Le Infezioni in Medicina, n. 3, 343-354, 2025
doi: 10.53854/liim-3303-13

Diphtheria: a serious asphyctic disease that reappears occasionally. Description of the disease in Northeastern Italy from the 16th century onwards

Carlo Contini[1], Omar Simonetti[2], Matteo Alvino[3], Stefano Manfredini[4], Chiara Beatrice Vicentini[4]

[1]Infectious Diseases, Department of Medical Sciences, University of Ferrara, Ferrara, Italy;
[2]Infectious Diseases Unit, University Hospital of Trieste, Italy;
[3]Istituto Comprensivo San Giovanni of Trieste, Minister for Education, University and Research, Trieste, Italy;
[4]Department of Life Sciences and Biotechnology, Section of Pharmaceuticals and Health Products, University of Ferrara, Ferrara, Italy.

Article received 9 June 2025 and accepted 18 August 2025

SUMMARY

Diphtheria is a serious and potentially fatal infection caused by *Corynebacterium diphtheriae*, which, before the introduction of universal vaccination, was the leading cause of illness and death among children and young adults, but which now causes sporadic but worrying outbreaks worldwide and not only among unvaccinated people.

We narrate the first descriptions of the disease until the introduction of seroprophylaxis and vaccination as well as the spread, clinical expression and treatment of diphtheria in Ferrara, and in North-Eastern Upper Adriatic Sea. We also deal with the dramatic resurgence of disease in particular categories of people and in certain countries. The sources consulted were the Academy of Sciences of Ferrara, the Ariostea Municipal Library, periodicals of Trieste and literature books.

In the period analyzed (1869-1898), 2794 people died in Ferrara, with a maximum of 44.24 per 10,000 inhabitants in 1883 and a minimum of 0.32 in 1898. Deaths from diphtheria were highly prevalent in the countryside compared to the cities (36% *vs* 23%, respectively); the female gender was most affected due the prolonged contact with sick people and unhealthy environments. Mortality was very high in those patients aged from 5 to 10 years and from 3 to 5 years, with a much lower percentage in the age groups between 1 to 3 and 10 to 15 years. Cauterization of tonsil plaques, brushing with hydrochloric acid, mucilaginous gargles, cinchona, astringent substances, were among the main remedies proposed by some distinguished academics of the time before the advent of serotherapy. Some authors were the first to describe the effects of post-diphtheria paralysis including phonation disorders. The academic Baldassari connected diphtheria trends to weather variations. In the Eastern Upper Adriatic region, diphtheria was such a threat in the last thirty years of the 19th century that it surpassed cholera and typhus in terms of mortality. The disease was more common in the coastal region than on the mainland. Istria, Koper, Poreč and Pula were the cities with the highest number of cases in 1871 and 1872. The disease hit hard between October 1894 and the first months of 1895. Prophylactic measures to combat the disease included closing schools, isolating the infected patients, and publishing recommendations text on school hygiene

Diphtheria, although almost completely eradicated in most industrialized countries thanks to mass vaccination campaigns, remains endemic where inadequate vaccination policies, low socioeconomic status, inaccessibility to public health care, wars, displacement, migratory movements are present.

Keywords: Diphtheria, seroprophylaxis, vaccination, Ferrara, Upper Adriatic Sea.

Corresponding author
Chiara Vicentini
E-mail: chiara.vicentini@unife.it

INTRODUCTION

Diphtheria is a potentially fatal infection mostly caused by toxigenic *Corynebacterium diphteriae* strains and occasionally by toxigenic *C. ulcerans* and *C. pseudotuberculosis* strains. The diphteria toxin has a necrotizing effect on previously healthy tissue and can cause serious lesions in many organs including the heart, kidney and nervous system. Before the introduction of universal vaccination in the 1940s - 1950, diphtheria was the primary cause of disease and death in children and young adults [1]. After the introduction of widespread immunization, the incidence of the disease has been reduced drastically to almost 5.000 annually worldwide. However, factors such as low socioeconomic status, inadequate income, inaccessibility to public health, wars and displacement, unvaccinated people, migratory movements, ineffective monitoring of the immunization schedule, have led to frequent sporadic but worrying outbreaks of the disease around the world [2].[1]

1. The causative agent of diphtheria *Corynebacterium diphtheriae* is a pathogenic, asporigen Gram-positive bacterium also called Klebs-Löffler bacillus. Its direct virulence factor is the toxin, an exotoxin produced by the bacterium at the site of infection and released by lysogenic strains for the bacteriophage β [3]. The tissue necrosis caused by diphtheria toxin forms a thick grey pseudo-membrane, which adhering to the nose, tonsils, larynx and throat, makes breathing and swallowing difficult. If the toxin enters the blood stream, it can cause damage to the heart (myocarditis), nerves (severe neuropathy), kidneys, rarely skin [3, 4]. Serious cardiac complications such as arhythmias, myocarditis and progressive heart failure may occur. Diphteria can be fatal even if adequately treated [4-6]. After an incubation period of 1-7 days, the disease presents with fever, asthenia, cervical lymphadenopathy, and severe sore throat. Human-to-human spread of the diphtheria bacterium occurs through the nose, respiratory droplets, coughing, sneezing, or singing [5]. People can also become ill through direct contact with infected wounds, skin ulcers, or contaminated objects. Individuals at greatest risk of infection are those living with sick people, close contacts, or those exposed to secretions of suspected infected people. Diphtheria has no animal reservoir like tuberculosis, nor environmental reservoirs like cholera and typhoid (water). The diagnosis is confirmed by isolation of Corynebacterium species on culture of the lesions and by toxigenicity testing. Individuals who develop the disease should be treated immediately with antitoxin and antibiotics (erythromycin or penicillin), then placed in isolation to prevent them from infecting others. They are usually no longer contagious after two days of treatment [2-5].

The objectives of our study were to narrate the earliest descriptions of the disease up to the introduction of tracheotomy, seroprophylaxis, and vaccination, as well as the dramatic reappearance of the disease in some countries of the world.
We also focused on the spread, clinical expression and treatment of diphtheria in North-East Italy and particularly in Ferrara city and in Upper Adriatic Sea.

MATERIALS AND METHODS

For the historical-scientific section, the main medical databases such as PubMed, Scopus, SciFinder, Google Books (Advanced Book Search), and OPAC (National Library Service Catalog, Italy) were searched, without time or language restrictions. For each publication found online, through interlibrary services or through direct contact with the authors, the bibliography was also consulted to expand the research. For the historical section (archive research), books, reports, manuscripts, and other documents dating back several years were consulted at the Academy of Sciences of Ferrara and the Ariostea Municipal Library. For the Adriatic Sea region the research was based on a careful historical investigation carried out mainly at the State Archives of Trieste. In addition to the archival work, an analysis of the press of the time was done reading articles from various Trieste newspapers of the time including il Piccolo, L'indipendente and L'Osservatore Triestino from the second half of the 19th century. Additional research was conducted at the "Biblioteca Civica Attilio Hortis" and in online databases (e.g Archive.org, Gallica) Trieste, Carso, and Istria).

Diphtheria in the past: first and late century AD
Diphtheria takes its name from the ancient Greek *diphthera*, (meaning skin, leather, or also military tent), due to the characteristic pseudo-membranes produced by *Corynebacterium diphtheriae* at the site of infection.
Diphtheria, as a suffocating throat affection with a contagious nature, was certainly known from ancient times. The Talmud mentions an affliction of the throat called 'Askerà' that was obligatory to signal to the community with the sounding of the tuba as a sign of alarm; this suggested a particularly dangerous and contagious form of a disease, which would later be called diphtheria [7]. Hippo-

crates describes various species of angina, one of which is shown to have the characteristics of diphtheria (hissing of the pharynx, back of the mouth covered with thick, viscous saliva that the sick person can spit out with great difficulty, inability of the sick person to lie down because of the danger of choking).
The first real description of diphtheria can be traced back to Archigene of Apamea, born in Apamea, Syria, who came to Rome under Trajan's empire (53-117 A.D.) and was mentioned by Juvenal as a good doctor, but above all a surgeon. However, it is *Areteus of Cappadocia* (late 2nd century A.D.) who describes the disease most exhaustively and dramatically [7, 8].
Since Roman times, the problem of how to resolve severe asphyxia caused by obstructive forms of the upper respiratory tract arose. Asclepiades of Bithynia (1st century AD) followed by Antillus (3rd century AD) were among the first to recommend tracheotomy [9].
In the Middle Ages, no documents have been found that have described symptoms attributable to diphtheria probably because the disease was in a dormant phase at that time. In fact, in the Middle Ages, after the fall of the Roman Empire, the population had thinned considerably, dispersing into small villages and towns had become depopulated, so epidemics were less likely to occur.

The disease in Europe from the 16th century onward
In the 16th century, numerous diphtheria epidemics were described in England, the Netherlands, France, Switzerland and Spain. Tracheotomy was recommended by the most skilled surgeons of the 16th and 17th centuries such as *Fabrizio d'Acquapendente* (1533-1619), a great anatomist and surgeon of Padua, who stressed that «*One must always cut, especially when there is a real danger of suffocation*» [10].
In 1617 Naples was also hit by a terrible epidemic, described in 1617 by Foglia and Sgambati who described the characteristic 'white membranes', difficulty in breathing and death by suffocation, accompanying the description with anatomopathological findings and differentiating it from other forms of angina [11]. To Tommaso Bartolini we owe the extraordinary intuition regarding the neurotoxicity of the disease, as he described it in his "De angina puerorum" [12]. He maintained that the "suffocating angina", as he called it, was caused by a contagious toxic virus (diphtheria exotoxin) that, passing through the nostrils, contaminated the brain and the spinal cord.
In the 18th century, the disease had not yet been classified nosologically; in fact, even one of the most famous pediatricians of that century, the Swedish Rosen de Rosenstein, wrote in his "Treatise on childhood diseases" "of children who died from unknown diseases" [13]. Subsequently, two terrible epidemics struck Cremona in 1747 and 1748. This pushed Martino Ghisi to conduct anatomo-pathological studies on the diphteric pseudomembranes found in the sputum of the sick and in the cadavers and to describe for the first time the velopendulum paralysis [14].
This work earned him the nickname "father of croup" by Bretonneau [15]. Ghisi distinguished between mild angina with pharyngeal localization and severe or "sensational" angina, indicating with this adjective the characteristic respiratory noise due to laryngeal obstruction.

The turning point in the 19th century: the large-scale use of tracheotomy and the discovery of the diphtheria bacillus
A breakthrough in the nosological classification of this infectious disease occurred in the 19th century when, in 1826, Bretonneau, admitted the identity of the pharyngeal and the laryngeal or croup form, assigning the disease the name diphtheria [16]. Bretonneau and later Trousseau, his pupil, admitting the infectious nature of the disease, stated that it, although localized to the throat, "injected its poisons into the entire organism, leading to death, warning of the presence of "toxins" [17]. Later, the German G. F. Dieffenbach attempted his first laryngeal catheterization in 1839 at the 'Charitè' hospital in Berlin. However, the real inventor of the intubation technique was the French paediatrician Bouchut who presented his method in September 1858 at the Academy of Medicine in Paris [18].
About thirty years later, in 1885, the American Joseph O' Dwyer, known as "the father of laryngeal intubation in croup", unaware of Bouchut's publications, announced his own method of intubation, the Fell-O'Dwyer apparatus (Figure 1), recommending it in severe cases as a substitute for tracheotomy [19]. O' Dwyer found the support of the great pediatrician Abraham Jacobi who launched it throughout America and the rest of the world, including Italy, where Francesco Egidi performed tracheal intubation in 1889 [20, 21].

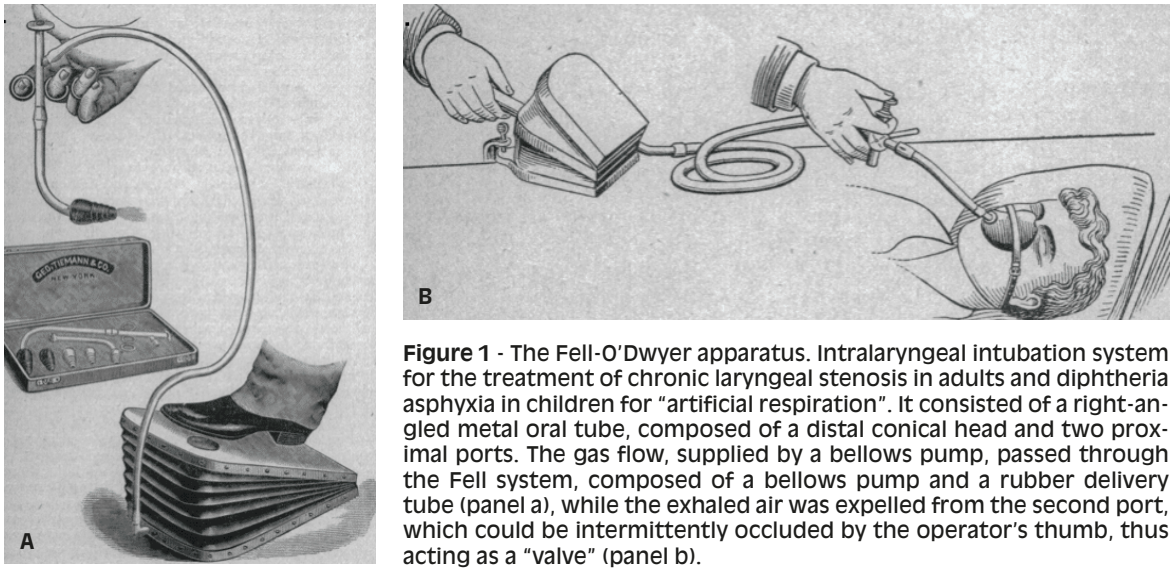

Figure 1 - The Fell-O'Dwyer apparatus. Intralaryngeal intubation system for the treatment of chronic laryngeal stenosis in adults and diphtheria asphyxia in children for "artificial respiration". It consisted of a right-angled metal oral tube, composed of a distal conical head and two proximal ports. The gas flow, supplied by a bellows pump, passed through the Fell system, composed of a bellows pump and a rubber delivery tube (panel a), while the exhaled air was expelled from the second port, which could be intermittently occluded by the operator's thumb, thus acting as a "valve" (panel b).

Finally, the identification of the causative agent of diphtheria was made by Klebs in 1883, when he succeeded in staining samples obtained from diphtheria membranes. The following year, in 1884, *Loeffler* cultivated the micro-organism in artificial medium and showed that it caused a fatal infection in guinea pigs very similar to the human disease [22]. He also found that diphtheria bacilli were only found in pseudo-membranes and not at systemic level.[2]

Seroprophylaxis and serotherapy

Even before the introduction of serotherapy, mortality from diphtheria in Europe had fallen, although epidemics occurred in Milan (from 1902 to 1934), and in the major urban centres of Europe such as Copenhagen, Berlin, Vienna, Paris, Zurich and London, thanks to early diagnosis, hygiene and isolation measures, compulsory reporting and the improved social and health conditions of the population in general. However, serotherapy and seroprophylaxis were not sufficient to interrupt the chain of transmission of the disease, let alone eradicate it. It is for this reason that one of the most illustrious Italian doctors Angelo Celli intervened in 1911 against the proposal to make diphtheria seroprophylaxis compulsory, both for its high cost and for its demonstrated inability to eradicate the infection, proposing instead, on the basis of the English model, to make its use limited to epidemic outbreaks in order to circumscribe them [23].

Towards the realization of the diphtheria vaccine

Available from 1920, the diphtheria vaccine containing the toxin modified as inactivated with formol proved to be stable and irreversible, so much so that it was no longer toxic, but capable of stimulating the immune system to produce protective antibodies against *C. diphteriae*. This modified diphtheria anatoxin had been obtained by Gaston Ramon, the veterinary 'inventor of the diphtheria vaccine' [24]. The anatoxin-based vaccine was used for the first time in France in several primary schools, sanatoriums and in the army with excellent results. It became mandatory for children under 18 months from 1938 onwards, reducing the incidence of diphtheria throughout France until its disappearance in the 1990s. Where the vaccine managed to cover a high percentage of children,

2. In 1898, Emile Roux stated: 'Microbes are above all dangerous because of the substances they produce' [25]. Together with the Swiss Alexandre Yersin, Roux identified diphtheria toxin as the virulence factor of *C. diphtheriae*. This discovery, together with Emil von Behring's studies on diphtheria antitoxin, led to the development of the first effective therapy against diphtheria [26].

the course of the diphtheria epidemic ceased, while it continued to claim victims where the vaccine covered only a small percentage of the population. Italy was among the first European countries to adopt vaccination, contributing to a drastic reduction in cases [27]. Highly effective, the diphtheria vaccine is administered together with the tetanus and pertussis vaccines (law of 20 March 1968, n. 419). Since 2001, diphtheria toxoid is a key component of the hexavalent vaccine.

Diphtheria/croup in Ferrara in the second half of the 19th century

The data below were collected from the Academy of Sciences of Ferrara (Accademia delle Scienze di Ferrara), formerly the Medical-Surgical Academy (Accademia Medico-Chirurgica), and the Ariostea Municipal Library (Biblioteca Comunale Ariostea).

The lectures by doctors who were members of the Academy, Nicola Boari, Rinaldo Turri, Luigi Baldassari, Arnaldo Trambusti and the reports by Alessandro Bennati are exhaustive for the period in question. Boari was a doctor in Francolino of Ferrara, Turri was President of the Academy in 1895-96. Trambusti, from Palermo, was a professor of General Pathology and Director of the Cabinet and Laboratory of General Pathology and Bacteriology and Baldassari was his Assistant. Alessandro Bennati was the Director of the Arcispedale S. Anna in Ferrara.

In January 1863, Nicola Boari reported to the Medical-Surgical Academy of Ferrara on pseudo-membranous angina known as "croup" (*Sull'angina pseudo membranosa crupale*), describing the symptoms and proposing remedies [28]. By citing Augustin Grisolle (physician at the Hôtel-Dieu in Paris), he suggested *sanguisugio alle fauci* (bloodletting and leeching, leeches applied to the jaws) and purgatives.

In his lecture Boari said: *To prevent the morbid exudate from spreading and the yellowish-white plaques from deepening, it is necessary to immediately modify the surfaces of the nasal and oropharyngeal mucous membranes by means of cautery; indeed, the possibility of cure lies precisely in the effectiveness of these modifications. I have resorted the cautery since the first signs of inflammation of the tonsils, the palatine arch, and the adjacent parts, regardless of the appearance or otherwise of the whitish spot or plaques appeared, which as an immediate product of exudation, constitute the main character of the disease. To prevent the exudate from extending and the yellowish-white plaques from going deeper, cauterization must be resorted to at the first sign of inflammation of the tonsils and palate.*

Boari also indicates the use of hydrochloric acid combined with miele rosato (rosé honey). The difficulties in the process of curing *piccoli fanciulli* (small children) are understandable.

Caustic substances, mucilaginous gargles, slight detergents, cinchona, astringent substances, and chloride of lime were used to improve one's breath's smell. The tongue was covered in several areas with a blackish-gray slimy substance. In the epidemic that lasted more than eight months, out of one hundred eighty-plus cases, two thirds and more were saved. The greatest mortality occurred in children in the first months of the epidemic, because that it was impossible to apply the remedies [28].

The after-Diphteria effects of the disease

In his lecture *Delle paralisi post-difteriche* (post-diphtheria paralysis) read at the Medical-Surgical Academy of Ferrara in July 1878, Rinaldo Turri precisely described the consequences that can be observed in a patient after a recovery from diphtheria which initially resolved successfully [29]. The case under analysis was that of one of his patients, a 47-year-old man whose evolution has been described with precision from the onset of the disease (September) to the first symptoms of paralysis, which occurred after 20 days up to the clear signs of recovery at the beginning of March. The manifestation of the disease corresponded exactly to what is reported and justified today. Neurological toxicity appears in a few cases but affects the cranial and peripheral nerves. Turri observes paralysis of the glossopharyngeal nerve with phonation disorders and paralysis of the velopendulus and hydro-alimentary reflux in the nasal cavities during swallowing. He also observes subsequent paralysis of the cranial, ocular, facial and spinal nerves affecting the trunk, limbs and diaphragm [29].

The incidence of diphtheria infection in the last thirty years of the 19th century (1869-1898). Therapy with antitoxic serum – Meteorological observations

Luigi Baldassari takes the trend of diphtheria infection (also including croup) in the last thirty years of the twentieth century in Ferrara [30]. The civil progress of the population, the health meas-

ures adopted, and serotherapy had reduced morbidity and brought mortality to a very low figure (*Il progresso civile della popolazione, i provvedimenti sanitari adottati, la sieroterapia hanno molto ridotto la morbilità e portato a cifra bassissima la mortalità*).

Table 1 - Mortality from diphtheria (1869-98) calculated per 10,000 inhabitants according to Baldassari [30].

Year	*Number of deaths*		*Total*	*Mortality calculated per 10,000 inhabitants*
	City	*Countryside*		
1869	6	35	41	5.74
1870	9	16	25	3.46
1871	12	11	23	3.17
1872	2	5	7	0.95
1873	4	5	9	1.25
1874	10	3	13	1.73
1875	43	6	49	6.46
1876	51	170	221	28.79
1877	37	160	197	25.45
1878	29	146	175	22.44
1879	60	236	296	37.8
1880	47	211	258	33.06
1881	40	105	145	18.82
1882	32	145	177	22.98
1883	59	281	340	44.24
1884	29	154	183	23.73
1885	8	74	82	10.46
1886	7	77	84	10.56
1887	2	37	39	4.84
1888	15	49	64	7.83
1889	9	22	31	3.73
1890	10	20	30	3.57
1891	5	18	23	2.72
1892	15	28	43	5.05
1893	51	40	92	10.73
1894	29	58	87	10.05
1895	12	19	31	3.54
1896	12	7	19	2.14
1897	2	5	7	0.77
1898	-	3	3	0.32
	647	2147	2794	

Baldassari collected the data from the death statistics, kept in the Civil Status Office (*Ufficio di Stato Civile*). It was very difficult to know the exact number of patients, although reporting was mandatory. The detection of mortality was, however, a well-definable data. In the thirty years under analysis from 1869 to 1898, 2794 individuals died in Ferrara with a maximum of 44.24 per 10,000 inhabitants in 1883 and a minimum of 0.32 in 1898.

Table 1 and Figure 2a show the figures giving the absolute and relative mortality; the diagram shows the trend of mortality calculated per 10,000 inhabitants.

The diphtheria diagram shows that a period of low mortality is followed by one with a consistently high, often very high, number of deaths. In the last 14 years of the period analyzed, the mortality rate remained within narrower limits, the disease lost ground and showed a certain resurgence, but it fell sharply and continuously from 1994 onwards. It was precisely in 1994 that antitoxic serum therapy was introduced, and it has since proven successful.

The average annual number of deaths per 10,000 inhabitants from 1894 to 1898 was 3.6 compared to National mortality rate which was higher than 14 per 10,000 inhabitants in 1888, while in 1889 decreased to 10 cases per 10.000 inhabitants [31, 32]. Excluding 1894, this figure dropped to 1.7. Meanwhile, from 1889 to 1893, it was 5.01, which was also a period of low mortality. In 1898, there was a minimum number of deaths (3 deaths out of 24 reported cases) in a 30-year span.

Note that the diagram shows rapid, slow and gradual decreases; the disease spread quickly but did not return to its previous proportions until several years later.

The study was conducted by Baldassari in parallel with the one on typhus. The author observed that both typhus and diphtheria had a very low mortality rate in 1891, the lowest for both diseases in the last thirty years [30]. This decrease was achieved thanks to a slow decline in the curve, which in both cases lasted eight years, since typhus ended the period of highest number of deaths and diphtheria marked the year of highest mortality. There was then a general increase in the number of deaths, which reached its maximum in 1893, followed by a new decrease. The analogy observed is surprising, given that these are different diseases. Many

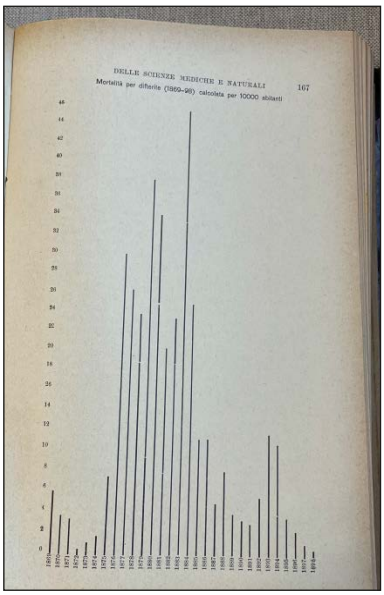

Figure 2a - Mortality from diphtheria (1869-98) calculated per 10,000 inhabitants.

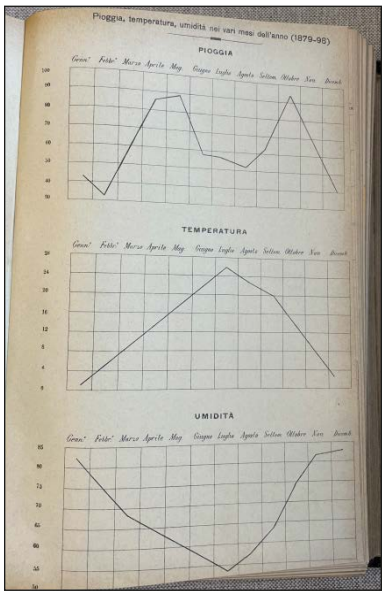

Figure 2b - Rain, temperature, humidity in the various months of the year (1879-98).

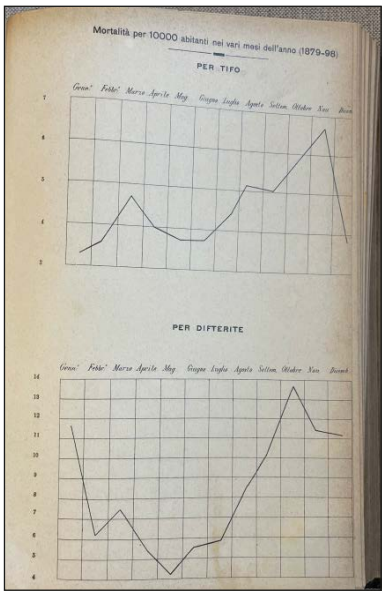

Figure 2c - Diphtheria mortality per 10,000 inhabitants in the various months of the year 1879-98

factors also favored the development and spread of infectious forms, such as poverty, agglomeration in unhealthy houses, unfavorable climatic conditions, etc. On the other hand, the hygienic improvements that were gradually implemented, served to prevent all diseases and especially infectious ones, which were usually the most affected by the effects of rehabilitation work.

With regard to the proportions of deaths occurred among rural and urban dwellers, we should note that the latter accounted for approximately 36% of the population of the entire municipality. The number of deaths from diphtheria in the cities is 23% of the total. This shows that diphtheria had a considerable prevalence in the countryside. It should also be noted that in 1875, the year preceding the period of highest diphtheria mortality, the number of deaths was by far the highest in the city. In the following years the opposite happened, with the countryside causing a much higher number of deaths than the cities. It seems that the contagion spread from the center to the outskirts, where it found more favorable conditions. It is likely that in the cities, sanitary measures were quicker, more effective and better followed by the more educated population. Moreover, in the countryside, the child population was larger and perhaps more neglected. Ferrara had a higher relative mortality rate than the whole of Emilia, but over the years it fell below the average for the region. This suggests that Ferrara was for a long time the center of a serious diphtheria infection.

This severity was not as great as the average for Italy as a whole, where many regions were in a worse condition, but compared to the average for Emilia, with which the comparison is more appropriate. At the end of the century, some improvement was noted, which should be maintained with good prophylaxis.

Baldassari examined the period 1881-90 with regard to sex and age, which includes years of high and low mortality [30]. During the period, 571 males and 604 females died of diphtheria. Compared to the statistics at national level, there were more deaths among females, an excess found in Ferrara in general mortality. Females had been in contact with sick people for a long time and had lived in unhealthy environments for a long time, with a greater susceptibility to becoming ill and, once ill, would become more vulnerable.

No deaths were reported in the first month of life. Mortality was very high from 5 to 10 years and also from 3 to 5 years, with a much lower proportion in

Table 2 - Distribution of deaths by age [30].

	1881	*1882*	*1883*	*1884*	*1885*	*1886*	*1887*	*1888*	*1889*	*1990*	*TOTAL*
0-1M	-	-	-	-	-	-	-	-	-	-	
1M-1Y	4	6	2	2	1	1	3	-	-	-	19
1M-3Y	19	27	43	25	10	16	9	12	5	4	170
3Y-5Y	36	40	60	41	19	17	9	18	7	7	254
5Y-10Y	52	71	142	72	31	29	16	23	16	12	464
10Y-15Y	20	25	63	27	10	18	1	7	1	4	176
15Y-20Y	8	1	15	9	5	-	-	3	1	2	44
20Y-30Y	-	3	7	6	5	3	-	1	-	1	26
30Y-	6	4	8	1	1	-	1	-	1	-	24
	145	177	340	183	82	84	39	64	31	30	1175

the 1 to 3 and 10 to 15 years age groups (Table 2).
Baldassari together with Giuseppe Bongiovanni, director of the Meteorological Observatory, looked for relationships between the incidence of the disease and weather patterns in the period from 1879 to 1898 (Figures 2, panel a, b and c) [30].
Diphtheria mortality was high from October to January and reached its lowest point in May. The curve is fairly regular and approaches that of humidity, while it follows an almost inverse trend to that of temperature. The maximum rainfall corresponds to the maximum mortality, but the heavy rainfall in April and May shows no influence. In October, on the other hand, the humidity is higher and the temperature is slightly lower.
Baldassari therefore concluded that rain, humidity and temperature variations favor diphtheria. Due to the lack of light and drying environment detrimental to the life of microorganisms, inflammatory events in the upper respiratory tract are more frequent, facilitating the possible establishment of the diphtheria bacterium. A period of low mortality occurs in the spring.
Baldassari states that careful vigilance and the timely and intelligent application of preventive disinfection methods are key to good results. Regarding the hospital situation, he notes that isolation is not as strict as it should be and that there is a lack of hot sterilization equipment for disinfection [30].
Baldassari did not fail to promote seroprophylaxis as a health officer, as can be seen in a printed document from the Laboratorio Comunale di Igiene di Vercelli (1900) [33]. After Ferrara, he was then active in Vercelli, Venice and Florence.

The Reports Alessandro Bennati - The Hospitalized people in 1876

The Reports of Doctor Alessandro Bennati, director of the S. Anna hospital in Ferrara at that time, represent an essential source even if limited to two years (1871 and 1876). 1871 was a year of low incidence of the disease, with 23 deaths and no hospitalizations [34].
It is interesting to seek confirmation of what Baldassari reported in his reports relating to the S. Anna Hospital, Arcispedale Sant'Anna.
In 1876 the disease exploded with a peak of 221 deaths [35].
As stated in the Report under Movement of patients with diseases treated in a separate ward with special service (*Movement of the sick with illnesses treated in separate ward with special service*), in 1876, 10 males and 2 females were admitted to the Arcispedale S. Anna, and they were treated in separate departments. In detail, 6 males and 2 females in the Medical Division and 4 males in the Surgical Division. Only 1 death occurred in the medical and surgical divisions respectively (May-August). With a high incidence of the disease, hospitalizations were observed on this occasion.
However, a limited number of people were hospitalized in proportion to the high number of sick people. The disease resolved with recovery in 85% of cases [35].
In summary, the study of diphtheria in Ferrara during the second half of the 19th century was very accurate and rich in information, thanks to members of the Academy above cited. Among

them, Antonio Trambusti carried out important studies of cellular physiology on the bone marrow of diphtheria patients [36, 37].[3]
Notable findings appear in the reports of Alessandro Bennati, director of the St. Anna Hospital, Arcispedale S. Anna. The city's health situation was serious in the context of Emilia Romagna, although much better than in other depressed areas of Italy.
According to the guidelines of the time, the study was correlated with meteorological surveys provided by Giuseppe Bongiovanni [30]. These studies highlighted the use of anti -toxic serum in Ferrara since 1894, leading to a consequent reduction in mortality. The Cabinet and Laboratory of General Pathology and Bacteriology at the University of Ferrara was in line with the latest knowledge of the time and promoted its use, thanks to Luigi Baldassari. Ferrara physicians also dealt with the after-effects of the disease and their resolution.

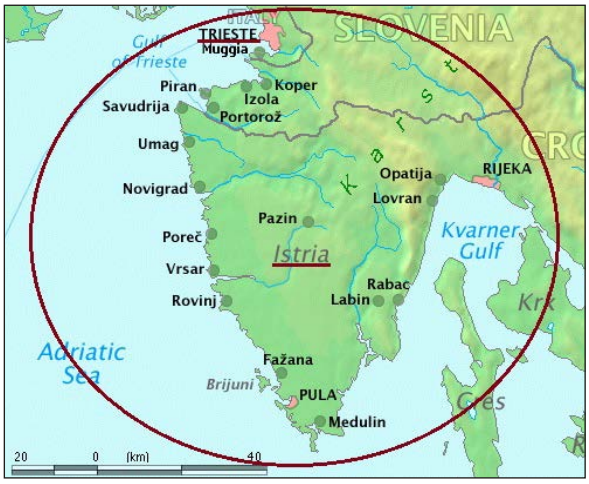

Figure 3 - Modern map of Istra, Karst and Trieste covering the area of diphtheria outbreaks in the period 1871-1903. Image edited by the authors from a picture in the public domain (link: https://it.m.wikipedia.org/wiki/File:Istria.png) - Wikimedia Commons).

Diphteria in Adriatic Sea Region (Trieste, Karst and Istria)
In the upper eastern Adriatic region (Österreichisches Küstenland), diphtheria was such a threat in the last 30 years of the 19th century that it surpassed cholera and typhus in terms of mortality. The disease was more common in the coastal region than on the mainland. In Istria, Koper, Poreč and Pola were the cities with the greatest number of cases in 1871 and 1872 with 193 and 248 cases respectively in this two-year period. Doctors such as Giovanni Baggio defined the disease as "snaking with epidemic genius" (*serpeggiando con genio epidemico*) (Figure 3) [38]. In the 1880s, the incidence of the disease declined in the upper eastern Adriatic region, only to rise again in the 1890s. The worst year in terms of contagion was 1895 with a total of 3540 cases reported in Istria. The mortality rate in the 30 years mentioned above was between 13 and 67% [39]. We also know from a chapter by *Dr. Lolli* in *Lo Sperimentale* (1873) that the diphtheria mortality rate in Trieste in the same years was around 30 deaths per month [40].
In the areas of the Austrian coastal country (Österreichisches Küstenland), it was customary at the time to publish weekly bulletins in local newspapers such as *Il Piccolo* (the most widely circulated newspaper in the city of Trieste) and *L'Indipendente* (the press organ of the irredentist world of Trieste), in which the number of infections and deaths from various infectious diseases was recorded: from smallpox to cholera and from tuberculosis to diphtheria itself. The period in which diphteria hit the city hardest was between October 1894 and the first months of 1895, when an average of 40 to 50 new infections occurred every week The most tragic bulletin was that of 14 October 1894, in which 61 new cases of diphtheria and 15 deaths were reported weekly [41]. This wave of infections, which occurred shortly after the start of the school year, led to a discussion in the local press about closing the schools, which was then decided by the local authorities until the health situation had improved [42].
Reports in the press and documents from the Littoral Lieutenancy provide data on the spread of

3. In a communication read at the Academy of Medical and Natural Sciences of Ferrara on 12 May 1896, Arnaldo Trambusti, an academician of Ferrara, presented some of his own observations "*Cytological research on bone marrow in diphtheria - contribution to the study of cellular physiology*". According to the author, the leukocytes of the bone marrow, in the early stages of diphtheria infection, show structural alterations (today we would say activated lymphocytes) expressing their increased functional activity also in terms of phagocytosis and therefore stimulation of the immune system. This activity decreases until it becomes extinct as the infection progresses, thus prefiguring very important concepts of humoral and cell-mediated immunity [37].

the disease in the various districts of the city. The old town and the harbour area were the worst affected, while the outlying districts and the villages of the Karst district were the least affected. Interesting, in this context is a document dated 12 March 1889, in which the city magistrate was informed of an investigation by the district doctor into a suspected case of diphtheria in the Karst district of Prosecco. This letter explicitly stated that many cases of diphtheria among "villagers" in the Karst village of Contovello had been brought in from the coastal area of Barcola [43].
Faced with the widespread spread of diphtheria in the town's schools, the local health authorities and doctors tried to take a whole series of measures to combat the disease: from the aforementioned closure of schools to the isolation of those infected and the publication of a text on school hygiene [44]. Interestingly, a 1894-1895 case series of post-mortem analysis in the city of Trieste revealed in 361 patients with diphtheria: croup, bronchitis, pneumonia and nephritis; frequently associated with signs of sepsis [45]. Diphtheria also appeared in literature in Trieste: In Italo Svevo's posthumously published short story *Incontro di vecchi amici* (1949) [46].

Vaccination against diphtheria today
The dismemberment of the Union in 1989 led to a collapse of vaccination policies in the various neighboring states, with the emergence of epidemics of worrying proportions [47, 48].
Recently, there have been outbreaks in many parts of the world, often associated with political unrest (Kutupalong, Bangladesh, 2017–2019; Venezuela, Haiti (2018) and Yemen (2018). In the 1990s, a 10-year epidemic in Eastern Europe caused 157,000 cases and 5,000 deaths [48, 49]. According to the Annual Epidemiological Report for 2022 based on data for 2022 retrieved from the European Surveillance System (TESSy) on January 2024, since the second half of 2022, an increase in diphtheria has been reported among migrants in several EU / EEA countries, with a peak in cases between September and December [50]. Overall, 359 cases of diphtheria due to toxigenic *Corynebacterium diphtheriae* (n=318) or *Corynebacterium ulcerans* (n=11) were reported to ECDC. The highest proportion of *C. diphtheriae* cases was among 15- to 44-year-old males; *C. ulcerans* cases were more common in adults aged 65 years and above. *C. ulcerans* has been increasingly isolated as emerging zoonotic agent of diphtheria from pet animals such as cats or dogs, indicating the enduring threat of this thought-to-be controlled disease [50]. Among *C. diphtheriae* cases with importation status available, 62% were reported as imported (having been outside the country of notification during the incubation period with no links to local transmission).
At present, diphtheria is endemic in many countries with low vaccination coverage such as Africa, Asia and Latin America, the South Pacific, Eastern Europe, Venezuela, Haiti and the Dominican Republic. In these countries, the disease occurs mainly in sporadic cases or small outbreaks [2, 51, 52]. Those who contract infection have a high mortality rate, ranging from 30% to 50%, mainly due to cardiomyopathy, airway compromise and organ failure, especially when diphtheria antitoxin therapy is not available [5, 53]. Consequently, the fight against this infection requires continuous improvement in vaccination coverage. Its efficacy is very high; approximately 90% of vaccinated persons are protected against this disease. Since protection is not long-lasting, additional booster doses are recommended every 10 years.

CONCLUSIONS

Diphtheria is a deadly re-emerging disease. Today, the risk of contracting diphtheria in the community is estimated to be non-existent for those who have completed the vaccination cycle. A moderate risk is estimated for unvaccinated people or those with an outdated vaccination schedule. Persons living or working in migrant reception centers or in precarious socio-economic conditions, especially the homeless, with a history of alcohol or drug abuse, and the immunosuppressed are at high risk [54, 55]. In the era of increasing globalization, it cannot be ruled out that there may be an increase in cases of this disease.

REFERENCES

[1] Sharma NC, Efstratiou A, Mokrousov I, et al. Diphtheria. *Nat Rev Dis Primers*. 2019; 5(1): 81.
[2] Galazka AM, Robertson SE. Diphteria: changing patterns in the developing world and the industrialized world. *Eur J Epidemiolgy*. 1995; 11(1): 107-117.
[3] Hoskisson PA. Microbe Profile: Corynebacterium diphtheriae - an old foe always ready to seize opportunity. Microbiology (Reading). 2018; 164(6): 865-867.

[4] Holbourn KP, Shone CC, Acharya KR. A family of killer toxins. *The FEBS Journal*. 2006; 273: 4579.
[5] Hadfield TL, McEvoy P, Polotsky Y, et al. The pathology of diphtheria. *J Infect Dis*. 2000; 181 Suppl. 1: S116-20.
[6] Truelove SA, Keegan LT, Moss WJ et al. Clinical and Epidemiological Aspects of Diphtheria: A Systematic Review and Pooled analysis. *Clin Infect Dis*. 2020; 71(1): 89-97.
[7] Tekiner H. Aretaeus of Cappadocia and his treatises on diseases. *Turk Neurosurg*. 2015; 25(3): 508-512.
[8] Areteo di Cappadocia, Delle cause, dei segni e della cura delle malattie acute e croniche, libri otto volgarizzati da Francesco Puccinotti, Livorno, Tipografia Bertani e Antonelli e C. 1844.
[9] Brady FA, Kelly BD. Asclepiades of Bithynia: Greek physician and medical reformer. *Ir J Med Sci*. 2023; 192(4): 1775-1778.
[10] Girolamo Fabrici d'Acquapendente, Operationes chirurgicae, In Padoua, per Giacomo Cadorino 1685. https://it.wikipedia.org/wiki/Girolamo_Fabrici_d%27Acquapendente http://www.treccani.it/enciclopedia/girolamo-fabrici-d-acquapendente/
[11] Sgambati G. De pestilenti faucium affectu (descrizione di una tremenda epidemia di difterite verificatasi a Napoli nel 1617). Neapoli, excudebat Tarquinius Longus. 1620.
[12] Bartholini Thomae. De angina puerorum Campaniae Siciliaeque epidemica exercitationes. Accedit De laryngotomia cl. v. Renati Moreau ... epistola; Bartholin, Thomas 1616-1680; Moreau, René 1587-1656; Varennes, Olivier: de Lutetiae Parisiorum: apud Olivarium de Varennes via Jacobaea sub vase aureo. 1646.
[13] English PC. Diphtheria and theories of infectious disease: centennial appreciation of the critical role of diphtheria in the history of medicine. *Pediatrics*. 1985; 76: 1-9.
[14] Lettere mediche del Dottor M. Ghisi (Cremona, 1749). The first letter deals with various illnesses cured by mercury; the second contains the history of epidemic angina in 1747 and 1748.
[15] Brétonneau P. Traité de la diphtérite, The history of diphtheria in France in the nineteenth century. Paris. 1826.
[16] Bretonneau PF, Des inflammations spéciales du tissu musquex et en particulier de la diphtérite, ecc., Paris. 1826.
[17] Trousseau' M. Trousseau's Views on Diphtheria. *Brit Med J*. 1862; 1(54): 44-45.
[18] Boushut E. Histoire de la medecine et de doctrines. Paris: [n.p.], 1873. 2 vols. 8vo. viii, 564; [iv], 634 First Edition.
[19] O' Dwyer, Joseph P. "Intubation in Laryngeal Stenosis caused by Diptheria", *American Lancet*. 1893.
[20] Garrison F. Dr. Abrham Jacobi. *Science*, *New Series*. 1919; 50(1283): 102-104.
[21] Wright J. History of laryngology and rhinology. Philadelphia: Lea & Febiger. 1914.
[22] Loeffler F. (1852-1915). Klebs-Loeffler Bacillus. *JAMA*. 1969; 210 (6): 1096-1097.
[23] Celli A. Manuale dell'Igienista, Torino, *Unione Tipografica Editrice Torinese*. 1912.
[24] Panisset M. Voila vingt cinq ans, un veteterinaire, Gaston Ramon decouvrait les anatoxines. *Can J Compar Med*. 1949; 13(83): 60-63.
[25] Roux E. Notice sur les travaux scientifiques du Dr E. Roux. Paris, Masson et Cie. 1899.
[26] von Behring E. "Serum Therapy in Therapeutics and Medical Science". Nobel Lecture, December 12, 1901. nobelprize.org
[27] Zakikhany K, Efstratiou A. Diphtheria in Europe: current problems and new challenges. Future Microbiol. 2012 May; 7(5): 595-607. *Can J Comp Med Vet Sci*. 1949; 13(3): 60-63.
[28] Boari N. Sull'angina pseudo membranosa crupale. Annotazioni pratiche del D. Nicola Boari. Adunanza 31 gennaio 1863, In Resiconti delle adunanze dell'Accademia medico-chirurgica di Ferrara, anno accademico XXXVI 1863. Tipografia Bresciani, Ferrara. 1864; 3-12.
[29] Turri R. Delle paralisi post-difteriche Lettura all'Accademia Medico-Chirurgica luglio 1878, In Principali memorie lette nell'Accademia Medico-Chirurgica di Ferrara negli anni dal 1878 al 1890, LV-LXVII dalla fondazione, anni accademici LI-LXIII S.n.r. Stab. Tip. Bresciani, Ferrara. 1878; 49-99.
[30] Baldassari L. Mortalità per Tifo e Difterite nel Comune di Ferrara nel trentennio 1869-98 [comunicazione fatta all'Accademia di Scienze Med. e Nat. in Ferrara il giorno 26 aprile 1899), Bresciani, Ferrara. 1899; 163-179.
[31] Sabbatani S, Sandri A. The use of antidiphterial serotherapy in Bologna in 1895. A pilot experience. *Infez Med*. 1999; 7(3): 195-202.
[32] Istituto Centrale di Statistica. Cause di Morte 1887-1955. Roma. 1958; 186.
[33] Baldassari L. Contributo alla sieroprofilassi della difterite. Tip. Agnelli, Milano. 1900.
[34] Bennati A. Resoconto Statistico Sanitario dell'Arcispedale per l'anno 1871. 1871; Manuscript.
[35] Bennati A. Rendiconto sanitario dell'a. 1876/redatto dal M. Alessandro Bennati. Bresciani, Ferrara. 1878.
[36] Trambusti A. Ricerche citologiche sul midollo delle ossa nella difterite: contributo allo studio della fisiopatologia cellulare. Tip. G. Carnesecchi e Figli, Firenze. 1896.
[37] Trambusti A. Ricerche citologiche sul midollo delle ossa nella difterite: contributo allo studio della fisiopatologia cellulare, Seduta del 31 maggio 1896. Atti della Accademia delle Scienze Mediche e Naturali in Ferrara, anno LXX 1895-96 dalla fondazione S.n.r. Tip. Bresciani, Ferrara. 1896: 125, 127-130.
[38] Malattie contagiose. (1894, 14 October). In Il Piccolo: Edizione del mattino. Trieste. 1.
[39] Cigui R. La minaccia invisibile: endemie ed epidemie in Istria alla fine dell'800. Endemie ed epidemie in Istria alla fine dell'800, Quaderni, vol. XXII. 2011; 47-90.

[40] Revue des sciences médicales en France et à l'étranger. https://gallica.bnf.fr/ark:/12148/bd6t54173395d/f12.item. Accessed on 11/04/2025.
[41] Veronese L. 1932. L'Indipendente storia di un giornale. Trieste: Stabilimento Tipografico Silvio Spazzal.
[42] La difterite e le scuole, 1894, 29 October. In Il Piccolo: Edizione del mattino. Trieste, 1; [40b]. La chiusura delle scuole (1894, 14 october). In Il Piccolo: Edizione del mattino. Trieste. 1.
[43] Archivio di Stato di Trieste, busta 602, fascicolo 39/29, Inclito magistrato Civico. 1889.
[44] De Giaxa V. Igiene della scuola: Malattia della scuola, edificio scolastico, arredi della scuola, igiene pedagogica, sorveglianza igienica delle scuole. 1880. Milano: Hoepli.
[45] Archivio di Stato di Trieste, busta 602, fascicolo 39/37, Estratto dell'ordinanza dell'I.r. Luogotenenza del Litorale del 7 maggio 1883 Nr. 1117 concernente la regolazione della visita dei morti nel Margraviato dell'Istria e nella Contea principesca di Gorizia e Gradisca (1883); Archivio d Stato di Trieste, busta 602, fascicolo 39/35, Protocollo sulla visita dei morti. 1895.
[46] Svevo I, Apollonio U. (A cura di). Corto viaggio sentimentale e altri racconti inediti. Milano: Mondadori. 1949; 210-215.
[47] Vitek CR, Wharton M. Diphtheria in the former Soviet Union: reemergence of a pandemic disease. *Emerg Infect Dis*. 1998; (4): 539-550.
[48] Markina SS, Maksimova NM, Vitek CR, et al. Diphtheria in the Russian Federation in the 1990s. *J Infect Dis*. 2000; 181 (Suppl. 1): S27-S34.
[49] Karyanti MR, Nelwan JN, Assyidiqie IZ, et al. Diphtheria Epidemiology in Indonesia during 2010-2017. *Acta Med Indones*. 2019; 51(3): 205-213.
[50] ECDC, 6 October 2022. Increase of reported diphtheria cases among immigrants in Europa due to Corynebacterium diphtheriae, 2022. *ECDC surveillance report. Diphtheria Ann Epidemiol Rep* for 2022.
[51] Truelove SA, Keegan LT, Moss WJ, et al. Clinical and Epidemiological Aspects of Diphtheria: A Systematic Review and Pooled Analysis. *Clin Infect Dis*. 2020 24; 71(1): 89-97.
[52] Galazka AM, Oblapenko GP, Robertson SE. Resurgence of diphteria. *Eur J. Epidemiol*. 1995; 11: 95-105.
[53] Zasada AA. Corynebacterium diphtheriae infections currently and in the past. *Przegl Epidemiol*. 2015; 69(3): 439-44, 569-574.
[54] Badenschier F, Berger A, Dangel A, et al. Outbreak of imported diphtheria with Corynebacterium diphtheriae among migrants arriving in Germany. *Euro Surveill*. 2022; 27(46): 1-5.
[55] Kofler J, Ramette A, Iseli P, et al. Ongoing toxin-positive diphtheria outbreaks in a federal asylum centre in Switzerland, analysis July to September 2022. Euro Surveill. 2022; 27(44): 1-4.