiz Çavuşoğlu (MD) is a graduate of Akdeniz University, Faculty of Medicine (1989). He practiced medicine in the Anatolian city of Kastamonu from 1989 to 1991 before joining the Ege University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology. He obtained specialisation in Clinical Microbiology and Infectious Diseases in 1996 and worked as a specialist until 2004 in the Department of Medical Microbiology. He became Associate Professor in 2004 and full Professor in 2011. He has been working in the Mycobacteriology Laboratory of the same department since 1998 and became the head of the laboratory in 2006. His research interests are in the field of mycobacteriology and molecular microbiology. He has 28 publications, international conference and workshop participations, 23 Genbank nucleotide deposits and Web of Science citations over 300 times. Presently he is a member of the Turkish Society for Microbiology and the Bacterial Genetics and the Mycobacterium Special Interest Groups.