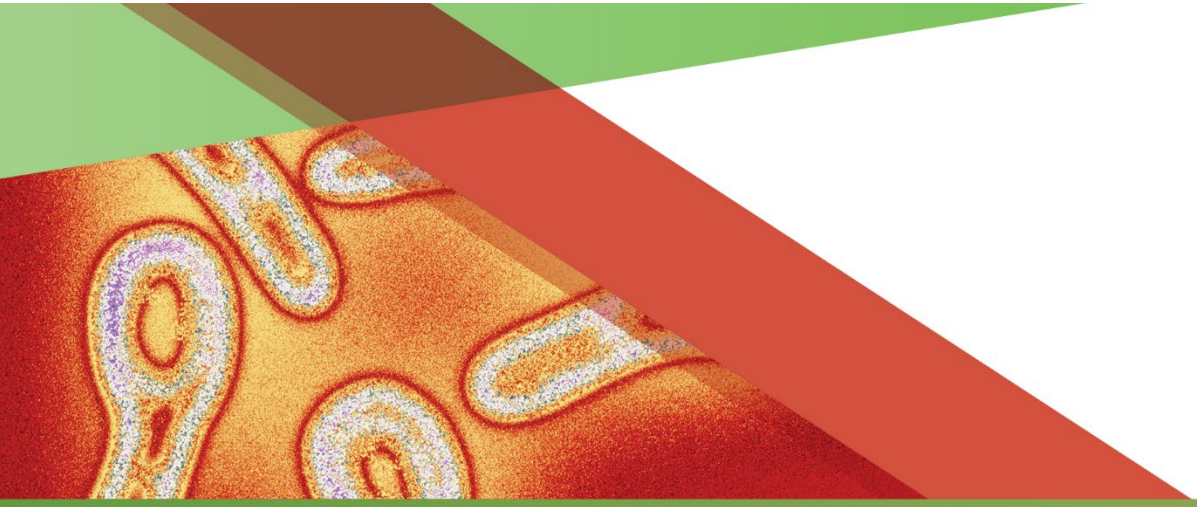


SURVEILLANCE REPORT

Diphtheria

Annual Epidemiological Report for 2022

Key facts

- In 2022, 359 cases of diphtheria due to toxigenic *Corynebacterium diphtheriae* (n=318) or *C. ulcerans* (n=11) were reported to ECDC.
- Since the second half of 2022, an increase of diphtheria among migrants was reported in several EU/EEA countries, with peaking case numbers in September to December.
- 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.
- 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), with 78% of the imported cases presenting with a cutaneous infection.
- Vaccination status was available for 39% of all cases. Seventy-five percent of the cases with known vaccination status were not vaccinated or were vaccinated with an unknown number of doses.
- Vaccination with the diphtheria toxoid vaccine is the only effective method of preventing the toxin-mediated disease. Achieving and sustaining high vaccination coverage in the population is critical for preventing toxigenic diphtheria from causing serious or fatal illness.

Introduction

Diphtheria is a bacterial infectious disease, which can be prevented by vaccination. Humans are the only significant reservoir for *C. diphtheriae* [1]. Transmission occurs via airborne respiratory droplets, direct contact with respiratory secretions or direct contact with exudate from infected cutaneous lesions [2]. The incubation period ranges from two to five days, but can be as long as 10 days [1].

Following an infection, unvaccinated individuals may present with skin infections (cutaneous diphtheria), classical respiratory diphtheria and in rare cases, systemic diphtheria [3]. In highly vaccinated populations, most infections by the bacterial species that can cause clinical diphtheria are asymptomatic or have a mild clinical course. The most common sites of symptomatic as well as asymptomatic infections are the pharynx, larynx, tonsils, nose, and skin. The critical diphtheria virulence factor is the production of exotoxin. The toxin kills tissue at the site of infection and produces systemic effects including myocarditis, nephritis, polyneuropathy, and paralysis when absorbed into the bloodstream.

The other two Corynebacteria species, *C. ulcerans* and *C. pseudotuberculosis* (very rarely), may also cause diphtheria disease. These infections are often zoonotic [2]. The diphtheria toxin is 95% homologous to that of *C. diphtheriae* and the biological effect and clinical presentation of *C. ulcerans* and *C. pseudotuberculosis* are similar to that caused by the toxin produced by *C. diphtheriae* [2,4].

Suggested citation: European Centre for Disease Prevention and Control. Diphtheria. In: ECDC. Annual epidemiological report for 2022. Stockholm: ECDC; 2024.

Stockholm, April 2024

Methods

This report is based on data for 2022 retrieved from The European Surveillance System (TESSy) on 22 January 2024. TESSy is a system for the collection, analysis and dissemination of data on communicable diseases.

An overview of the national surveillance systems is available online [5].

Following an increase of diphtheria cases in 2022, ECDC updated its reporting mechanism for diphtheria to monitor any ongoing outbreaks. All diphtheria cases should be reported to TESSy on a monthly basis; they are published in the interactive 'Surveillance atlas of infectious diseases' on a monthly basis [6]. An annual data call, including zero reporting, is also carried out to analyse the data for the respective Annual Epidemiological Report.

In 2022, 30 European Union/European Economic Area (EU/EEA) countries reported data on diphtheria and related toxigenic pathogens. Of these, 11 countries reported cases of *Corynebacterium diphtheriae* or *C. ulcerans.*

The majority of countries reported data on diphtheria according to the 2008 (n=6), 2012 (n=7) or 2018 (n=12) EU case definition. Five countries used an alternative case definition. Regardless of the case definition used, only cases caused by or with a clinical syndrome consistent with toxigenic strains should be reported at the EU level [7].

All countries reported data from a comprehensive and compulsory case-based surveillance system [8].

Epidemiology

In 2002, 356 cases of laboratory-confirmed diphtheria and related toxigenic pathogens, two possible cases and one probable case of diphtheria were reported (Table 1, Figure 1). Some 315 confirmed cases, two possible cases, and one probable case were reported as *C. diphtheriae*, and 41 confirmed cases were reported as *C. ulcerans* (Table 2). The overall notification rate was 0.01 per 100 000 population.

Diphtheria caused by *C. diphtheriae* was reported by 11 countries (Table 2). Among these countries, Germany (n=149) and Austria (n=61) reported the highest number of cases, followed by France (n=52).

Diphtheria caused by *C. ulcerans* was reported by seven countries. More than 70% of these cases were reported in Germany (n=22) and in France (n=8).

Between 2018 and 2022, 600 cases of diphtheria were reported in the EU/EEA (Table 1), of which 437 cases were due to *C. diphtheriae*.

Table 1. Diphtheria cases by country and year, EU/EEA, 2018–2022

Country	2018	2019	2020	2021	2022
	Number		Number		Number
Austria	0	0	2	2	62
Belgium	2	6	3	4	31
Bulgaria	0	0	0	0	0
Croatia	0	0	0	0	0
Cyprus	0	0	0	0	0
Czechia	0	0	0	0	5
Denmark	0	0	0	1	0
Estonia	0	0	0	0	0
Finland	0	0	0	0	0
France	9	19	18	22	60
Germany	26	15	24	22	171
Greece	0	1	0	0	0
Hungary	0	0	0	0	0
Iceland	0	0	0	0	0
Ireland	0	0	0	0	0
Italy	1	0	0	0	3
Latvia	4	3	0	0	0
Liechtenstein	NDR	NDR	NDR	0	0
Lithuania	0	0	0	0	0
Luxembourg	0	0	0	1	0
Malta	0	0	0	0	0
The Netherlands	2	0	3	0	6
Norway	1	2	0	0	8
Poland	0	0	0	0	0
Portugal	0	0	0	0	0
Romania	0	0	0	0	0
Slovakia	1	2	0	4	8
Slovenia	0	0	0	0	0
Spain	1	2	1	1	1
Sweden	5	4	0	4	4
EU/EEA (30 countries)	**52**	**54**	**51**	**61**	**359**
United Kingdom	11	12	NDR	NA	NA
EU/EEA (31 countries)	**63**	**66**	**51**	**NA**	**NA**

Source: country reports; ASR: age-standardised rate; NDR: no data reported; NRC: no rate calculated; NA: not applicable.
No data from 2020 onwards were reported by the United Kingdom, due to its withdrawal from the EU on 31 January 2020.

Figure 1. Distribution of diphtheria cases by country, EU/EEA, 2022

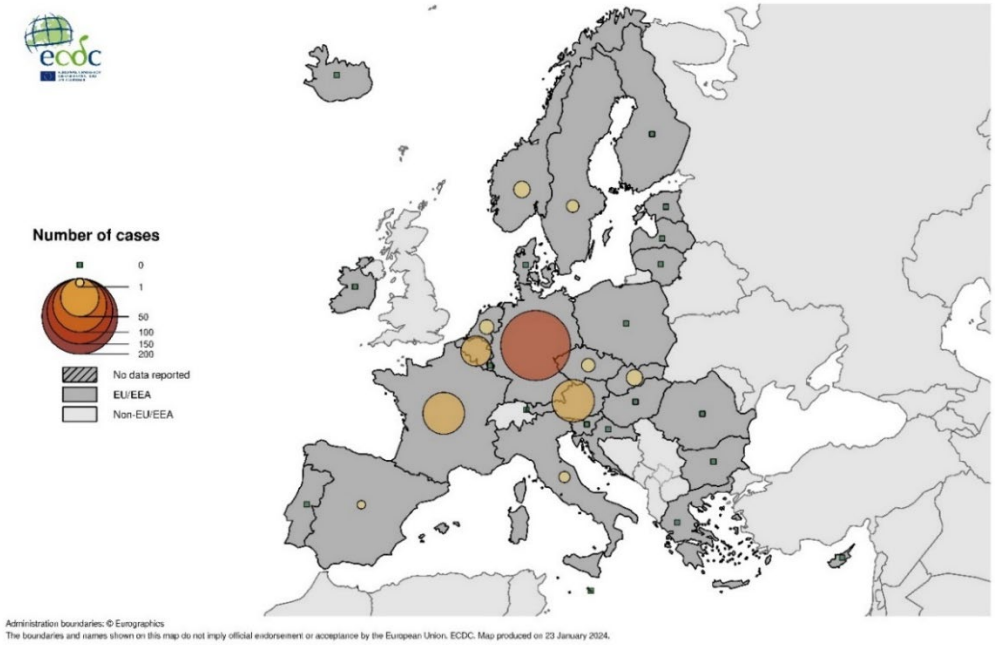


Table 2. Number of reported cases of diphtheria by country and species, EU/EEA, 2022

Country	*C. diphtheriae*	*C. ulcerans*
Austria	61	1
Belgium	26	5
Bulgaria	0	0
Croatia	0	0
Cyprus	0	0
Czechia	3	2
Denmark	0	0
Estonia	0	0
Finland	0	0
France	52	8
Germany	149	22
Greece	0	0
Hungary	0	0
Iceland	0	0
Ireland	0	0
Italy	3	0
Latvia	0	0
Liechtenstein	0	0
Lithuania	0	0
Luxembourg	0	0
Malta	0	0
The Netherlands	5	1
Norway	8	0
Poland	0	0
Portugal	0	0
Romania	0	0
Slovakia	8	0
Slovenia	0	0
Spain	1	0
Sweden	2	2
EU/EEA	**318**	**41**

Source: country reports

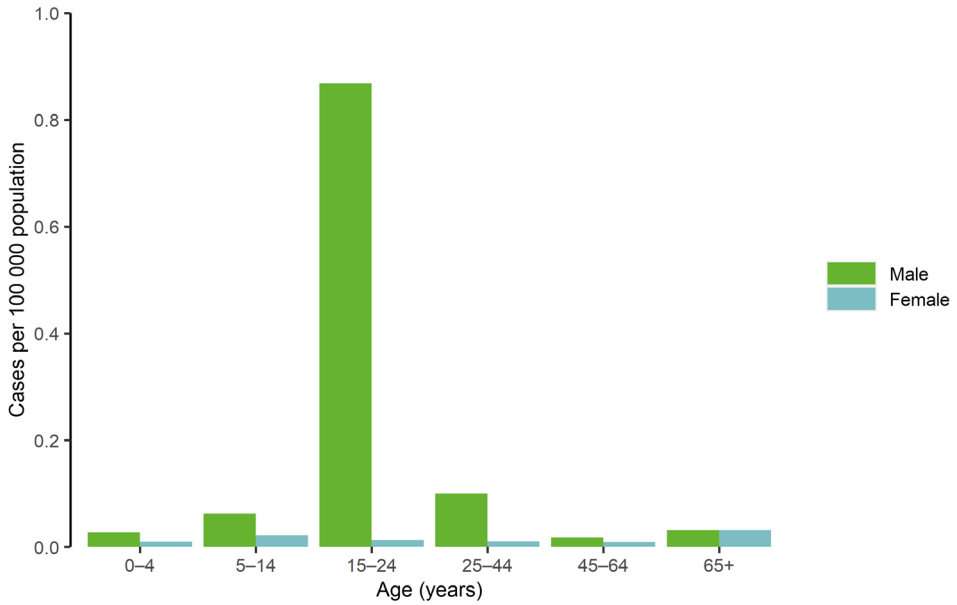
Age and gender distribution

In 2022, cases were reported among all age groups, with a preponderance among those aged 15–24 years (62%) and 25-44 years (18%), respectively (Figure 2). Of the 357 cases with age reported, 317 (89%) were males.

Of the 313 *C. diphtheriae* cases with known age, 23 (7%) were below 15 years, 217 (69%) were reported in teenagers and young adults from 15–24 years, and 73 (23%) were reported in adults 25 years and over (Figure 3). Of the 316 cases with known gender, 298 (94%) were reported in males (Figure 3).

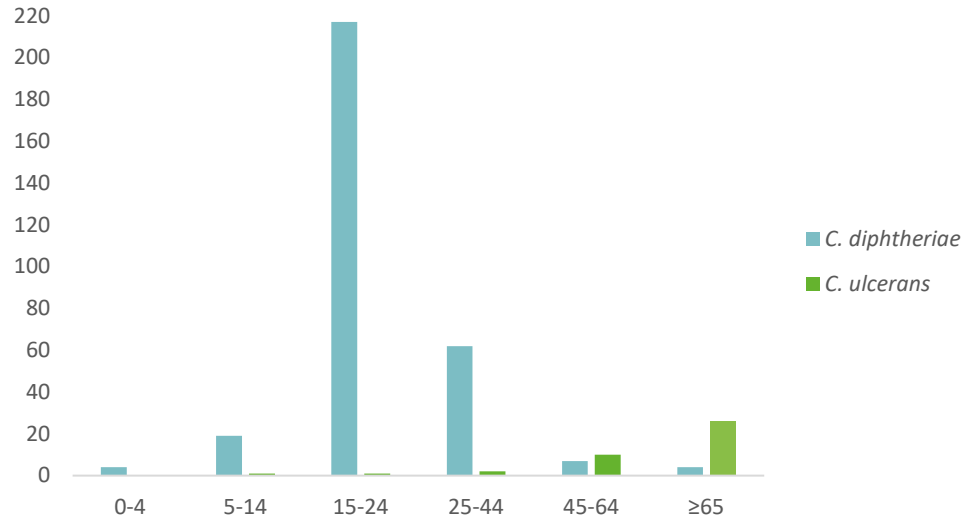
Of the 40 *C. ulcerans* cases with known age, four (10%) were reported below 44 years and 36 (90%) cases were reported in adults 45 years and over (Figure 3). Nineteen (46%) of the *C. ulcerans* cases were reported in males (Figure 3).

Figure 2. Diphtheria cases per 100 000 population, by age and gender, EU/EEA, 2022



Source: country reports

Figure 3. Age distribution of diphtheria cases by species, EU/EEA, 2022

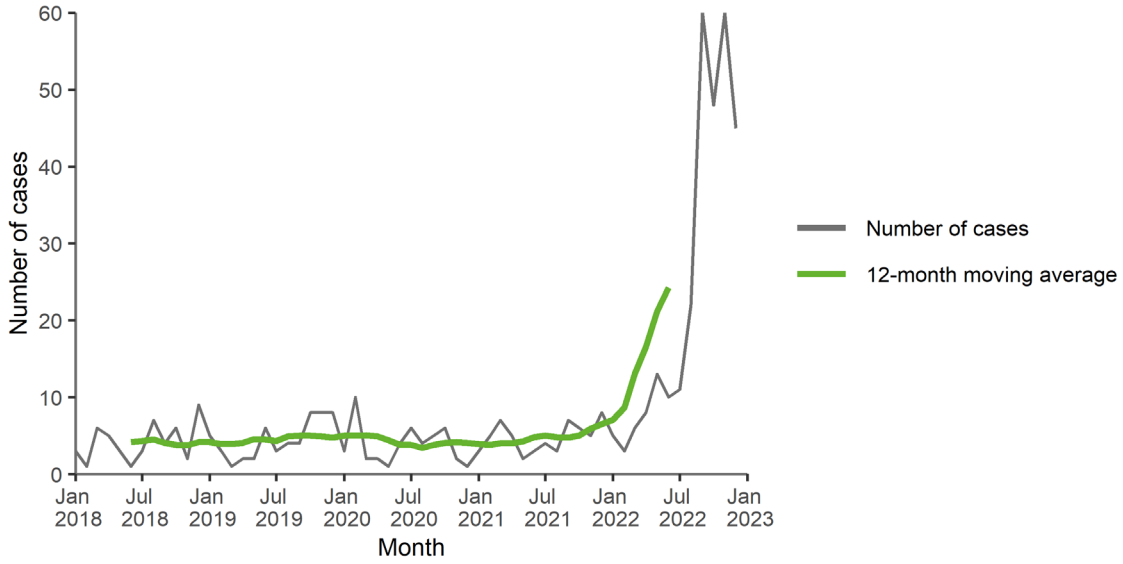


Source: country reports

Seasonality

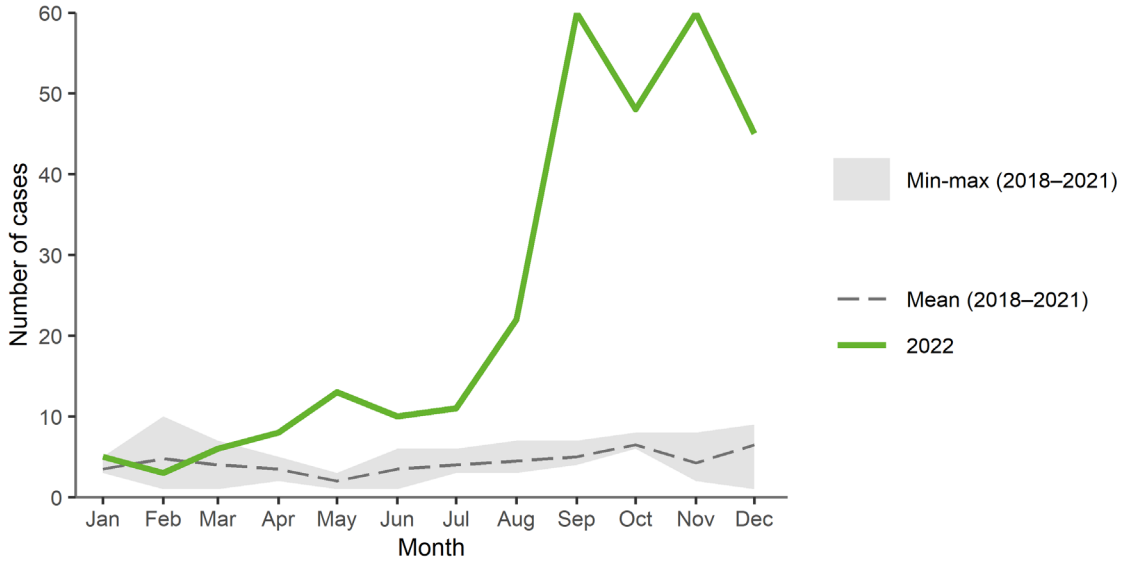
The low number of cases reported does not allow for analysis of seasonal variation (Figure 4). While in previous years cases were reported throughout the year and peaked during the last quarter, in 2022 an increase of cases was reported starting in summer, leading to a major increase of cases in the second half of the year, with peaking case numbers in September to December compared to the first half of the year (Figure 5).

Figure 4. Diphtheria cases by month, EU/EEA, 2018–2022



Source: country reports.

Figure 5. Diphtheria cases by month, EU/EEA, 2022 and 2018–2021



Source: country reports.

Clinical presentation, biotype and outcome

Two hundred and sixty *C. diphtheriae* cases were reported with known clinical presentation. Twelve of these cases (4.6%) were reported as classical respiratory diphtheria, by Austria (8), Germany (3) and Belgium (1). Eighteen cases (6.9%) were reported as respiratory infection without membrane, by Austria (9), Germany (8) and Netherlands (1). Austria (2), the Netherlands (2), and Italy (1) reported five cases (1.9%) with a respiratory and cutaneous infection. Germany (136), Austria (42), Belgium (23), Slovakia (5), Norway (4), Czechia (3), Italy (2),

the Netherlands (2), Sweden (2), and Spain (1) reported 220 *C. diphtheriae* cases (85%) with cutaneous infections. Germany reported two cases (0.8%) with nasal infection, and Slovakia reported three cases (1.2%) with 'other' clinical presentation. France (52), Norway (4), and Belgium (2) reported 58 cases with unknown clinical presentation.

For 33 of the *C. ulcerans* cases, clinical presentation was reported as known. Twenty-seven of these cases (82%) had cutaneous infection. These were reported from Germany (20), Belgium (3), Austria (1), Czechia (1), the Netherlands (1), and Sweden (1). Belgium (1) and Germany (1) reported two cases (6.1%) with classical respiratory infection, and Germany (1) and Sweden (1) reported two cases (6.1%) as respiratory infection without membrane. Czechia reported one case (3.0%) with nasal infection and Belgium reported one case (3.0%) with 'other' clinical presentation. France reported eight cases with unknown clinical presentation.

Thirty-five *C. diphtheriae* cases were due to biotype Var gravis and 72 *C. diphtheriae* cases were due to biotype Var mitis. For 154 *C. diphtheriae* cases, the biotype was unknown, and it was not available for 57 *C. diphtheriae* cases.

Information on eventual outcome was available for 304 cases. Five deaths were reported: four deaths due to *C. diphtheriae* in France (2), Austria (1), and Slovakia (1), and one death due to *C. ulcerans* in Germany. Clinical presentation of the deaths due to *C. diphtheriae* was reported as classical respiratory diphtheria (1), other clinical presentation (1), and unknown (2). The death due to *C. ulcerans* presented with cutaneous infection (1). The vaccination status for the four deaths due to *C. diphtheriae* was unknown for three cases and one case was not vaccinated. Vaccination status for the death due to *C. ulcerans* was unknown.

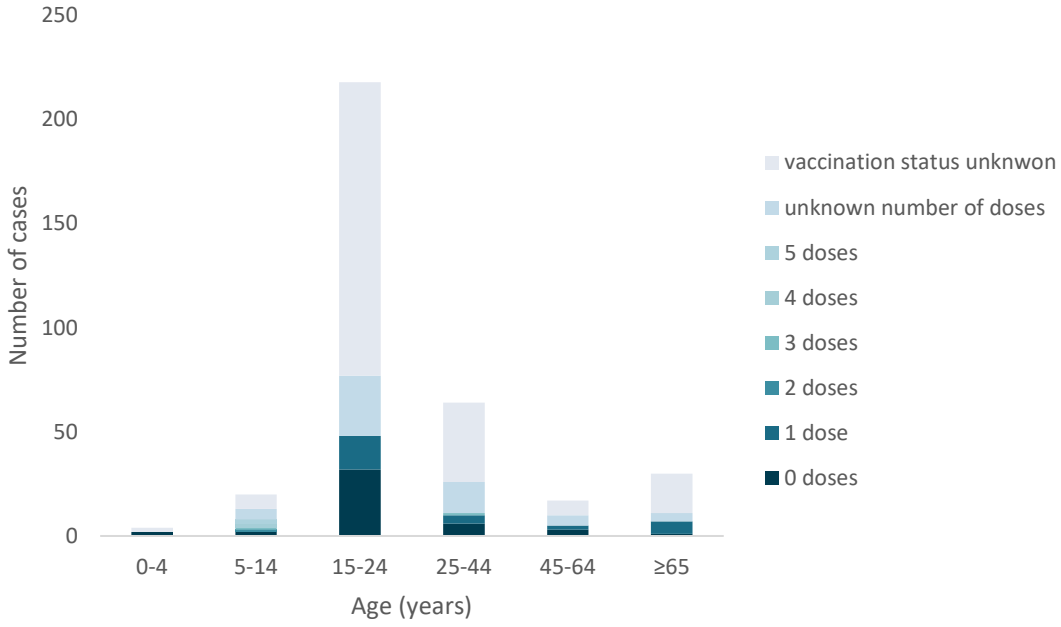
Vaccination status

Vaccination status was available for 119 *C. diphtheriae* cases. Twenty-six of these (22%) were reported to have been vaccinated with a known number of doses: 20 (17%) received one dose, one (0.8%) received two doses, two (1.7%) received three doses, two (1.7%) received four doses, and one (0.8%) received five doses (Figure 6). Fifty *C. diphtheriae* cases (42%) were vaccinated with an unknown number of doses and 43 cases (36%) were not vaccinated.

For 20 *C. ulcerans* cases, vaccination status was available. Nine *C. ulcerans* cases (45%) were reported to have been vaccinated with a known number of doses: eight (40%) received one dose and one (5.0%) received five doses. Eight C. ulcerans cases (40%) were reported as vaccinated with an unknown number of doses and three *C. ulcerans* cases (15%) were reported as not vaccinated at all.

The vaccination status was unknown for 220 *C. diphtheriae* and *C. ulcerans* cases.

Figure 6. Number of cases of diphtheria by vaccination status and age group, EU/EEA countries, 2022



Source: country reports

Importation status

Importation status was available for 215 cases, and of these 134 cases (62%) were reported as imported cases. An imported case is defined as a case having been outside the country of notification during the incubation period of the reported disease, and no links to local transmission has been identified. All imported cases were caused by *C. diphtheriae*. No case due to *C. ulcerans* was imported. One-hundred-four (78%) of the imported cases presented with cutaneous disease while three cases (2.2%) presented with respiratory infection without membrane, two cases (1.5%) with classical respiratory diphtheria and two cases (1.5%) with respiratory and cutaneous infection and clinical presentation was unknown for 23 cases (17%).

The probable country of origin was known for 91 cases (68%). They were imported from Afghanistan (37), Syria (13), Serbia (8), Bulgaria (4), Türkiye (4), Czechia (4), Austria (3), Madagascar (2), Mali (2), Bosnia and Herzegovina (1), Congo (1), Comoros (1), France (1), Latvia (1), Liechtenstein (1), Nigeria (1), Poland (1), Senegal (1), Slovenia (1), Sudan (1), Switzerland (1), Thailand (1), and Ukraine (1).

Seven cases (3.3%) were reported as import-related cases. An import-related case is defined as a case epidemiologically linked to an imported case, i.e. cases that acquired the infection locally through a direct link to an imported case in the first chain (only) of transmission as supported by epidemiological and/or virological evidence.

All imported-related cases were caused by *C. diphtheriae* and the probable country of infection was unknown for all seven cases.

Cluster-relatedness, whole genome sequencing and antibiotic susceptibility testing

Following the increase of diphtheria cases in 2022 and the updated reporting mechanism, ECDC introduced new metadata for diphtheria including variables to identify if a case is part of an outbreak or a cluster, information on whole genome sequencing and information on antibiotic susceptibility testing.

In 2022, information on cluster-relatedness was available for 85 cases. Twenty-two cases (26%) were reported as being related to a cluster while 63 cases (74%) were not related to a cluster. Information on whether whole genome sequencing (WGS) has been performed on isolates from the case was available for 259 cases. For 65 cases (25%) WGS has been performed, for 10 cases (3.9%) it has not been performed, and for 184 cases (71%) WGS status was unknown. Information on antibiotics tested for susceptibility was available for 299 cases. Four cases (1.3%) were tested for susceptibility to clindamycin, while this information was unknown for 295 cases (99%). Further details including information on cluster setting (setting where a cluster-related case has been identified), diphtheria sequence type, and antibiotic susceptibility testing results cannot be described due to limited reporting of these variables.

In addition to the enhanced reporting to ECDC, a pan-European consortium was created to assess the microbiological features of the diphtheria outbreak in migrants. Bacterial isolates underwent whole genome sequencing and phylogenetic analysis. Four major genomic clusters were identified, revealing the multiclonal nature of the outbreak. Genomic variation within the four genomic clusters led to estimate their most recent common ancestors between 2017 and 2020.

Discussion

This report includes cases due to *C. diphtheriae* and *C. ulcerans*. While all countries had surveillance in place for *C. diphtheriae*, few countries reported cases to ECDC from 2017–2022. It is likely that countries with reported cases of all species causing diphtheria in consecutive years have a higher awareness of these pathogens [9].

Diphtheria case detection is strongly influenced by the availability of laboratory resources, expertise and surveillance systems [10,11]. This varies across Europe, and in the past, few countries have performed toxigenicity testing [10-12]. Therefore, under-ascertainment and under-reporting are possible.

The majority of *C. diphtheriae* cases with known clinical presentation were reported as cutaneous. The majority of imported *C. diphtheriae* cases with known probable country of infection were imported from endemic geographical areas. The number of susceptible individuals in the EU, such as travellers and migrant populations, are likely to have contributed to distribution [13,14]. European travellers may become infected and develop cutaneous diphtheria while travelling or working in endemic countries. ECDC data presented in this report show that most cutaneous cases had an uncertain vaccination status or were unvaccinated. Unvaccinated individuals exposed to overcrowding and poor hygiene conditions are at risk for acquiring diphtheria and transmitting the infection. The vaccination status of travellers to diphtheria-endemic areas should be checked, and catch-up or booster doses should be offered and made accessible at any relevant opportunity. Furthermore, ensuring equitable access to vaccination for migrants is essential, considering the specific challenges faced by such populations in accessing the

healthcare system. Vaccination of individuals in the EU should be kept up to date, including necessary boosters in adult and older age groups, on the basis of national vaccine recommendations [3,14–17].

During the second half of 2022, a substantial increase of cutaneous diphtheria among migrants was observed in EU/EEA countries [14,18]. ECDC monitored this event through event-based surveillance and enhanced indicator-based surveillance [14,18] and continues to do so.

Communication with countries experiencing diphtheria cases suggest that a significant effort is required for the clinical and public health management of cases for a disease rarely seen in Europe.

Public health implications

Vaccination with the diphtheria toxoid vaccine is the only effective method of preventing the toxin-mediated disease. Achieving and sustaining high vaccination coverage in the population is critical for preventing toxigenic diphtheria from causing serious or fatal illness. In addition, special attention should be given to travellers and migrants arriving from endemic countries, as well as healthcare and social workers.

If cases occur, prompt clinical recognition, laboratory confirmation and treatment are essential, including rapid investigation and management of close contacts of cases. The rapid administration of diphtheria antitoxin (DAT), according to national or local guidelines, is required for the successful treatment of respiratory diphtheria, in combination with antibiotic treatment, and may also be required for other forms of diphtheria. When used, DAT should be administered upon clinical suspicion of diphtheria, whether or not symptoms of systemic toxicity are present. Timely mobilisation of available DAT stocks in individual countries should therefore be ensured. This may require support from other countries if domestic DAT stocks are depleted.

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