



Diphtheria Epidemiology in Türkiye Throughout History

Türkiye'de Difteri Hastalığının Tarihsel Epidemiyolojisi

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Abstract

Diphtheria has long been related to epidemics and has been one of the primary causes of death among children. The discovery and widespread use of diphtheria antitoxin at the end of the nineteenth century resulted in significant reductions in the fatality rate. The discovery of a diphtheria toxoid vaccine in the early 1920s led to a drop in epidemics, and the World Health Organization's introduction of the Expanded Program on Immunization in 1971 resulted in a more than 90% reduction in diphtheria cases. However, diphtheria outbreaks continue to occur around the world due to factors such as wars, migration, and vaccine hesitancy, which result in a drop in immunization coverage. Diphtheria epidemics were common in the Ottoman Empire around the end of the nineteenth and beginning of the twentieth centuries. Diphtheria antitoxin production began in the empire in 1895, a notification mandate was introduced with the issued regulations and circulars, and detailed instructions were provided for the steps to be followed for the diagnosis, treatment, and control of the disease. Preventive services were prioritized in the early days of the Republic, and the Refik Saydam Institute of Hygiene and Public Health was established for vaccine production and diagnostic work, as well as the School of Public Health for personnel training. With the dissemination of health service provision, the execution of the Expanded Program on Immunization, and the continuance of effective immunization with all its components, diphtheria, which caused 4999 cases and 661 deaths recorded in 1958, has had zero instances notified since 2011.

Keywords: Diphtheria, immunization schedule, Türkiye

Öz

Difteri hastalığı çok eski çağlardan bu yana salgınlarla seyreden ve çocukluk döneminin önde gelen ölüm nedenlerinden biri olmuştur. On dokuzuncu yüzyılın sonlarında difteri antitoksinin bulunması ve sonrasında yaygın kullanımıyla fatalite hızında önemli düşüşler sağlanmıştır. 1920'lerin erken dönemlerinde difteri toksoid aşısının geliştirilmesiyle salgınlarda azalma görülmüş, 1971 yılında Dünya Sağlık Örgütü tarafından Genişletilmiş Bağışıklama Programının hayata geçirilmesiyle difteri vakalarında %90'ın üzerinde azalma sağlanmıştır. Bununla birlikte dünyada halen aşılama kapsayıcılığında düşüşle sonuçlanan savaşlar, göçler, aşı tereddütü gibi nedenlerle difteri salgınları görülmeye devam etmektedir. Difteri hastalığı 19. yüzyıl sonları ve 20. yüzyıl başlarında Osmanlı İmparatorluğu coğrafyasında yaygın olarak salgınlarla seyretmiştir. 1895 yılından itibaren difteri antitoksinini imparatorlukta üretilmeye başlanmış, çıkarılan nizamname ve layihalar ile bildirim zorunluluğu getirilmiş, tanı, tedavi ve hastalığın kontrolüne yönelik alınması gereken önlemlere yönelik ayrıntılı talimatlar verilmiştir. Erken Cumhuriyet döneminde, koruyucu hizmetlere ağırlık verilmiş, aşı üretimi ve tanı olanakları için Refik Saydam Merkez Hıfzıssıhha Enstitüsü ve personel eğitimi için Hıfzıssıhha Okulu açılmış, 1930'da hastalık ve salgınların önlenmesine yönelik önlemlere yer veren Umumi Hıfzıssıhha Kanunu çıkartılmıştır. Sağlık hizmet sunumunun yaygınlaştırılması, Genişletilmiş Bağışıklama Programının hayata geçirilmesi ve tüm bileşenleriyle etkin bir aşılama hizmetinin sürdürülmesiyle 1958 yılında 4999 vaka ve 661 ölümün bildirildiği difteri hastalığı 2011 yılından bu yana bildirimi yapılmamış bir hastalık durumuna gelmiştir.

Anahtar Kelimeler: Difteri, genişletilmiş bağışıklama programı, Türkiye

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Introduction

Diphtheria is caused by *Corynebacterium diphtheriae*, a toxin-producing bacteria, or, in rare cases, by *Corynebacterium ulcerans*. The exotoxin produced by these bacteria is responsible for the development of the clinical manifestation (1).

There are two clinical manifestations of diphtheria. The first is respiratory tract diphtheria, which is marked by prodromal symptoms followed by inflammation in the pharynx, tonsils, and larynx, along with associated symptoms. In cutaneous diphtheria, there is skin involvement. Throughout history, respiratory tract diphtheria has drawn attention due to its clinical presentation and fatalities. Today, the World Health Organization only requests the notification of respiratory tract diphtheria (2).

Diphtheria, which was one of the primary causes of death in children, has been mostly eradicated. According to World Health Organization data, 7097 cases of diphtheria were reported in 2016, with over one million cases documented in the previous century (3). Although the introduction of diphtheria antitoxin in 1888 and penicillin in 1943 both contributed to this accomplishment, the diphtheria toxoid vaccine, discovered in 1923 and implemented in the 1930s, was the most significant. Turkey's successful diphtheria control efforts guaranteed that no cases were seen, except for a single case reported in 2011. In this paper, we hope to emphasize Turkey's approach and practices regarding diphtheria which has always been ahead of its time, as well as share disease statistics.

History of Diphtheria

Although ancient Greek scholars Hippocrates (V. century BC), Aetius (VIII. century AD), and Arataeus (II. century AD) reported diseases with similar clinical presentations to diphtheria, this disease first appeared in Egyptian manuscripts in the second millennium BC (1). In 1550 BC, ancient Egyptian pediatric texts of magic and prescriptions describe a throat ailment (b) that is treated with herbs. The clinical symptoms of the condition were described in a papyrus of pediatric magical text from the Middle Kingdom era after 1854 BC as transient paralysis, which commonly affected small children, and cyanosis, which could result in cardiac complications (4).

The first documented diphtheria epidemic was the devastating one that emerged in Spain in the 17th century, and sporadic reports of diphtheria have been documented up to the present day (1). The Spaniards named diphtheria sore throat "garrotillo" at the turn of the century, and the 1613 outbreak in Spanish history became known as "el año de los garrotillos," or "the year of diphtheria" (5,6). During the 18th century, outbreaks occurred every 12 years in southwestern Europe (1). Samuel Bard described diphtheria in America for the first time

in 1771, even though epidemics had occurred in the American colonies (1).

The French doctor Pierre Bretonneau (1778-1862) pioneered a successful tracheostomy as a treatment method at the beginning of the nineteenth century, giving the disease its name and clearly describing the clinical presentation of diphtheria (1). Diphtheria is a Greek term that means skin or hide (pseudomembrane) and refers to a coating that forms in the throat. Bretonneau also distinguished diphtheria from scarlet fever (7). Severe epidemics continued to spread in the major cities of the United States and Europe in the second half of the nineteenth century (1). Edwin Klebs described the characteristics of the organism in 1883, and Friedrich Löffler grew it in culture a year later (8).

Emile Roux and Alexandre Yersin proved in 1888 the presence of a potent exotoxin and that the toxin can cause diphtheria symptoms by itself (1,9). It was later demonstrated that inactivated cultures or serum produced in animals could prevent death from diphtheria (1,10). In 1901, Emil von Behring was awarded the first Nobel Prize in physiology and medicine for their work on serum therapy, particularly the use of serum against diphtheria (11). Theobald Smith introduced the concept of active immunization in 1907 when he observed that a mixture of diphtheria toxin and antitoxin might confer long-term immunity in guinea pigs (1,12). Following Emil von Behring's successful immunization of children with a toxin-antitoxin mixture, immunization programs were launched in several European and American cities (1). Bela Schick, an Austrian pediatrician, described a skin test to indicate immunity in 1913 (13). Gaston Ramon demonstrated in the early 1920s that diphtheria toxin lost its toxic properties after being treated with heat and formalin, but retained the ability to protect against the disease, giving rise to today's diphtheria toxoid vaccination (1,14). Glenny et al. discovered in 1926 that aluminum-treated toxoid was more immunogenic, and in the mid-1940s, diphtheria toxoid was combined with tetanus and pertussis vaccines (1).

Epidemiology

Throughout history, diphtheria has been one of the most feared infectious diseases, causing outbreaks that mostly affect children and result in fatalities. The respiratory diphtheria fatality rate reached 50% during major diphtheria epidemics in Europe and America in the 1880s. With the widespread use of diphtheria antitoxin in treatment, the case fatality rate in Europe decreased to approximately 15% during World War I. The diphtheria epidemic that ravaged Europe during World War II resulted in 1 million cases and 50,000 deaths in 1943. Diphtheria toxoid vaccines were introduced in Europe and North America in the late 1940s, resulting in a reduction in epidemics.

Before the widespread use of the vaccine in the 1970s, it was estimated that 1 million cases of diphtheria occurred each year in low- and middle-income countries, with 50.000-60.000 deaths (15). The World Health Assembly proposed in 1974 that World Health Organization member countries implement and maintain immunization and surveillance programs for all or some of the diseases such as diphtheria, polio, pertussis, tetanus, measles, tuberculosis, and smallpox (16). Diphtheria, polio, pertussis, tetanus, measles, and tuberculosis were the first diseases addressed in the World Health Organization's Expanded Program on Immunization, which was designed to build immunization programs all over the world (17). Following the program's adoption, there was a more than 90% reduction in diphtheria cases reported between 1980 and 2000 (15).

The most recent outbreak was reported in the 1990s from the Russian Federation and the former Soviet Republics. More than 157.000 cases and 5.000 deaths were documented in the outbreak between 1990 and 1998. Between 2011 and 2015, India had the largest number of cases recorded each year, with a total of 18.350 cases reported across five years. It was followed by Indonesia with 3203 cases and Madagascar with 1633 cases. When notifications made to the World Health Organization were analyzed, it was revealed that there was under-reporting, particularly in Africa and the Eastern Mediterranean regions, although it was stated that 99-55% of the cases reported each year during these years were from the South-east Asian region (15).

Diphtheria outbreaks continue to occur around the world due to factors such as wars, migration, vaccine hesitancy, low quality of immunization services, and crowded living conditions, which contribute to the drop in immunization coverage. In Yemen, where a civil conflict has been raging since early 2015, a massive diphtheria outbreak emerged in October 2017, with 5701 probable cases and 330 deaths reported until April 2020 (19). The diphtheria outbreak that started in 2017 in the Cox Bazar district of Bangladesh, where Rohingya refugees were sheltered, resulted in 9321 cases and 50 deaths (20). DBT3 vaccination coverage in the Americas fell from 94% to 84% between 2010 and 2020. Since the beginning of the diphtheria outbreak in Venezuela in mid-2016, 1612 confirmed cases and 280 deaths have been documented, with the

fatality rate among confirmed cases increasing to 6% (21). A diphtheria outbreak started in Haiti at the end of 2014, with 406 confirmed diphtheria cases and 80 deaths recorded until the third quarter of 2021. There was one confirmed case reported from Colombia, and 18 from the Dominican Republic until November 2021 (22).

Diphtheria Epidemiology and Disease Control in the Late Nineteenth and Early Twentieth Centuries in the Ottoman Empire

Reviewing the documents in the Ottoman archives from the late nineteenth and early twentieth centuries showed that, although notifications were made and records were kept during the outbreak in the Ottoman Empire, disease statistics were not recorded regularly throughout the empire (23,24). However, it was observed that diphtheria was one of the diseases that the Ottoman Empire fought intensively (23,24). It is known that in the event of the disease, the Sultan's decree required the gathering of information and data regarding the reports generated and the steps taken, which was communicated among local doctors, governors, and central government officials in İstanbul (23). However, given the characteristics of the period, it is clear that similar situations existed in other countries. It is known that in 1906, a committee of students was formed at the Medical Faculty¹ to ascertain the characteristics of diseases that occur in İstanbul and rural areas, and the statistics were published in newspapers in an attempt to protect public health (23).

The Health Committee and Public Health Inspectorate published weekly journals², and administrative bodies were kept up to date on the course and severity of epidemics in İstanbul. Tables were created based on the name, nickname, age, area of residence, disease, and nationality of the deceased (23).

According to the documents, the number of people who received treatment and recovered from infectious diseases in the provinces, the level of serum administration by doctors, and the needs of the region, such as serum, were constantly monitored and labeled "urgent"; information was gathered from local and international media, and newspapers were used to inform the public about the disease (23).

¹Known as the School of Medicine after 1839, the institution was established on March 14, 1827, by the will of Sultan Mahmud II (25).

²Due to an increase in diseases such as scarlet fever, measles, and diphtheria within the Municipality's First Arrondissement, Abidin Bey, the Head of the Medical Board, performed an investigation and discovered eight cases of scarlet fever, nine cases of measles, and one case of diphtheria. Some of the cases were primary school children. The primary schools in the vicinity of Şehzadebaşı and Çemberlitaş, as well as the Yakup Ağa Primary School in Laleli and the Oruçgazi İsmail Ağa Primary School in Aksaray, were disinfected. The Greek school, which was located in the Havuzlu Church in Kumkapı, was closed for 12 days, and the situation was reported to the Ministry of Education.

According to documents in the Ottoman archive, the disease was widespread throughout the imperial territory. In 1899, a case of diphtheria was detected in a school in İstanbul. In Mitrovica, 30 cases and six deaths occurred due to diphtheria. In 1906, an appeal for assistance was made in response to a two-year-long disease in Konya. In 1909, a request was made for serum and syringes to be used in the Adana and neighboring areas during an epidemic. Scarlet fever and diphtheria first appeared in İzmir in 1910, and when they spread to Aydın, Nazilli, and Söke, correspondence was sent to take the required precautions. When a diphtheria epidemic broke out in the center of Van province in 1906, the Armenian patriarchate asked for precautions to be taken. Each year, several children in Yozgat died as a result of diseases such as scarlet fever and diphtheria (23).

The fight against the disease was carried out most effectively by the municipalities. Municipalities were founded initially in İstanbul, and then in other rural Ottoman provinces beginning in the 1860s. Municipal doctors, sanitary inspectors, and sterilization officers were the main officials fighting the disease, and services such as disinfection, patient treatment, and drug supply were offered as epidemic control measures. In 1866, the *Mektep-i Tibbiye-i Mülkiye* civilian medical school was established to train physicians for service in cities and towns. In 1869, *Cemiyet-i Tibbiye-i Mülkiye* was established to appoint healthcare staff such as doctors, pharmacists, vaccinators, and midwives to municipalities (23,26).

In locations where diphtheria occurred, protective measures such as delivering serum and syringes to the region, monitoring the progress of the disease by gathering daily information about the severity of the disease, temporarily isolating affected areas (schools, etc.), and disinfection were implemented (23). These practices are seen to be compatible with modern epidemic control practices, and the Ottoman Empire used modern epidemic control methods in the nineteenth century.

Atomizers were used to clean the air in the environment where sick people were present, and *tebhir* (steam) machines were used for the disinfection of clothes and used items. Steam rooms (*tebhirhane*) three have provided important services in the control of infectious diseases (23).

In 1894, serum therapy for diphtheria was adopted in Paris hospitals. In the same year, Emile Roux reported at the International Congress on Hygiene and Demography in Budapest that diphtheria mortality in Paris children's hospitals had reduced from 52% to 25% (10). Andre Chantemesse⁴, who came to İstanbul with the congress delegates, brought a box of this serum and presented it to Abdulhamid the Second.

In other words, diphtheria serum arrived in İstanbul only a few days after it was first introduced to the scientific community. After meeting with Andre Chantemesse, Abdulhamid II wanted this serum to be produced at *Bakteriyolojihane-i Şahane*. *Bakteriyolojihane-i Şahane* began producing diphtheria serum on December 4th, 1895, at the same time as other modern states such as Germany and France (end of 1894), America (commercially in 1895), and Canada (1913-1914) (29-32). This was the first immunity serum used in the Ottoman Empire (23). Since 1897, thanks to this serum, no more than 100 deaths have been recorded in İstanbul, even while diphtheria was at its peak (24).

The Ottoman Empire kept up with scientific advances in the field of infectious diseases, and researchers were dispatched to Europe to do so. In this context, it is clear from the documents examined that the empire sent Doctor Nizameddin Bey, the sanitary inspector of the Beirut Province, to Paris to learn how to administer diphtheria serum to patients and that he prepared the guidance "Serum Treatment Against Diphtheria" based on the work done in Monsieur Pasteur's operating room in Paris hospitals. Following the foundation of the Bacteriology laboratory, Doctor Nicole was dispatched to Paris to meet with Monsieur Ro, an expert in this field, to obtain information about the establishment of a diphtheria laboratory and its costs (23).

During the Ottoman period, legal arrangements were made to combat infectious diseases. There were also regulations⁵ directly related to diphtheria disease (24). Examples are given below.

Typhoid fever, typhus, smallpox, scarlet fever, measles, diphtheria, cholera, plague, dysentery, meningitis, yellow fever, and puerperal fever were among the infectious diseases that had to be reported under the 1910 regulations (24).

³Tebhirhanes were healthcare units that disinfected the clothes and belongings of people suffering from infectious diseases such as cholera, typhoid fever, plague, smallpox, chickenpox, scarlet fever, measles, typhus, dysentery, tuberculosis, puerperal fever, whooping cough, and diphtheria with pressurized water vapor, as well as the infected areas with chemicals. A clause added to the Provincial Administration of Sanitary Regulations issued in 1913 mandated the construction of *tebhirhanes* in the province and *sanjak* municipalities, as well as the provision of formalin equipment, sprayers, and disinfection medications to districts based on population size (23).

⁴André Chantemesse (1851-1919) wrote a thesis on tuberculous meningitis and succeeded in preventing typhoid in animal trials he conducted with Widal. Bacillary dysentery, vaccination of humans, and bacteriological examination of water were other studies he conducted (27). When a cholera epidemic broke out in İstanbul in 1893, he traveled from France for epidemic control and advocated the construction of a bacteriology laboratory in İstanbul (28).

The 1910 health circular included general information about the disease, as well as information and instructions about the clinical findings of diphtheria, precautions to be taken, disease notification, contact precautions, disinfection procedures, treatment, and instructions to end the patients' isolation (24).

The 1913 circular recommended that when diphtheria affected children, a physician be called immediately, prescribing serum treatment and informing the villagers about the disease (24).

Even though many innovations were introduced starting with the end of the nineteenth century, continuous and heavy wars [Ottoman-Russian War (1877-1878), Tripoli War (1911), Balkan Wars (1912-1913), World War I (1914-1918), War of Independence (1919-1922)] brought famine, poverty, infectious diseases, and other problems that impacted the entire population (34).

Diphtheria Epidemiology and Vaccine Practices in the Republic

Because of the priority placed on health, the establishment of the Ministry of Health was one of the first acts of the Turkish Grand National Assembly, which was established on April 23, 1920. Following the Ağnam Law, a tax law that contributed to the state's power and economic resources, which was accepted on the second day of the Assembly's inauguration, the Law on Treason was enacted on April 29, 1920, to eliminate the threat posed by the authority vacuum and internal revolts throughout Anatolia. Umur-ı Sıhhiye ve Muavenet-i İçtimaiye Vekaleti (Ministry of Health) was established as one of 11 ministries established with the Law No. 3 on the Jurisdiction of the Executive Ministers of the Grand National Assembly, adopted on May 2, 1920 (34-38).

Refik Bey, who was the first Minister of Health of the Republican era, served as the Minister of Health for about 15 years and carried out important activities in the field of preventive services (39). The Ministry conducted a study titled Turkey's Sanitary-Social Geography to learn more about the country's population, socioeconomic, and health-related situations, as well as to develop solutions to problems. With this study, an assessment of the country's health institutions and healthcare

staff, diseases, and other related issues was made. Based on the research, the determinants of public health between 1920 and 1930 were lack of education, personal and environmental hygiene conditions, the impact of nutrition and heavy working conditions, and the inadequacy of healthcare staff, healthcare institutions, and medicines. Malaria, tuberculosis, syphilis, smallpox, diphtheria, cholera, dysentery, typhoid fever, trachoma, intestinal diseases, as well as some other diseases have been identified as the most serious threats to public health (34).

The number of deaths due to certain infectious diseases between 1925 and 1930 was as follows: Scarlet fever 2201, measles 1407, smallpox 1220, diphtheria 715, typhoid fever 623, typhus 124, pertussis 117, amoebic dysentery 115, puerperal fever 108, and tetanus 89 (40).

Vaccinations and serums were produced in İstanbul and Sivas during the early years of the Republic, according to documents, and the İstanbul Bacteriology and Serum Institution produced 7493 bottles of diphtheria serum in 1925 (40).

The Republic of Turkey's Central Institute of Hygiene and Public Health Law, enacted on May 17, 1928, required scientific research and evaluations on public health, the production of vaccines and serum, the performance of necessary examinations, the control of drugs and other medicinal products imported from abroad, the dealing with all matters concerning public health, social health, and infectious diseases and the provision of opinions to entities that request information, as well as public health training for healthcare workers (41). To strengthen the fight against infectious diseases, the Refik Saydam Institute of Hygiene and Public Health was opened in 1928 for vaccine production and laboratory diagnostic facilities, and then the School of Public Health was opened to conduct research on infectious diseases and to perform personnel training (39).

On April 24, 1930, the Law on Hygiene and Public Health was enacted. The law, which is currently in effect, contains numerous regulations addressing public health, as well as articles related to the prevention of infectious diseases and epidemics, and surveillance services. The law specifies measures such as isolation, quarantine, disinfection, and immunization,

Regulations were issued in various domains during the Tanzimat Period to suit the requirements of society and the state, to ensure unity of law, and, most importantly, to become a contemporary European state. Through these regulations, state institutions and society became more systematic, and state institutions and the legal system gained a more secular structure. This Nizamname movement, which started in the Tanzimat Period, enabled the Ottoman Empire to turn into a constitutional state in the following period, and this transformation laid the groundwork for a secular, contemporary, and more modern state of law in the Republic Period (33).

and it requires the notification of 21 diseases, including diphtheria (39).

Diphtheria toxins and anatoxins were first produced in 1934 at the Institute of Hygiene and Public Health; diphtheria-tetanus combination vaccine production began in 1944 and was ramped up after 1947; typhoid-diphtheria vaccine production began in 1947; pertussis-diphtheria vaccine production began in 1948, and pertussis-diphtheria-tetanus combination vaccine production began in 1957 (42).

In 1961, Law No. 224 on the Socialization of Health Services was adopted, and a new service concept and practice were introduced, with the goal of bringing health services to individuals in the farthest reaches of the country. The socialization strategy, which was launched in Muş province, grew over time, leading to the establishment of health clinics in all 71 provinces by 1989 (43).

In Turkey, family medicine practice was started as a pilot practice in Düzce in 2005, and it became widespread by the end of 2010 throughout the country (44). Thus, immunization services began to be carried out by family physicians. Teams from community health centers provide vaccination services, particularly in schools. Vaccination services are also provided in public and private healthcare facilities in accordance with Ministry of Health regulations. Immigrants are provided with vaccination services in family medicine centers and immigrant health centers (45).

1. Diphtheria Vaccination Practices

The diphtheria vaccination became widely used in Europe, North America, Australia, and Japan in the 1940s and 1950s (46). Diphtheria vaccination has been widely used in Canada since 1930, and it became mandatory in Italy in 1939. Its national use in England started in 1940. Its administration in the United States began in the mid-1920s and had spread across the country by the late 1940s. It was first included in the routine vaccination program in Japan in 1948 (47-51).

Smallpox vaccination, mandated by the Law on Hygiene and Public Health issued in 1930, was the first effective and continuous immunization regimen in Turkey (52). According to information obtained from the Republic of Turkey Presidential State Archives, the diphtheria vaccine was initially used in Turkey in the early 1930s, during outbreaks in Konya and İstanbul (53). According to another source, vaccination against diphtheria started to be given to children aged 0-4 years in Turkey in 1968 in the form of a "combination vaccine," with pertussis and tetanus vaccines (52,54).

Due to a lack of adequate equipment and personnel, vaccination efforts were initially carried out with teams estab-

lished in provincial or district centers. With the socialization of healthcare starting in 1963, vaccination activities evolved into widespread systematic vaccination practices (52). In the 1970s, vaccination services were widely available, methodical, and campaign-style (for age groups at high risk, seasonally, and at certain times of the year as needed) (45).

By endorsing the World Health Organization's target for expanded vaccination by 1990, efforts were initiated in 1980 to incorporate the core components of the immunization program (43). In 1981, Turkey initiated the Extended Immunization Program to obtain high immunization rates to minimize disease morbidity and mortality in population groups sensitive to vaccine-preventable diseases. The aim was to attain a 90% countrywide coverage rate for each vaccine, fully vaccinate 80% of 0-11-month-old children in each region, deliver booster and missed doses to children under the age of five, and immunize all identified pregnant women against tetanus (43). However, the desired vaccination percentages were not achieved by the target date due to issues with the program's essential components, such as vaccine supply constraints, the inadequacy of cold chain materials, transportation vehicles, and personnel, the need for training, insufficient community participation and inter-sector cooperation, and poor vaccination record keeping. Turkish National Immunization Campaign was launched in 1985 to meet the WHO target of immunizing children against six vaccine-preventable diseases by 1990. The campaign aimed to vaccinate children aged 0-60 months against five diseases (diphtheria, pertussis, tetanus, polio, and measles), and immunization activities were carried out in three rounds. In the third round, 68.5% (3,005,189 doses) of DBT 3rd dose coverage was achieved in children under the age of 5 (52).

Table 1 shows the vaccination schedules including diphtheria for children in Turkey in and after 1980 (45).

In line with the recommendations of WHO, adult-type diphtheria-tetanus (Td) vaccine application has been started since 2004 for all cases including injuries and pregnancy vaccinations that require tetanus-toxoid (TT) administration (45).

TT vaccine has been substituted by the Td vaccine in routine vaccination of pregnant women/women of reproductive age under the Maternal and Neonatal Tetanus Elimination Program since 2004. Between 2006 and 2007, primary Td vaccination of women of reproductive age (15-49 years) was completed in three rounds as part of the elimination campaign, predominantly in 18 provinces (and high-risk areas in 42 provinces identified based on risk assessment). The end-of-round campaign coverage percentages were 77% for the 1st round, 73% for the 2nd round, and 78% for the 3rd round (45).

Table 1. Childhood diphtheria immunization in Turkey by years

Year	Administered Vaccine	1 st dose	2 nd dose	3 rd dose	Booster	Booster	Booster
1980	DBT	2 months	4 months	6 months	13-24 months	-	-
	DT	-	-	-	-	6 years	-
1987	DBT	end of 2 nd month	end of 3 rd month	end of 4 th month	16-22 months	-	-
	DT	-	-	-	-	1 st grade	-
1990	DBT	end of 2 nd month	end of 3 rd month	end of 4 th month	16-24 months	-	-
	DT	-	-	-	-	1 st grade	-
1997	DBT	end of 2 nd month	end of 3 rd month	end of 4 th month	16-24 months	-	-
	DT	-	-	-	-	1 st grade ¹	-
	Td2	-	-	-	-	-	5 th grade
1998	DBT	end of 2 nd month	end of 3 rd month	end of 4 th month	16-24 months	-	-
	Td3	-	-	-	-	1 st grade	5 th grade
2003	DBT	end of 2 nd month	end of 3 rd month	end of 4 th month	16-24 months	-	-
	Td	-	-	-	-	1 st grade	8 th grade
2008	DaBT-İPA-Hib	end of 2 nd month	end of 4 th month	end of 6 th month	18-24 months	-	-
	Td	-	-	-	-	1 st grade	8 th grade
2010	DaBT-İPA-Hib	end of 2 nd month	end of 4 th month	end of 6 th month	18-24 months	-	-
	DaBT-İPA4	-	-	-	-	1 st grade	-
	Td	-	-	-	-	-	8 th grade
2012	DaBT-İPA-Hib	end of 2 nd month	end of 4 th month	end of 6 th month	end of 18 th month	-	-
	DaBT-İPA	-	-	-	-	1 st grade	-
	Td	-	-	-	-	-	8 th grade
2020	DaBT-İPA-Hib	end of 2 nd month	end of 4 th month	end of 6 th month	end of 18 th month	-	-
	DaBT-İPA	-	-	-	-	48 th month ⁵	-
	Td	-	-	-	-	-	13 years

¹With the enactment of Law No. 4306 on August 16, 1997, mandatory primary education included eight uninterrupted years beginning with the 1997-1998 academic year. With this Law, the "primary school and secondary school phrases were changed to elementary school", which was used separately. This regulation was amended by the Law No. 6287 dated 30.03.2012, beginning with the 2012-2013 academic year, to state that "... primary education is a National Education and Training Institution consisting of a four-year compulsory primary school and a four-year compulsory secondary school." (55,57).

²Td vaccine replaced the tetanus toxoid vaccine for students in 5th grade starting with the 1997-1998 academic year.

³After 1998, the DT vaccine administered in 1st grade was replaced with the Td vaccine.

⁴In October 2010, the 4DaBT-İPA vaccination was introduced in the first grade.

⁵Administered to all 48-month-old children born after July 1, 2016.

Primary immunization of all women of reproductive age should be completed, and pregnant women who have never been vaccinated should receive at least two doses of Td vaccine, with the second dose finished at least two weeks before delivery, according to program guidelines. Booster vaccination should be continued at 10-year intervals in women of reproductive age (15-49 years) who have received five doses of the Td vaccine (45).

Adults have been routinely vaccinated with combinations containing tetanus toxoid (Td vaccine) since 2008 (45). Accordingly, the Td (adult-type diphtheria-tetanus) vaccine is administered to adults whose previous vaccination status is unknown. The primary administration scheme consists of three doses. The interval between the first and second doses should

be at least four weeks, and the interval between the second and third doses should be at least six months. The vaccination schedule is continued with booster doses administered every ten years (45).

Furthermore, the use of the Td vaccine in tetanus prophylaxis in injuries and military immunizations provided an extra opportunity for adults to be immunized against diphtheria (45).

2. Diphtheria Epidemiology

No cases of diphtheria have been reported in Turkey since 2011 (43). The last case reported in 2011 was a 33-year-old female who was possibly unvaccinated. Following the notification of the case, epidemic control measures such as collect-

ing swab samples from close contacts, prophylactic antibiotic medication, and immunization were implemented, and the epidemic was contained to a single case (43).

According to Ottoman archives, the notification of diphtheria became mandatory with the regulations and status reports issued during the Ottoman Empire's final periods. These regulations specified who should submit the notice, as well as the steps to be taken for diagnosis, treatment, and control (24). Following the foundation of the Republic, notifiable diseases, including diphtheria, were designated in the Law on Hygiene and Public Health, which went into effect in 1930, and regulations concerning surveillance and efforts to prevent infectious diseases and epidemics were implemented (59).

With the adoption of the Notification System of Communicable Diseases Directive in 2004, the list of notifiable communicable diseases was updated, and standard case definitions for notifiable communicable diseases were specified. The directive requires that notifications be based on laboratory findings rather than clinical observations, and notifications were categorized based on specific criteria. In this context, probable and confirmed cases of diphtheria were defined, and all healthcare institutions were instructed to notify provincial health directorates of probable and confirmed cases and the Ministry of Health of confirmed cases (60). In addition to routine reporting, diphtheria is a notifiable disease. In case of a probable and confirmed diagnosis of diphtheria, healthcare authorities should be notified by phone without waiting for the regular notification. A case study should be conducted, a field investigation should be initiated, and epidemic investigations should be carried out in conjunction with case notification/reporting (61).

Diphtheria outbreaks resulted in a large number of cases and deaths during periods when vaccinations were not extensively and systematically delivered (Figure 1).

Figure 1 illustrates diphtheria cases, number of deaths, and morbidity rates, as well as DBT3/DaBT-IPA Hib3 vaccination coverage by year (43,62).

The Ministry of Health has been keeping track of diphtheria cases since 1925. Turkey is one of the few countries that can evaluate epidemiology over time.

When morbidity rates since 1925 are examined, it is notable that the highest morbidity rates occurred between 1954 and 1963. However, given the possibility of difficulties with disease notification and reporting, it should not be overlooked that the morbidity rate may have been higher in earlier years. The morbidity rate between 1954 and 1963 was reported as the lowest at 11.2 per hundred thousand in 1954 and the highest at 19.6 per hundred thousand in 1957. During this period, most cases were documented in 1958, with 4999 cases and 661 deaths. In the same period, mortality rates varied between 1.20 and 2.60 per hundred thousand, while the highest mortality rate in all years was 2.60 per hundred thousand in 1958. No deaths have been reported since 2001, except for the death of 1 patient reported in 2011 (Figure 1-3) (43,62).

As of 1956, the annual health statistics show the number of people who were vaccinated with diphtheria-containing combinations between 1950-1984 and the total number of vaccine doses administered. Table 2 shows the number of vaccines containing diphtheria that were administered between 1950-1984. Vaccination coverage data could not be provided because information on the age groups and number of doses

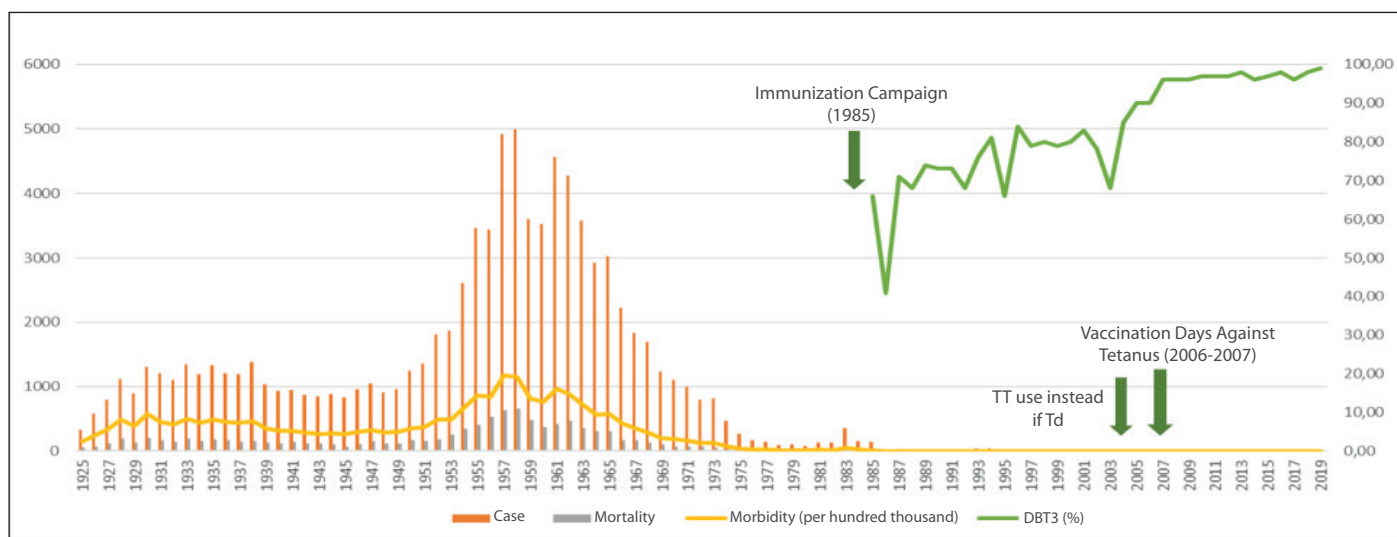


Figure 1. Diphtheria cases and deaths by years, morbidity, and DBT3 (0 age group diphtheria-pertussis-tetanus vaccine 3rd dose) vaccination rates, Turkey (1925-2019).

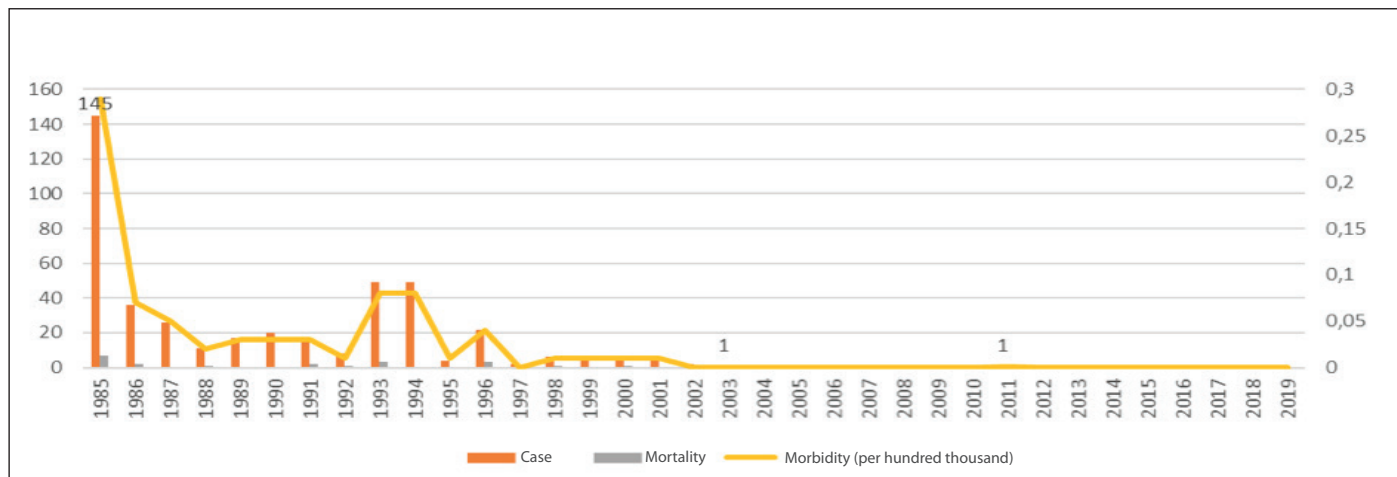


Figure 2. Diphtheria cases and deaths by years, morbidity rates, Turkey (1985-2019).

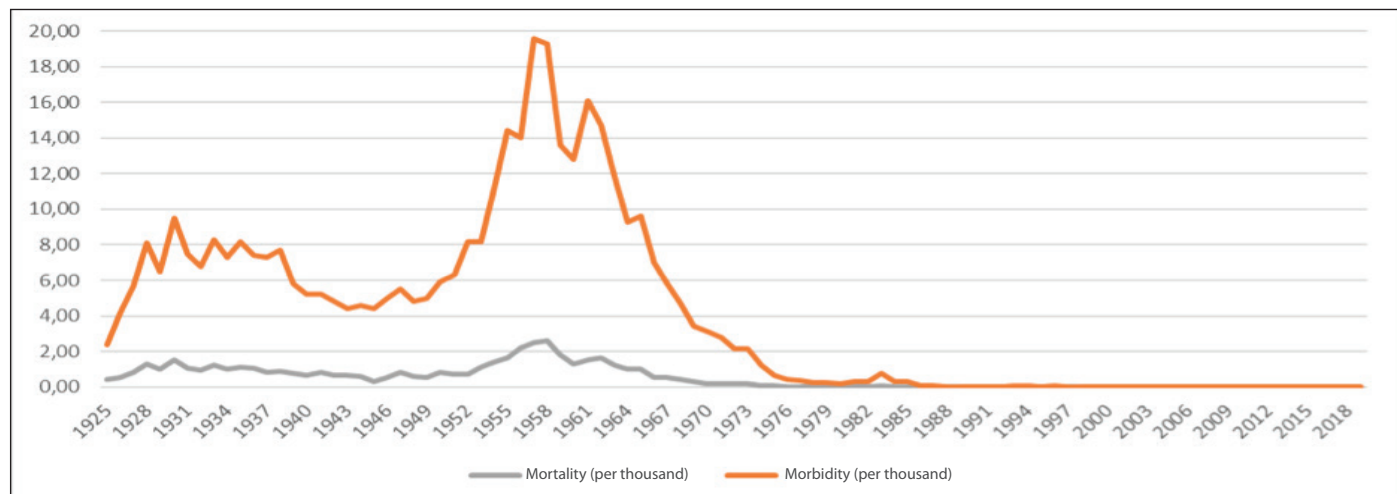


Figure 3. Distribution of morbidity and mortality rates of diphtheria cases, Turkey (1925-2019).

for the specified period could not be obtained. While the overall population was 21.008.354 the 0-4 age group 3.162.070 the 5-9 age group 2.636.311 and the 10-14 age group 2.309.880 in 1950, the number of persons who received the diphtheria vaccine was 102.931 in 1950, indicating that vaccination coverage was quite low in the risk group.

An increase in vaccination has been observed since the 1960s (Table 2). Since the mid-1960s, there has been a fairly significant decline in the incidence of diphtheria, which may be attributed to increased immunization (43,62). Parallel to this, after 1965, the diphtheria antitoxin demand of healthcare facilities from the Refik Saydam Institute of Hygiene and Public Health decreased rapidly, from 997 liters in 1965 to 324 liters in 1970, and 92 liters in 1975 (63).

Vaccination services were offered in the 1970s through widely carried out and regularly repeated campaigns. How-

ever, it is known that the vaccine can be administered to age groups at high risk, even before the seasons in which the disease occurs (45).

The Turkish National Immunization Campaign was launched in 1985 to immunize 0-60 month-old unvaccinated or under-vaccinated children against five diseases (diphtheria, pertussis, tetanus, polio, and measles), increasing vaccination coverage, meeting logistical needs related to vaccination services, strengthening the cold chain, ensuring intersectoral cooperation in healthcare services, improving registries, and enhancing the infrastructure required for systematic vaccination through personnel training (52,64). Before the campaign, DBT 3 coverage was reported to be 7.9% in the 0-12-month group, 41.3% in the 13-60-month group, and 34.1% in the 0-60-month group in a survey of 5800 households conducted between August 1 and 22, 1985.

Table 2. Number of vaccines against diphtheria administered by year in Turkey (1950-1984)¹

Year	Diphtheria	DBT	Typhoid Diphtheria Tetanus	Diphtheria Tetanus
1950	102931	–	–	–
1951	129485	–	–	–
1952	136414	–	–	–
1953	306879	–	–	–
1954	420349	–	–	–
1955	500860	–	–	–
1956	389782	–	–	–
1957	450093	–	–	–
1958	966237	–	–	–
1959	359605	–	–	–
1960	904815	–	–	–
1961	1020100	–	–	–
1962	1262360	–	–	–
1963	1247624	–	–	–
1964	2213892	–	–	–
1965	5312935	–	–	–
1966	3952530	–	–	–
1967	4540145	–	–	–
1968	5402802	–	–	–
1969	5267522	–	–	–
1970	5348476	–	–	–
1971	2199366	–	–	–
1972	3409955	–	–	–
1973	–	2403768	4034921	–
1974	–	3056498	2078225	–
1975	–	2797472	2091012	–
1976	–	2836993	2207063	–
1977	–	2889605	1762038	–
1978	–	2708250	1583972	–
1979	–	2528320	1422305	–
1980	–	2154222	311544	–
1981	–	2914489	–	690481
1982	–	2528128	–	867400
1983	–	4279960	–	103326
1984	–	4626524	–	1068228

¹The number of people vaccinated between 1950-1963 and the number of 1st, 2nd, 3rd and booster doses administered between 1964-1984 are provided (9).

In the same survey, it was discovered that only a small percentage of children had a vaccination card, that a substantial proportion of vaccinated children were vaccinated after the recommended ages, and that the rate of discontinuation was high (43,52,64).

The Turkish National Immunization Campaign was carried out in three rounds: September 1985, October 1985, and November-December 1985 (52).

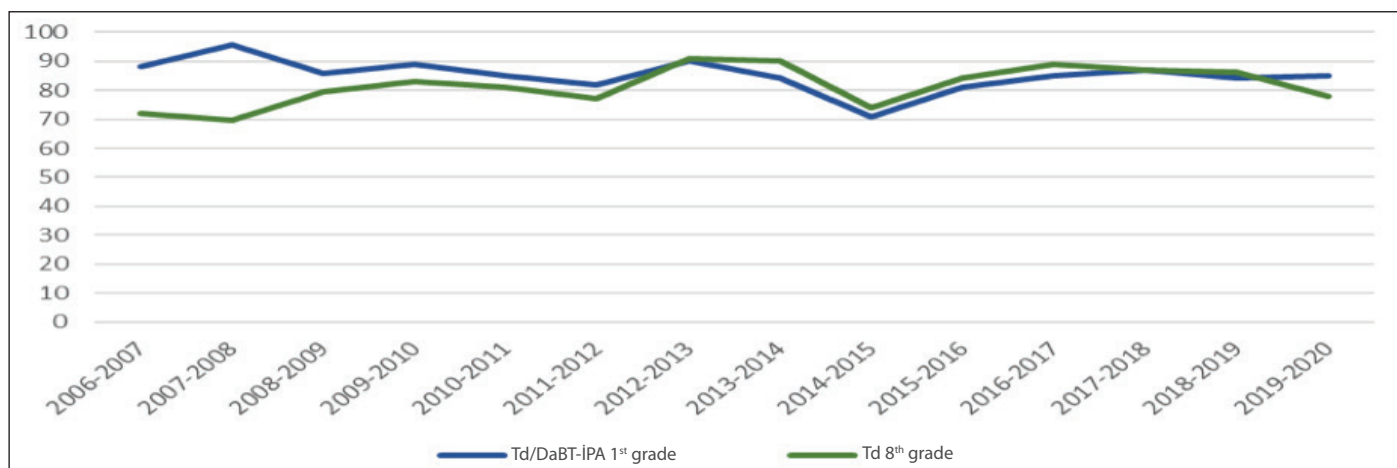


Figure 4. Diphtheria vaccine coverage by school age over the years, Turkey (2006-2007; 2019-2020).

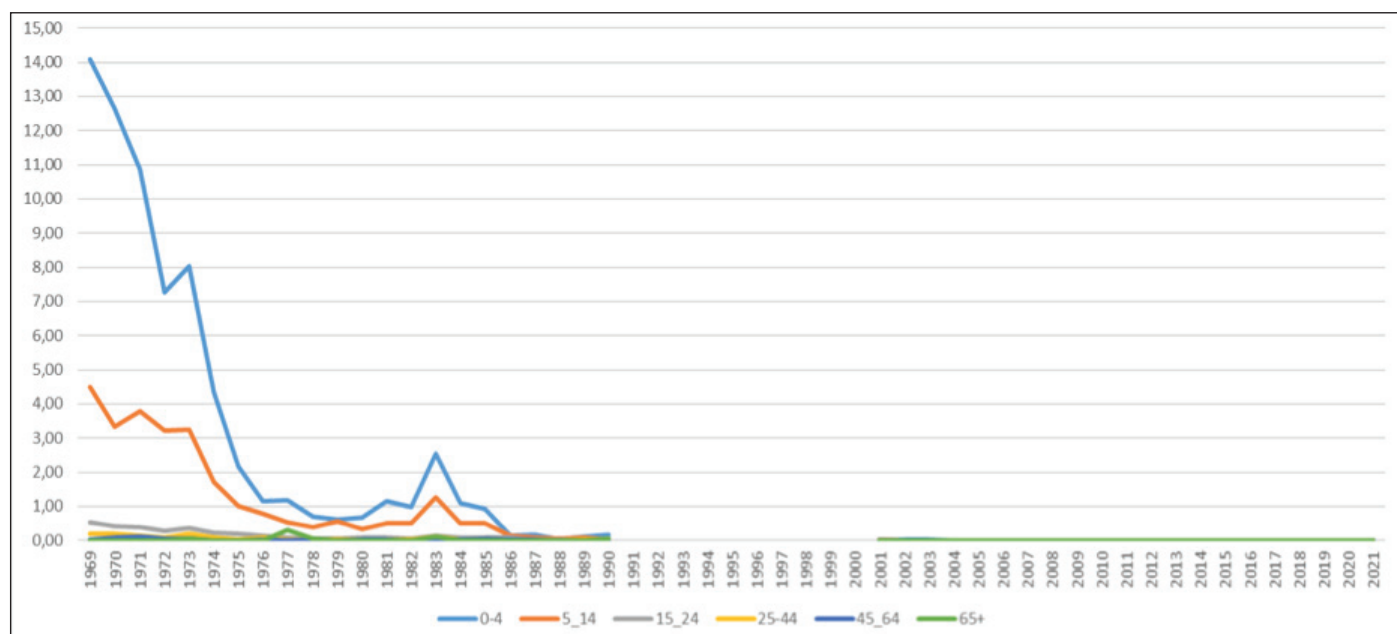


Figure 5. Distribution of diphtheria incidence rates specific to age groups by years (hundred thousand), Turkey (1969-2011).

Important steps were taken during the campaign to ensure intersectoral cooperation in healthcare, such as assigning teachers to vaccination teams, providing vehicle and fuel support from other public institutions, particularly the Ministries of National Defense and National Education, and delivering pro-vaccination messages in collaboration with the Presidency of Religious Affairs. Furthermore, health-related broadcasts were given additional airtime on the national television channel, the PTT waived fees for phone calls made to healthcare organizations in certain areas, and provincial governors championed the cause. Records such as household evaluation slips and child monitoring cards have been reorganized in healthcare facilities, cold chain materials have been replenished to a large extent, physicians and non-physician healthcare personnel have been trained on vaccination, public education efforts

have been undertaken, and new arrangements on immunization and cold chain officers have been made in central and provincial health organizations.

DBT3 or DBT booster vaccine coverage in the target population (5.123.559) of infants and children with or without immunization was 66.1% in the 0-12-month group, 79.7% in the 13-60-month group, and 76.8% in the 0-60-month group at the end of the campaign. Several field surveys conducted before the campaign revealed that DBT vaccination coverage ranged between 25% and 35% of fully vaccinated infants. When this rate is taken as 25% and the campaign coverage percentages are included, the percentage of children aged 0-60 months who received DBT3 or a booster dose was calculated to be 82.5%. (64).

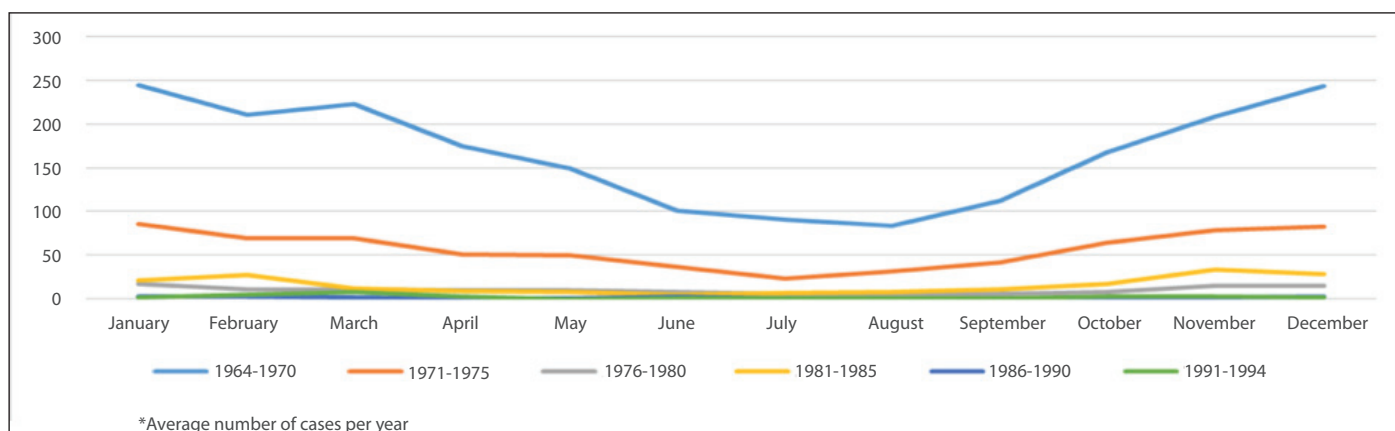


Figure 6. Distribution of diphtheria cases by months, Turkey (1964-1994).

The incidence of diphtheria had ranged from 3.14 to 0.19 per hundred thousand between 1970 and 1985 and decreased to 0.07 and 0.05 per hundred thousand in 1986-1987 following the immunization campaign. However, there were still spikes in the number of cases every 2-3 years (Figure 1-3) (43,52).

With Circular No. 5110/23, issued to provincial health directorates on October 24, 1986, the Ministry of Health and Social Services announced the system of monthly monitoring of babies who need to be vaccinated to prevent the accumulation of unvaccinated babies. The monthly monitoring method is based on knowing the number of babies expected to be born each month in a particular region and on the principle of vaccinating as many children every month (65). Currently, vaccination coverage is estimated using the same method.

Vaccination coverage fell to 41% in 1986 after the campaign, has generally been around 80% since the mid-1990s, and remained at 90% and above in 2005 and beyond. The incidence of diphtheria remained at 0.001 per hundred thousand between 1998 and 2001, and sporadic cases were reported, including one in 2003 and one in 2011 (Figure 1-3) (43).

In addition to maintaining a high level of DBT3 vaccination coverage in infancy since 2005, 80% or higher immunization coverage, including diphtheria, has been reached in school age (1st and 8th grade) (43).

Age-specific diphtheria incidence rates for the years 1969-2021 are given in Figure 5. Since the age information of diphtheria cases between 1991 and 2000 could not be obtained, there are no age-specific incidence rates from that period in the Figure.

The age-specific incidence rates given in Figure 5 until 1990 show that the incidence rates were high under the age of 15, reflecting the low childhood vaccination coverage (43,66). The highest incidence of diphtheria was 14.10 per hundred

thousand in the 0-4 age group and 4.49 per hundred thousand in the 5-14 age group in 1969. Later, it fell fast in both age categories, to 0.69 and 0.38 per hundred thousand in 1978, respectively. The disease, which appeared in outbreaks every one or two years, began to drop in incidence following the 1985 Turkish National Immunization Campaign. In 1990, the incidence of diphtheria was 0.17 per hundred thousand in the 0-4 age group, and 0.03 per hundred thousand in the 5-14 age group.

When the seasonal characteristics of cases reported between 1964 and 1994 were examined, it was discovered that the number of cases increased primarily during the winter and autumn (Figure 6) (43).

Table 3 depicts the distribution of hospitalized, cured, and deceased diphtheria patients in healthcare facilities, including public and private hospitals, as well as mortality rates over time. Although there are inconsistencies between the number of cases reported by inpatient treatment facilities and the overall number of cases reported throughout Turkey between 1955 and 2003, the declining trend reported over the years in both data sources is comparable (43).

The fatality rates of the cases reported from inpatient treatment facilities and the total number of cases reported in Turkey are presented in Figure 7. The fatality rates recorded by inpatient treatment institutions and the total number of cases reported in Turkey are both similar. Until 1965, diphtheria fatality rates in Turkey ranged from 8.3% to 16.9% but have since declined to between 8.4% and 14.0% between 1981 and 1984. Because the number of cases reported after 1985 was very low, fatality rates varied, and the fatality rate for all cases recorded in and after 1986 was 5.3% (Figure 7) (43).

Diphtheria-associated fatality rates were 52% in the 1880s, while it was 7% in the 1940s-1950s. In these periods, in our country, the rates varied between 8% and 15%. Today, the rate

Table 3. Distribution of the number of inpatients, cured and deceased cases and mortality rates by years in healthcare facilities, public and private hospitals with the diagnosis of diphtheria in Turkey² (1955-2003)

Year	Health Centers						Public and Private Hospitals					
	Admitted	Cured	Died	Fatality rate (%)	The rate of mortality per 1000 admitted	Overall mortality (per 1000)	Admitted	Cured	Died	Fatality rate (%)	The rate of mortality per 1000 admitted	Overall mortality (per 1000)
1955	-	-	-	-	-	-	2218	1818	400	18	0.8	19.7
1956	-	-	-	-	-	-	2358	1945	413	18	0.7	18.2
1957	221	189	32	14.5	0.4	19	3475	2819	656	19	1.1	26.2
1958	312	261	51	16.3	0.5	32.6	3998	3366	632	16	1	27.5
1959	210	171	39	18.6	0.4	25.8	2926	2442	484	17	0.8	22.9
1960	187	155	32	17.1	0.3	18.5	2950	2512	438	15	0.7	19.7
1961	200	180	20	10.0	0.2	14	3662	3141	521	14	0.8	21.7
1962	218	193	35	16.1	0.2	16.6	3911	3323	588	15	0.8	23.8
1963	213	189	24	11.3	0.2	15.4	3887	3319	568	15	0.8	22.4
1964	181	150	27	14.9	0.23	18.8	3496	2944	488	14	0.38	19.1
1965	286	265	19	6.6	0.17	15.1	3483	3016	393	11	0.46	14.6
1966	100	86	11	11.0	0.1	9.7	2636	2327	262	10	0.28	9.1
1967	84	78	5	6.0	0.04	4.3	2348	2091	224	10	0.23	7.8
1968	45	41	4	8.9	0.039	3.89	2314	2120	194	8	0.2	6.5
1969	69	61	7	10.1	0.066	6.79	1863	1730	133	7	0.13	4.06
1970	45	41	3	6.7	0.031	3.5	2115	1993	122	6	0.11	3.67
1971	36	23	3	8.3	0.035	3.97	2420	2280	140	6	0.12	4.91
1972	42	36	4	9.5	0.047	5.52	2140	2007	133	6	0.11	3.32
1973	-	-	-	-	-	-	2322	2122	148	6	0.1	3.38
1974	7	7	-	0.0	-	-	1028	925	18	2	-	0.65
1975	-	-	-	-	-	-	773	719	54	7	-	-
1976	-	-	-	-	-	-	664	593	71	11	-	-
1977	-	-	-	-	-	-	510	480	30	6	-	-
1978	-	-	-	-	-	-	528	482	46	9	-	-
1979	-	-	-	-	-	-	297	268	29	10	-	-
1980	-	-	-	-	-	-	321	295	26	8	-	-
1981	-	-	-	-	-	-	249	203	46	18	-	-
1982	-	-	-	-	-	-	230	195	35	15	-	-
1983	-	-	-	-	-	-	287	242	45	16	-	-
1984	-	-	-	-	-	-	237	211	26	11	-	-
1985	-	-	-	-	-	-	349	321	28	8	-	-
1986	-	-	-	-	-	-	79	71	8	10	-	-
1987	-	-	-	-	-	-	141	137	4	3	-	-
1988	-	-	-	-	-	-	83	77	6	7	-	-
1989	-	-	-	-	-	-	59	57	2	3	-	-
1990	-	-	-	-	-	-	60	58	2	3	-	-
1991	-	-	-	-	-	-	71	68	3	4	-	-

Table 3. Distribution of the number of inpatients, cured and deceased cases and mortality rates by years in healthcare facilities, public and private hospitals with the diagnosis of diphtheria in Turkey² (1955-2003) (continued)

Year	Health Centers						Public and Private Hospitals					
	Admitted	Cured	Died	Fatality rate (%)	The rate of mortality per 1000 admitted	Overall mortality (per 1000)	Admitted	Cured	Died	Fatality rate (%)	The rate of mortality per 1000 admitted	Overall mortality (per 1000)
1992	-	-	-	-	-	-	193	190	3	2	-	-
1993	-	-	-	-	-	-	135	131	4	3	-	-
1994	-	-	-	-	-	-	65	63	2	3	-	-
1995	-	-	-	-	-	-	71	70	1	1	-	-
1996	-	-	-	-	-	-	160	156	4	3	-	-
1997	-	-	-	-	-	-	130	129	1	1	-	-
1998	-	-	-	-	-	-	113	113	0	0	-	-
1999	-	-	-	-	-	-	102	102	0	0	-	-
2000	-	-	-	-	-	-	182	182	0	0	-	-
2001	-	-	-	-	-	-	-	-	-	-	-	-
2002	-	-	-	-	-	-	150	149	1	1	-	-
2003	-	-	-	-	-	-	177	176	1	1	-	-

* The data from all public and private hospitals and healthcare facilities for the years 1955-1956.

**The distribution of all hospitalized patients in Turkey since 1975. The admitted column includes the total of discharged and deceased patients.

¹In the First Ten-Year National Health Plan prepared in 1947, the solution to the problems encountered in preventive and curative health services was discussed and it was stated that the service should be directed to rural areas in particular. In this plan, it was envisaged to establish a health officer and a village midwife for every 10 villages, and a health center with ten beds for an average of 40 villages. However, this plan, which was prepared with great hopes and foresight, could not be implemented. Later, in 1954, another plan to establish a health center in each group of villages with a population of 7.000 and each district, failed to materialize (43).

²Until the end of 1956, the A150 list was kept in 23 major provinces and the C50 list was kept in the remaining provinces by healthcare facilities. Disease statistics of all public and private hospitals (except for health centers, mental facilities, and maternity and childcare centers) were consolidated as of 1957 and all establishments were obliged to issue the A150 list. Health centers continued to keep C50 lists while separate statistical charts were developed for mental facilities (43).

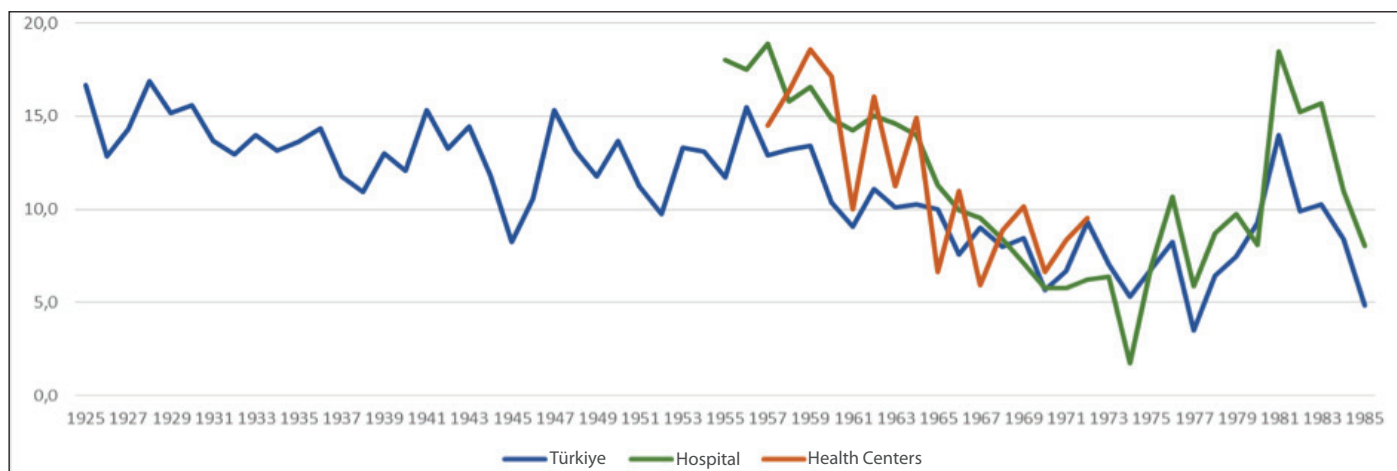


Figure 7. Fatality rates of diphtheria cases reported from hospitals and healthcare facilities in Turkey (1925-1985), Turkey (1925-1980).

in different parts of the world varies between 3% and 33%, depending on the availability of resources (3).

As of March 1957, deaths in provinces and districts were monitored by sending a copy of the Burial Permit issued by

the municipalities to the Turkish Statistical Institute through local authorities. Figure 8 shows diphtheria mortality rates by age group based on the aforementioned data (43). Figure 8 does not show age-specific mortality rates since data was not available between 1960-1963 and 1980-1985.

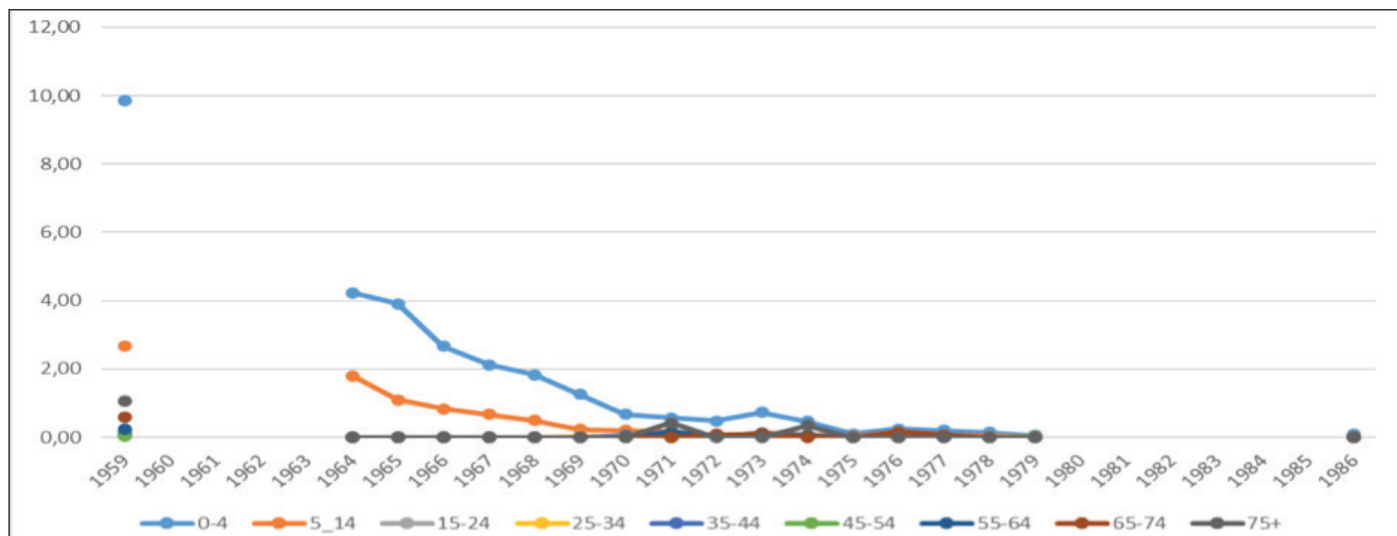


Figure 8. Distribution of age-specific diphtheria mortality rates by years (hundred thousand), Turkey (1959-1986).

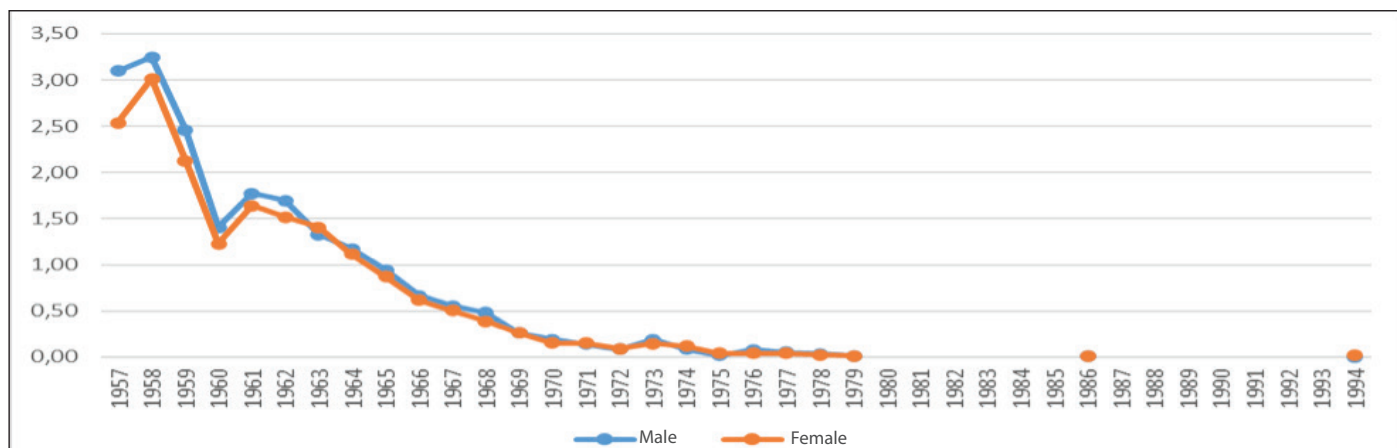


Figure 9. Distribution of gender-specific diphtheria mortality rates by years, Turkey (1957-1979).

When the mortality rates were analyzed by age group, it was found that the diphtheria mortality rate was high under the age of 15, which was consistent with the age-specific incidence rates (43). Diphtheria mortality rates in the 0-4 and 5-14 age groups were 9.87 and 2.66 per hundred thousand in 1959, respectively, and 0.08 and 0.01 per hundred thousand in 1986.

Figure 9 depicts gender-specific diphtheria mortality rates (43). Figure 9 does not show age-specific mortality rates since data was not available between 1980-1985 and 1987-1993.

Diphtheria mortality rates are comparable in men and women (Figure 9).

Despite substantial progress against diphtheria in our country, the disease remains a severe threat, as illustrated by the epidemic that resulted in 9321 cases and 50 deaths in Ban-

gladesh's Cox Bazar district (20). Similarly, recent diphtheria outbreaks in Venezuela (1612 confirmed cases, 280 deaths), Yemen (5701 probable cases, 330 deaths), and Haiti (406 confirmed cases, 80 deaths) demonstrate that political turmoil, natural disasters, migration, and displacement all contribute to an increase in risk. Knowing our historical data and what has been done, as well as maintaining vaccination methods with the same commitment and meticulousness, will ensure the continuation of success.

We would like to thank all healthcare professionals who helped control diphtheria in Turkey, the Presidency of the Turkish Statistical Institute for supplying demographic data, and Dr. Mehmet Ali Biliker for providing age-specific morbidity data.

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