

Increase of reported diphtheria cases among migrants in Europe due to *Corynebacterium diphtheriae*, 2022

6 October 2022

Summary

As of 26 September 2022, 92 cases of diphtheria among migrants have been reported by seven European countries for the year 2022. Sixty-six of these cases presented with cutaneous diphtheria caused by *Corynebacterium diphtheriae*. Cases of respiratory diphtheria have also been reported, including one fatal case. The cases are among males, and most have been diagnosed in reception centres for migrants. Additionally, one case of cutaneous diphtheria was detected in a staff member at a reception centre in Switzerland. Most of the cases reported by EU/EEA countries and the UK in 2022, were infected by strains of *C. diphtheriae* for which toxin production was confirmed. For a limited number of cases, mainly in Switzerland, the toxigenicity has not been determined or reported.

Diphtheria is a rare disease in the EU/EEA. An average of 52 cases were annually reported across the EU/EEA to ECDC between 2016 and 2020. Around 50% of reported cases were caused by *Corynebacterium (C.) diphtheriae*. Of the 128 cases caused by *C. diphtheriae* reported between 2016–2020, 60 were cutaneous, 25 respiratory, and one had both a cutaneous and respiratory presentation. Forty-two cases had a different clinical manifestation or missed information about the clinical manifestation. During this five-year period, 69 *C. diphtheriae* cases were classified as imported in eleven EU/EEA countries (an average of 14 imported *C. diphtheriae* cases per year), and of these, 46 presented with a cutaneous disease. It was not possible to confirm the potential migratory status of these cases as their reason for travel to the EU/EEA was not reported.

The number of cases reported so far in 2022 represents an increase compared to the average number of imported cases seen in recent years. This increase could be explained by an increased volume of migrants from diphtheria-endemic countries, by an increased circulation of the pathogen in the countries of origin, or by an increased risk of transmission in specific settings such as migrant reception centres. As of 26 September 2022, ECDC is not aware of any evidence indicating outbreaks in the broader EU/EEA population resulting from the increased number of imported cases.

An analysis of sequences from the cases reported in migrants in 2022 revealed three different sequence types (ST): ST377, ST384 and ST574. The phylogenetic analysis showed clustering between the isolates within each of the STs reported. The public health relevance of this finding is currently under investigation with the collection of additional epidemiological information from cases. The risk for individuals in the broader community of contracting diphtheria is very low, provided they have completed their diphtheria vaccination schedule. However, the risk is assessed to be moderate for individuals who are unvaccinated or immunosuppressed and live or work in reception centres or other similar crowded settings in the EU/EEA, but low for fully vaccinated individuals in those settings.

The options for response for this event include the following:

- Identification and vaccination of individuals residing in migrant centres who have incomplete vaccination status, are unvaccinated or have unknown vaccination status, through the administration of a booster dose or a complete course of a diphtheria toxoid-containing vaccine, according to national guidelines.
- Provision of information to migrant centres' health service providers for the rapid identification and isolation of possible cases pending diagnostic confirmation.
- Respiratory droplet isolation of all confirmed or suspected cases with respiratory diphtheria is required. If facilities are not available for droplet isolation, screens should be placed between cases to limit potential transmission.
- Contact precautions, such as avoiding contact with wounds and the dressing of wounds, are required for confirmed and suspected cases of cutaneous diphtheria.
- All confirmed cases, whether presenting with respiratory or cutaneous disease, should remain in isolation until the elimination of the organism is demonstrated by two negative cultures obtained at least 24 hours apart after completion of antimicrobial treatment.
- Identification of close contacts, especially contacts who may have been directly exposed to oral and skin ulceral secretions from the cases. This may include personnel giving assistance to confirmed cases, especially if they performed procedures without appropriate personal protective equipment (PPE). The clinical conditions of contacts should be monitored regularly for 10 days and swabbing (nose and throat) of close contacts should be performed regardless of their immunisation status.
- Antimicrobial post-exposure prophylaxis and vaccination of incompletely vaccinated or unvaccinated close contacts after nasopharyngeal and throat swabs have been collected, regardless of culture result and according to national or regional recommendations. Further clinical management of confirmed cases, including the use of DAT, should be undertaken according to national guidelines.
- Alerting clinicians to the possibility of cutaneous and/or respiratory diphtheria among migrants and travellers returning from endemic areas, and provision of testing algorithms and instructions on how to take samples and how to transport samples to the laboratory. For countries where toxigenicity needs to be assessed in the WHO Reference Laboratory, timely transportation is crucial to ensure early diagnosis.
- Collection of data on the country of origin and migratory route from all suspected diphtheria cases, with collection of detailed information on their stays in migrant camps or overcrowded accommodations where diphtheria transmission may have occurred in order to identify settings where transmission of diphtheria may have occurred.
- Ensure that the vaccination status for all personnel working in reception centres for migrants is up-to-date, according to their national vaccination calendars.
- Limiting situations of overcrowding in migrant centres.
- Verification of the availability of laboratory diagnostics in each country, as timely laboratory confirmation of cases is vital for implementing control measures.
- Timely reporting to competent national and international authorities of cases confirmed according to the EU case definition.
- Enhanced surveillance, including molecular typing and whole genome sequencing of patient isolates to improve the understanding and monitoring of transmission patterns. The timely collection and sharing of sequencing data combined with epidemiological information can support generating hypotheses on where transmission has occurred. ECDC can offer WGS support for Member States seeking assistance. For further information and instructions regarding this support, contact typing@ecdc.europa.eu.

Event background

This report assesses the risks associated with a current increase of diphtheria cases observed among migrants¹ in Europe in 2022, caused by toxigenic *Corynebacterium (C.) diphtheriae*.

Following the identification of diphtheria cases among migrants in Austria and Switzerland (first case reported by Austria via the Early Warning and Response System (EWRS) platform on 1 June 2022 and cases from Switzerland detected from official and media reports), ECDC encouraged all EU/EEA countries to report recent detections of all diphtheria cases through EpiPulse as the data reported through routine surveillance in The European Surveillance System (TESSy) for 2021 and 2022 were incomplete.

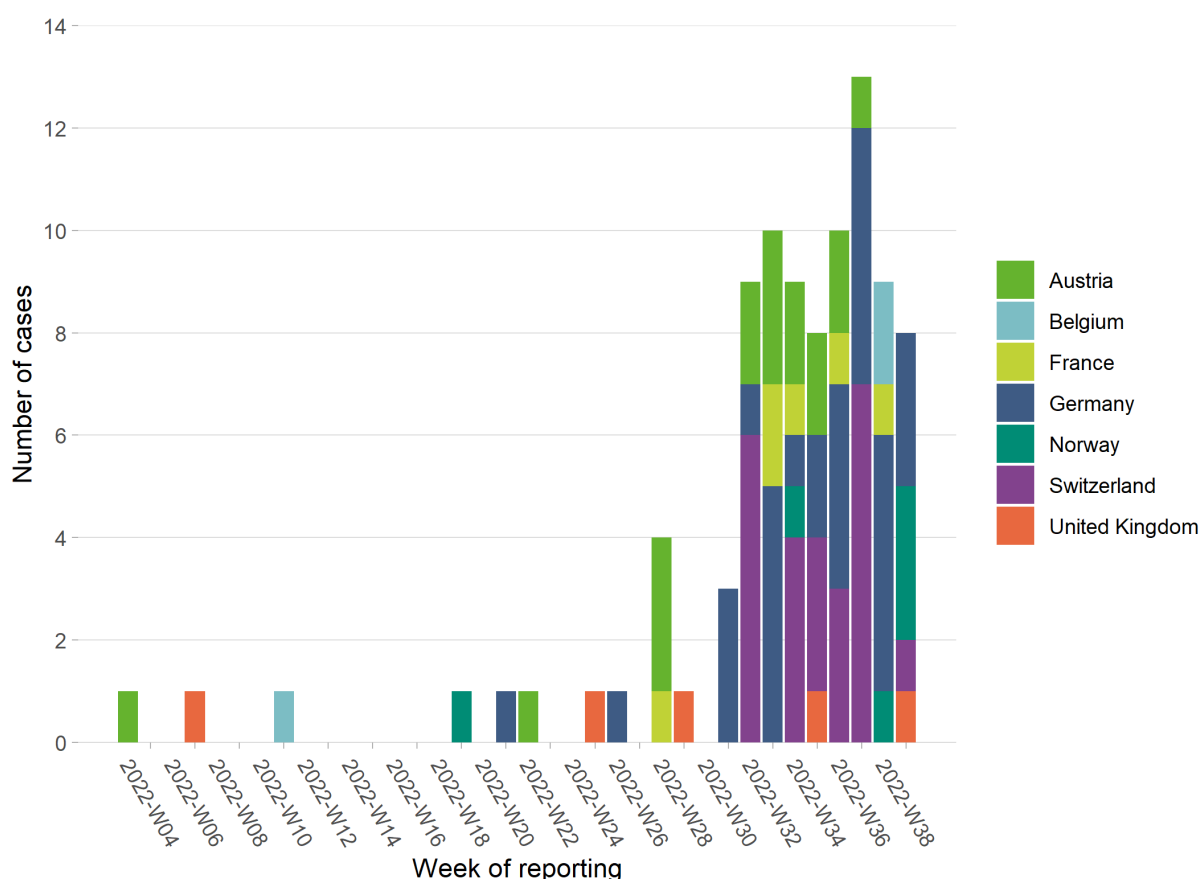
As of 26 September 2022, 92 cases of diphtheria among migrants have been reported by seven European countries for the year 2022. Sixty-six of these cases presented with cutaneous diphtheria caused by *Corynebacterium diphtheriae*. A total of 63 diphtheria cases were reported among migrants in the EU/EEA, of which 61 were confirmed to be caused by toxigenic strains of *C. diphtheriae*. For two cases, information on toxigenicity was not available at the time of publication. Among the 61 confirmed toxigenic diphtheria cases, different laboratory methods were used to determinate the toxigenicity; Austria (ELEK test: all 17), Belgium (unspecified method: one case), France (unspecified method: all six), Germany (PCR and ELEK tests: 23; PCR test: six; ELEK test: two) and Norway (ELEK test: four; PCR test: two).

For the cases reported in the UK, toxigenicity was confirmed for four out of five cases through an unspecified method. Information on toxigenicity was available for nine of the 25 cases reported in Switzerland, and while all nine cases were toxigenic, the laboratory method used was unspecified. Cases of respiratory diphtheria have also been reported, including one death. No epidemiological links have been identified among the cases. Additionally, one case was identified in a staff member at a reception centre for migrants.

While most cases arrived in Europe recently and most resided in migrant reception centres at the time of disease onset, some had been residing in the reporting countries for a longer time and we have limited information on these cases' travel history. However, data on nationality or a country of origin was available for 64 cases out of the total 92 cases reported. As shown in Figure 2, most cases were Afghan (38), followed by Syrian (17), Moroccan (2), Tunisian (2), Bangladeshi (1), Indian (1), Liberian (1), Turkish (1) and one EU/EEA national. Of note, the DTP3 vaccine coverage in 2021 in Afghanistan (66%) and Syria (48%) was very low as reported to WHO/UNICEF Estimates of National Immunization Coverage [1].

¹ A **migrant**, as defined by the European Migration Network (EMN) [1], is 'a person who either: (i) establishes their usual residence in the territory of an EU/EFTA Member State for a period that is, or is expected to be, of at least 12 months, having previously been usually resident in another EU/EFTA Member State or a third country; or (ii) having previously been usually resident in the territory of the EU/EFTA Member State, ceases to have their usual residence in the EU/EFTA Member State for a period that is, or is expected to be, of at least 12 months.' Migrants are therefore a highly heterogeneous group and it is difficult to generalise about their health and social needs.

Figure 1. Number of diphtheria cases among migrants per week, by country, and date of reporting in 2022.



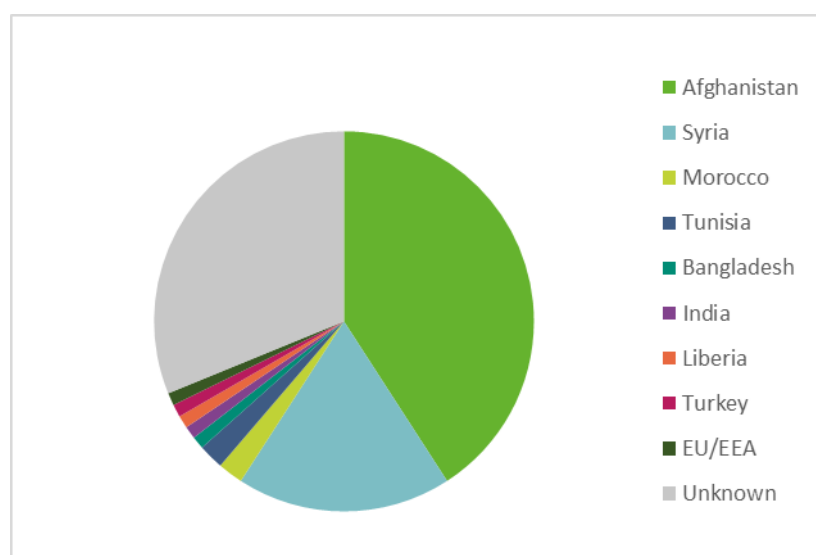
Source: EpiPulse; direct communication with countries and official reports.

Note: Date of reporting for Switzerland is the date of publication of official or media reports.

Note 2: There is an inherent delay between the date of disease onset, the date of detection and the date of reporting, resulting in a reporting lag. This should be taken into consideration when interpreting this figure.

Note 3: Figure includes cases of respiratory diphtheria from Austria (4), Germany (1) and Switzerland (10).

Figure 2. Nationality/country of origin among migrants with diphtheria for cases reported in 2022



Source: EpiPulse and direct communication with countries

Table 1 shows the total number of diphtheria cases (47) reported in year 2021, which is considerably lower than the 92 cases reported among migrants alone in Europe in 2022 and mainly since July 2022.

Table 1. Number of diphtheria cases reported in 2021 by reporting country

Reporting country	Number of cases
Austria	2
Belgium	3
Denmark	1
France	9*
Germany [2]	21
Slovakia	4
Spain	1
Sweden	4
Switzerland	4
United Kingdom	10
Total	47

Source: WHO Global Health Observatory data repository [3] for all countries except for Germany [10] and France (direct communication).

* Metropolitan France (3), French Guyana (3), Mayotte (3)

Note: For the cases presented in this table, no further specification is available on the pathogen and the clinical presentation. EU/EEA countries not shown in the table reported zero cases of diphtheria for year 2021

According to the [Displacement Tracking Matrix \(DTM\) Europe Quarterly Regional Report April – June 2022](#), in the second quarter (Q2) of 2022, a total of 38 008 migrants and refugees were registered arriving in Europe, 8% higher than in Q2 of 2021 and nearly four times the number registered in 2020. Arrivals in Q2 of 2022 are 48% higher than in Q1. Afghanistan, Morocco, Bangladesh, Egypt and Syria are the most frequently reported countries of origin among all registered arrivals to Europe in 2022.

Disease characteristics

Diphtheria is a bacterial infectious disease, the severe consequences of which can be prevented by vaccination. Humans are the only significant reservoir for *C. diphtheriae* [4]. Transmission occurs via airborne respiratory droplets, direct contact with respiratory secretions or direct contact with exudate from infected cutaneous lesions [5]. The incubation period ranges from two to five days but can be as long as 10 days [4].

Following an infection, unvaccinated individuals may present with skin infections (cutaneous diphtheria), classical respiratory diphtheria and in rare cases, systemic diphtheria [6]. In highly-vaccinated populations, most infections by the bacterial species that can cause clinical diphtheria are asymptomatic or have a mild clinical course. Such cases are rarely diagnosed unless detected during contact tracing, and asymptomatic carriers tend to be underreported. 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 gene that encodes this toxin (tox+) is carried by a lysogenic beta phage. The presence of the tox+ phage gene in a *C. diphtheriae* strain does not mean that the gene is always expressed. While non-toxigenic tox gene bearing (NTTB) *C. diphtheriae* are rare, they are likely to be underreported in countries that do not perform phenotypic toxigenicity assays. The WHO manual for the diagnosis of diphtheria recommends phenotypic toxigenicity assays to be performed on all samples or isolates that have tested positive for the tox gene [7]. The proportion of strains that carry the tox+ phage gene is comparatively low in high income countries. However, there is a risk that non-toxigenic strains may acquire the phage gene, either in the environment or during laboratory experiments, and then convert into a toxigenic strain [5,8]. The toxin kills tissue at the site of infection and produces systemic effects including myocarditis, nephritis, polyneuropathy and paralysis when absorbed into the bloodstream.

Respiratory infections with *C. diphtheriae* are most commonly reported in temperate climates, while cutaneous infections with *C. diphtheriae* dominate in tropical areas and under conditions of poor hygiene and overcrowding [6,9,10]. The cutaneous lesions caused by *C. diphtheriae*, which are described as shallow greyish non-healing ulcers, are often associated with infected insect bites and can occur anywhere on the body. The ulcers are often co-infected with other pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes*. In high income countries the cutaneous forms are most frequently reported among returning travellers and migrants arriving from endemic countries, individuals with waning immunity, and disadvantaged populations e.g. persons with alcohol use disorder, drug users, or the homeless [11-15].

Although transmission from respiratory cases via droplets is the most effective mode of infection, cutaneous carriage of *C. diphtheriae* should also be considered as it is an important source of person-to-person transmission of the pathogen, particularly in communities where vaccination coverage is low and/or where hygiene conditions are poor. For instance, in a 1975 epidemiological study from a rural, most likely underprivileged community in the US, transmission was shown to be even higher among contacts of patients with cutaneous infections than in those with respiratory tract infections, possibly due to environmental contamination [16]. Transmission from cutaneous lesions can cause both respiratory and cutaneous disease in susceptible contacts [17].

The highly effective toxoid-based vaccine makes it very unusual for immunised individuals to develop the systemic toxin-mediated form of disease from cutaneous diphtheria, but they can become asymptomatic carriers of toxigenic strains and thereby facilitate spread [18]. Several studies highlight the role of cutaneous diphtheria infections in the spread of diphtheria and the relevance of accumulation of carriers as an increased risk for an epidemic [5,17].

The other two *Corynebacteria* species, *C. ulcerans* and *C. pseudotuberculosis* (very rarely), may also cause diphtheria disease. These infections are often zoonotic [9,19,20]. 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* [5,8].

Microbiological information

As part of the response to the event, countries were invited to share sequencing data if available. Among the 31 sequences available for analysis, three different sequence types (ST), including ST377, ST384 and ST574, were identified. These sequences have been analysed in the context of the global *C. diphtheriae* phylogeny. Current findings indicate genetic clustering (with an allelic difference of under 5 alleles) between isolates from the recent cases, within each of the STs reported. In particular, isolates from ST377 and ST384 from recent cases form unique branches, separated from publicly-available sequences collected from NCBI. Further epidemiological and bioinformatic studies are needed to confirm and further elaborate these observations. It is too early to draw epidemiological conclusions, but ECDC encourages countries to submit any available sequencing data for extended analysis, as well as collecting epidemiological information, including the country of origin and migratory route, that can provide further information on related transmission events.

Diphtheria epidemiology in the EU/EEA

Diphtheria caused by *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* is a notifiable disease in the EU and Member States are expected to report new cases to ECDC on a monthly basis following the 2018 EU case definition for communicable diseases [21] and ECDC reporting surveillance guidelines via The European Surveillance System (TESSy).

The EU case definition distinguishes the pathogen (*C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis*) for the purpose of official reporting and requires isolation of toxin-producing bacteria from a clinical specimen for laboratory confirmation.

During the period 2016–2020, 260 cases were reported through TESSy in the EU/EEA and the UK (Table 2), with 128 cases of *C. diphtheriae* (125 confirmed, one possible, two unknown) including six deaths. Increased numbers of *C. diphtheriae* cases were reported in 2018 and 2019 compared to the two previous years, however, the increase was mostly in one country. In 2020, case numbers decreased to the level observed in 2017 and 2018, however, this may be a consequence of the COVID-19 pandemic, including the broader effect of public health measures and a higher degree of under-ascertainment and/or under-reporting.

Of the 128 *C. diphtheriae* cases, 60 were reported as cutaneous infections, 25 cases were reported as respiratory infection and one case showed both a cutaneous and respiratory presentation. Forty-two cases had a different clinical manifestation or missed information about the clinical manifestation. All six deaths reported were among cases affected by *C. diphtheriae*.

Fifty of these 128 cases were indigenous cases² reported from 12 countries (Belgium, France, Germany, Greece, Italy, Latvia, the Netherlands, Norway, Slovakia, Spain, Sweden and the United Kingdom). In France the indigenous cases were reported from the Overseas Territories Mayotte and French Guyana. Eleven countries (Austria, Belgium, France, Germany, Ireland, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom) reported a total of 69 imported³ and two additional cases from the United Kingdom were import-related⁴. Out of the 69 imported cases, 46 cases were reported as cutaneous infections, three as respiratory infections and for 20 cases the clinical manifestation was different or unknown. The probable origin of the imported cases were Afghanistan (4), Burkina Faso (1), the Comoros (3), Egypt (1), the Gambia (1), Ghana (1), Guinea (3), India (1), Indonesia (1), Kenya (2), Madagascar (1), Mali (1), Myanmar (1), Namibia (1), Nigeria (1), the Philippines (8), Senegal (5), Slovakia (1), Somalia (3), Sri Lanka (5), Tanzania (1), Thailand (6) and Tunisia (5).

² An indigenous case is defined as a case infected within the country of residence (based on epidemiological and virological evidence) and that is not import-related, or any case with an unknown source of infection (no epidemiological or virological evidence).

³ 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.

⁴ 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.

For 12 cases the probable country of infection was unknown. Of the 69 imported cases, 26 were vaccinated with at least one dose, four cases were not vaccinated and for 39 cases the vaccination status was reported as unknown or uncertain.

The available surveillance data at European level show a wide age range of cases, with the majority of cases in adults and the elderly.

Table 2. Number of cases of *C. diphtheriae* and *C. ulcerans* reported to ECDC (TESSy) in the EU/EEA and the UK, by year and country, 2016–2020

Year	2016	2017	2018	2019	2020	Total
<i>C. diphtheriae</i>						
Reporting country						
Austria	1	0	0	0	1	2
Belgium	1	1	0	1	0	3
France	6	1**	4	13	8	32
Germany	3	2	7	3	4	19
Greece	0	0	0	1	0	1
Ireland	1	0	0	0	0	1
Italy	1	1	0	0	0	2
Latvia	6	3	4	3	0	16
Netherlands	1	2	2	0	1	6
Norway	1	1	1	2	0	5
Slovakia	0	0	1	2	0	3
Spain	1	0	1	1	1	4
Sweden	2	2	4	4	0	12
United Kingdom	4	4	5	9	N.A.	22
Total	28	17	29	39	15	128
<i>C. ulcerans</i>						
Reporting country						
Austria	1	0	0	0	1	2
Belgium	5	0	2	5	3	15
France	2	6**	5	6	10	29
Germany	8	8	19	12	12	59
Italy	0	0	1	0	0	1
Netherlands	1	2	0	0	2	5
Spain	0	0	0	1	0	1
Sweden	2	2	1	0	0	5
United Kingdom	2	4	5	3	N.A.	14
Total	21	22	33	27	28	131
All diphtheria cases	49	39	63*	66	43	260

*In 2018, one case with unknown pathogen was reported from the UK. ** For the purpose of this risk assessment France reported two *C. diphtheriae* cases and five *C. ulcerans* cases for 2017 by email

Note 1: The following countries not shown in the table reported zero diphtheria cases for the period 2016–2020: Bulgaria, Croatia, Cyprus, Estonia, Finland, Hungary, Iceland, Luxembourg, Malta, Poland, Portugal, Romania, Slovenia.

Note 2: Data for the UK are displayed as reported to TESSy by the 31 December 2019. Therefore, any potential reclassifications and corrections of the data conducted after the 31 December 2019 are not reflected here. For the purpose of this risk assessment the UK reported to ECDC by email updated data: A total of 33 diphtheria cases were reported for the time period between 2016 and 2020 including 16 *C. diphtheriae* cases (2016: 4, 2017: 4, 2018: 8, 2019: 0, 2020: 0) and 17 *C. ulcerans* cases (2016: 2, 2017: 1, 2018: 3, 2019: 10, 2020: 1). Of the 16 *C. diphtheriae* cases, six were reported as cutaneous infections, three cases were reported as respiratory infections, three cases showed both a cutaneous and respiratory presentation, one case showed other presentation and three cases were asymptomatic. One death due to *C. ulcerans* was reported for 2019. Nine imported diphtheria cases and three import-related diphtheria cases were reported. The probable origin of the imported and import-related cases are Cambodia (1), Ghana (3), Philippines (1), Senegal (2), Sierra Leone (1), Somalia (1), Sri Lanka (3).

Further information can be found in ECDC's Annual epidemiological report [22] and the online *Surveillance atlas of infectious diseases* [23].

Diphtheria vaccination

Universal immunisation is the only effective method of preventing the toxin-mediated disease. The occurrence of disease in fully vaccinated individuals is very rare. The vaccine effectively protects against the effects of the exotoxin produced by *C. diphtheriae* and *C. ulcerans*, but vaccinated individuals can still be infected by the bacteria, become asymptomatic carriers of toxin-producing strains and transmit these to others.

In the EU/EEA, in 2021, the primary vaccination series consists of two or three doses of diphtheria toxoid-containing vaccines, administered by six months of age. The primary course, as well as the first booster, consist of a full dose of diphtheria-toxoid (D) as part of a combined vaccine (often part of the hexavalent vaccine, combining diphtheria and tetanus toxoids, acellular pertussis (DTaP) adsorbed, inactivated poliovirus (IPV), Haemophilus influenzae type b (Hib) conjugate, and hepatitis B (HepB) (recombinant) vaccine), with few exceptions. The frequency of booster dose administration after 24 months varies across countries. Depending on the age of booster administration, the vaccine may contain a full dose (D) or a reduced dose (d) of diphtheria toxoid.

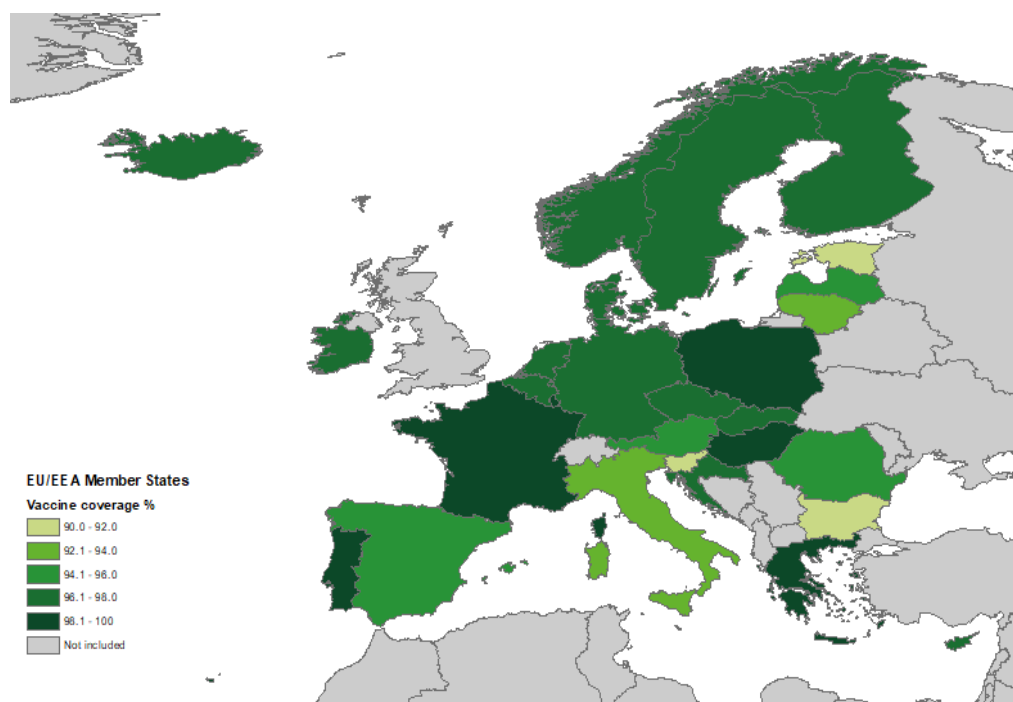
A recent seroprevalence study conducted in 16 European countries showed insufficient seroprotection levels against diphtheria in individuals aged 40-59 years [24]. This underscores the importance of diphtheria toxoid containing booster doses following the immunisation with three doses of DTP/DTaP vaccine.

Policies for the administration of a diphtheria-toxoid-containing booster vaccine are very different across EU/EEA countries. While all countries recommend the administration of booster doses, different schedules are implemented, particularly when boosting the adult population. Some countries recommend the booster every 20 or 15 years and others every 10 years or every 10 years in older age groups only. In adults, the frequency of booster dose administration also varies, and the frequency of administration may increase in older adult individuals (65-year-old and older).

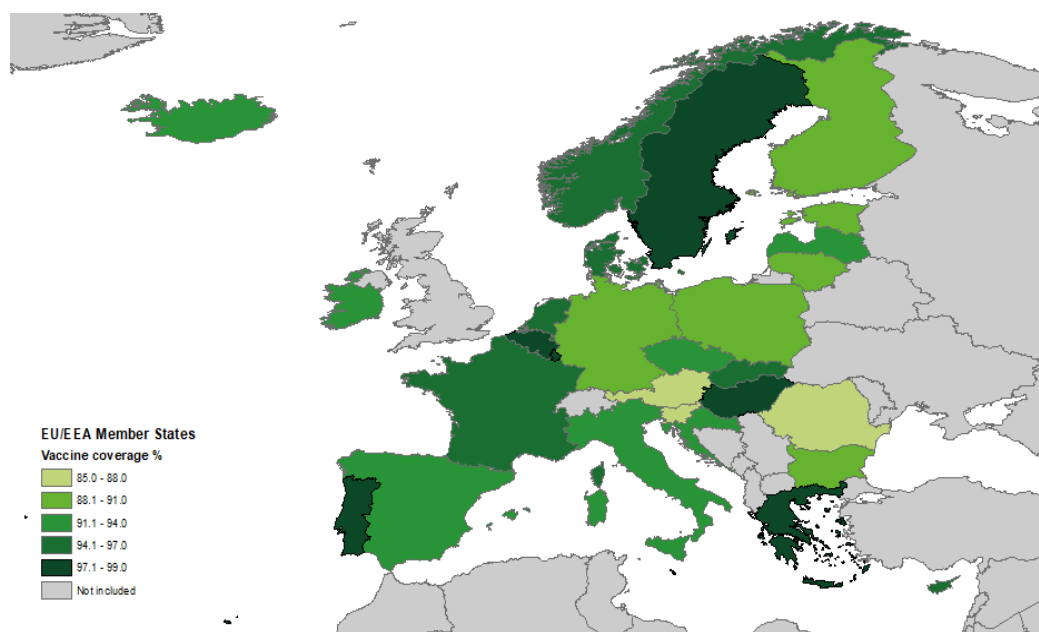
Diphtheria vaccination coverage in the EU/EEA

In the EU/EEA, as reported by annual WHO/UNICEF estimates of national immunisation coverage (WUENIC) for 2021, most Member States have a high vaccine coverage for both the first dose of diphtheria, tetanus toxoid and pertussis vaccine (DTP1) and the third dose of diphtheria, tetanus toxoid and pertussis vaccine (DTP3) among infants [25]. As shown in the maps below, DTP1 vaccine coverage in the EU/EEA ranged from 91% in Estonia to 99% in France, Greece, Hungary, Luxembourg, Malta, Poland and Portugal in 2021. In the same period, DTP3 vaccine coverage in the EU/EEA ranged from 85% in Austria to 99% in Greece, Hungary, Luxembourg, Malta and Portugal.

Figure 3. DTP1 vaccine coverage in the EU/EEA 2021



Source: WHO Immunization Data portal [33]

Figure 4. DTP3 vaccine coverage in the EU/EEA 2021

Source: WHO Immunization Data portal [33]

Treatment of diphtheria

The rapid administration of equine 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, as it binds to circulating toxin but does not neutralise toxin that has already bound to or entered the cells. As DAT neutralises circulating toxin but not bound toxin, DAT stops progression of disease but does not reverse symptoms. The entire therapeutic dose should be administered at once. The amount of antitoxin recommended varies between 20 000 and 100 000 units, with larger amounts recommended for persons with extensive local lesions and with a longer interval from disease onset. The dose is the same for children and adults [6]. DAT treatment initiated later than 48 hours after the onset of systemic toxic symptoms has limited impact on the clinical outcome although DAT is, when necessary, offered at any stage of the disease [26]. Administration of DAT can cause acute and delayed hypersensitivity reactions. DAT is included in the World Health Organization Essential Medicines List [27].

According to WHO, treatment with DAT is of limited value in cutaneous disease. In most cutaneous infections, large-scale toxin absorption is unlikely. Therefore, the risk of giving an antitoxin is usually considered substantially greater than any benefit. Nevertheless, if the cutaneous ulcer is sufficiently large (more than 2 cm squared) and membranous, then anti-toxin may be justified [28]. Surgical debridement in addition to antibiotic therapy can also help treating cutaneous diphtheria [29].

Antibiotic treatment, in addition to the DAT treatment, is necessary to eliminate the bacteria and prevent further spread to susceptible individuals. Furthermore, patients should receive immunisation with diphtheria toxoid upon recovery since natural diphtheria infection does not always confer long-standing protective immunity.

Delays in appropriate treatment with DAT and antibiotics are often the result of delayed clinical suspicion of disease because the treating physician may not have seen cases of diphtheria before as it is now a very rare disease. Countries should follow national guidelines on case management. Most guidelines recommend treatment with benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V) or a macrolide (erythromycin, azithromycin or clarithromycin) for a period of 14 days. Individuals who continue to harbour the bacteria after treatment should receive an additional course of oral erythromycin and submit a new sample for culture after completion of the course. Antibiotic resistance seems rare but strains with intermediate susceptibility to penicillin G and erythromycin have been increasingly reported in recent years [30-32]. Some respiratory diphtheria cases are particularly severe and may need tracheotomy, mechanical removal of the pseudo-membranes, intubation and ventilation (including ECMO). Patients should be monitored for cardiac complications.

Availability of DAT in EU/EEA Member States

Following the significant decline in incidence of the disease after the introduction of mass vaccination in Europe, the production, supply and availability of DAT to treat diphtheria infection has significantly declined in Europe and globally. A limited number of countries in the EU/EEA hold a stockpile at the national level which enables immediate administration when needed. In many cases, such stocks are close to expiring or have expired, and several countries do not hold a stock at all.

Attempts by EU/EEA governments to procure DAT from producers outside the EU have often encountered difficulties. Globally, there are very few manufacturers of DAT due to the decline in its demand. DAT is derived from equine immunoglobulin. In addition, there are quality assurance issues for non-licensed pharmaceutical products. Some EU/EEA regulatory agencies work closely by testing and conducting research to analyse the potency of DAT concentrations and to assure the quality of the product.

The general lack of availability of DAT is of concern, although this has improved in recent years. DAT is needed in the EU/EEA for immediate use when clinicians suspect a diphtheria case, which is rare, but still occurs every year, as reported in this rapid risk assessment.

DAT is listed by WHO as an essential medicine that should be available in all functioning health systems. There is an urgent need for EU Member States to be able to access DAT in the 48 hours following initial symptoms when a diphtheria case is suspected. Solutions to pool critical demand of DAT may help provide a more sustainable demand and supply base of DAT and ensure accessibility in the EU/EEA. Cross-border solutions to facilitate the exchange of DAT between countries in critical need should also be considered. Nonetheless, the shortage of DAT stock simply emphasises the importance of the maintenance of high vaccine coverage in all countries. Vaccination should remain the primary strategy to prevent diphtheria cases.

Diagnostics of diphtheria

Diagnostic tests used to confirm diphtheria include the isolation of *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* by culture and toxigenicity testing. Clinical suspicion of cutaneous diphtheria depends on epidemiological circumstances and morphological characteristics of the wound. Skin infections may be manifested by a scaling rash or by ulcers with clearly demarcated edges and membrane, but any chronic skin lesion may harbour *Corynebacteria* along with other pathogens.

There are no commercial tests available for the diagnosis of diphtheria. Laboratory identification and confirmation of diphtheria requires isolation of *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* by culture from a clinical specimen (nasal swabs, pharyngeal swabs or swabs from pseudo-membrane, wound or skin lesions) and toxigenicity testing. Direct and real-time polymerase chain reaction (PCR) assays can detect the *C. diphtheriae* toxin gene within a few hours, but confirmation of diphtheria toxin expression must be undertaken with the Elek test [7,33,34]. Procedures for the collection of specimens are available in the WHO Manual for laboratory diagnosis of diphtheria [7]. According to WHO guidelines, tox-gene positive samples should be treated as probable cases and sent for phenotypic toxigenicity confirmation and further biotyping to the [WHO Collaborating Centre for diphtheria](#) in the UK if these assays cannot be performed nationally.

Case detection is strongly influenced by the availability of laboratory resources (techniques, methods, reagents and the quality of these reagents) and the technical expertise. A reliable, sensitive and prompt diphtheria laboratory service is necessary for the timely diagnosis and treatment of infections, as well as to demonstrate the absence of diphtheria transmission in the population.

The results of the External Quality Assessment exercise carried out in 2013 in EU/EEA Member States indicate challenges in several EU/EEA laboratories in providing quality diagnostic methods for diphtheria as well as challenges in availability of reagents for the tests [35]. More recently, a WHO EQA was undertaken with a similar outcome [36]. Limitations in the capacity to confirm toxigenic infections may delay diagnosis, treatment and public health interventions in some EU Member States. Enhanced surveillance, molecular typing and whole genome sequencing of patient isolates have the potential to improve the understanding and monitoring of transmission patterns of diphtheria.

ECDC risk assessment for the EU/EEA

This assessment is based on evidence available to ECDC at the time of publication. It follows the ECDC rapid risk assessment methodology, where the overall risk is determined by a combination of the probability of infection and the impact of the disease on affected populations. ECDC will keep monitoring the event and will reassess the risk depending on its evolution and the implemented response measures.

What is the risk of diphtheria spreading in the EU/EEA?

Risk for the broader population

Despite the increased number of diphtheria cases observed in the EU/EEA in 2022, in most Member States this increase is driven by multiple importations from diphtheria-endemic countries. As of 16 September 2022, most cases described in Europe this year were being reported among migrants who recently arrived in the EU/EEA. As of 16 September 2022, ECDC is not aware of any evidence indicating outbreaks in the broader population linked to the importation of these diphtheria cases from endemic countries. Thus, the probability of exposure of the broader population due to the reported diphtheria cases is considered very low. The occurrence of the disease is very rare among fully vaccinated individuals. High immunisation coverage in the community consequently prevents outbreaks of clinical diphtheria in the broader population. According to the WHO Immunisation Data portal [25], the immunisation coverage estimates for DTP3 in 2021 in the EU/EEA varied across the Member States, ranging from 85% to 99%. Therefore, the probability for individuals residing in the community to develop the disease is very low provided they have completed a full diphtheria vaccination series and have an up-to-date immunisation status. The impact of this outbreak is therefore expected to be very low for the broader EU/EEA population. Nevertheless, the possibility of secondary infections in the community cannot be excluded and severe clinical diphtheria is possible in unvaccinated or immunosuppressed individuals.

Considering the very low probability of exposure and the very low impact described above, the risk assessed for the broader population in the EU/EEA is considered to be **VERY LOW**.

Risk for specific populations and settings

Most of the current cases are being reported among migrants residing in potentially crowded settings and where some individuals may be unimmunised or under-immunised, or lacking a complete diphtheria vaccine schedule (as they originate from countries with low community DTP vaccine coverage [25]). In addition to the vulnerability of migrants, the probability of exposure may increase due to the difficult travel conditions en route to Europe. Therefore, the probability that individuals residing, working or volunteering in these centres may be exposed to the pathogen is considered moderate.

In exposed unvaccinated or immunosuppressed individuals in these settings, a severe outcome following a diphtheria infection is possible. The impact of an outbreak in this setting would thus be higher than in the broader population especially if vaccination uptake is incomplete among those residing or working within settings where there is an increased risk of exposure. Such an impact may be heightened in instances where response measures are delayed due to chemoprophylaxis and DAT not being readily available. Nevertheless, the impact of the disease for individuals with a complete diphtheria vaccine course is considered to be low.

Considering the moderate probability of exposure and the potential individual impact as described above, the risk is considered to be **MODERATE** for unvaccinated or immunosuppressed individuals in reception centres or other similar crowded settings in the EU/EEA, but **LOW** for fully vaccinated individuals in those settings.

Options for response

The options for response for this event include the following:

- Identification and vaccination of individuals residing in migrant centres who have incomplete vaccination status, are unvaccinated or have unknown vaccination status, through the administration of a booster dose or a complete course of a diphtheria toxoid-containing vaccine, according to national guidelines.
- Provision of information to migrant centres' health service providers for the rapid identification and isolation of possible cases pending diagnostic confirmation.
- Respiratory droplet isolation of all confirmed or suspected cases with respiratory diphtheria is required. If facilities are not available for droplet isolation, screens should be placed between cases to limit potential transmission.
- Contact precautions, such as avoiding contact with wounds and the dressing of wounds, are required for confirmed and suspected cases of cutaneous diphtheria.
- All confirmed cases, whether presenting with respiratory or cutaneous disease, should remain in isolation until the elimination of the organism is demonstrated by two negative cultures obtained at least 24 hours apart after completion of antimicrobial treatment.

- Identification of close contacts, especially contacts who may have been directly exposed to oral and skin ulceral secretions from the cases. This may include personnel giving assistance to confirmed cases, especially if they performed procedures without appropriate personal protective equipment (PPE). The clinical conditions of contacts should be monitored regularly for 10 days and swabbing (nose and throat) of close contacts should be performed regardless of their immunisation status.
- Antimicrobial post-exposure prophylaxis and vaccination of incompletely vaccinated or unvaccinated close contacts after nasopharyngeal and throat swabs have been collected, regardless of culture result and according to national or regional recommendations. Further clinical management of confirmed cases, including the use of DAT, should be undertaken according to national guidelines.
- Alerting clinicians to the possibility of cutaneous and/or respiratory diphtheria among migrants and travellers returning from endemic areas, and provision of testing algorithms and instructions on how to take samples and how to transport samples to the laboratory. For countries where toxigenicity needs to be assessed in the WHO Reference Laboratory, timely transportation is crucial to ensure early diagnosis.
- Collection of data on the country of origin and migratory route from all suspected diphtheria cases, with collection of detailed information on their stays in migrant camps or overcrowded accommodations where diphtheria transmission may have occurred in order to identify settings where transmission of diphtheria may have occurred.
- Ensure that the vaccination status for all personnel working in reception centres for migrants is up-to-date, according to their national vaccination calendars.
- Limiting situations of overcrowding in migrant centres.
- Verification of the availability of laboratory diagnostics in each country, as timely laboratory confirmation of cases is vital for implementing control measures.
- Timely reporting to competent national and international authorities of cases confirmed according to the EU case definition.
- Enhanced surveillance, including molecular typing and whole genome sequencing of patient isolates to improve the understanding and monitoring of transmission patterns. The timely collection and sharing of sequencing data combined with epidemiological information can support generating hypotheses on where transmission has occurred. ECDC can offer WGS support for Member States seeking assistance. For further information and instructions regarding this support, contact typing@ecdc.europa.eu.

General considerations related to immunisation policy

Universal immunisation with diphtheria toxoid-containing vaccine remains the only effective preventive measure for diphtheria and for controlling its impact. To achieve the highest levels of protection and maximise opportunities for the prevention of diphtheria diseases, EU/EEA countries are encouraged to consider the following key actions:

- Strengthen the implementation of routine immunisation programmes, seeking to achieve high vaccination coverage rates with the primary series of three doses of the diphtheria toxoid-containing vaccine, followed by booster doses;
- Implement systems, including the use of immunisation information systems, to identify and reach out to the unvaccinated or partially vaccinated population with a primary immunisation series and/or booster doses; this is of priority in the context of lockdowns implemented across many Member States during the earlier phases of the COVID-19 pandemic, which may have led to interruptions in the delivery of routine childhood vaccination programmes, thus leaving pockets of the population insufficiently protected;
- Ensure the provision of booster vaccination doses to the adult and elderly population, considering waning protection from the primary series. Booster doses of diphtheria should be considered when more than 10 years have passed since the previous vaccination, in line with national recommendations. Checking immunisation status at key healthcare encounters and vaccinating, when necessary, could be an effective mechanism to better integrate immunisation efforts as part of healthcare delivery services and promote optimal uptake.
- Promote and monitor equity of access to immunisation. This applies particularly to vulnerable populations or population groups at risk of being socially marginalised, such as migrants, refugees and asylum seekers. These groups may be entering the EU/EEA being insufficiently immunised due to interruption in their immunisation programme as a consequence of war or social unrest. Vaccination against priority diseases such as diphtheria, poliomyelitis and measles, which are particularly prone to spread in crowded areas and settings such as refugee centres, should be offered promptly to children, adolescents, and adults alike. In the absence of documentation of prior vaccination, vaccination should be offered promptly [37].
- Traveller vaccination is also critical. Countries should continue to advise travellers to diphtheria-endemic countries to check whether they have completed primary vaccination against diphtheria before departure, and to receive a booster dose of diphtheria toxoid if more than 10 years has passed since the last dose, in line with national recommendations.

- Develop and roll out training programmes for vaccine providers to be better equipped when faced with vaccine hesitancy among parents. Similarly, develop and roll out targeted and tailored programmes for vaccine receivers to better understand why they are offered vaccination. Families and individuals who do not vaccinate or are hesitant about vaccination tend to cluster geographically, creating pockets of unvaccinated communities within otherwise highly vaccinated populations. This increases the risk of developing the disease if *C. diphtheriae* is introduced into these communities.
- Ensure through regular training programmes that clinicians have the knowledge required to promptly recognise and treat diphtheria, and have access to testing algorithms and instructions for how to collect and transport samples to the laboratory. Laboratories and countries that lack capacity for confirming toxigenic diphtheria infections should make provisions to send samples to the WHO reference laboratory.
- While prioritising immunisation to prevent disease, regularly assess the level of access to DAT and, if required, consider cross-border options for securing rapid access for all patients with suspected or confirmed diphtheria-toxin-induced disease, in the context of global DAT shortages.

Limitations

This assessment was undertaken based on information known to ECDC at the time of publication. Case definition and classification among non-EU/EEA countries may differ from the EU case definition used for diphtheria. There may be a potential under-ascertainment and/or under-reporting of diphtheria in Europe. However, it is estimated that additional cases related to this event would not substantially alter the risk assessment conclusions in this document, as long as they share the same epidemiological profile.

Source and date of request

ECDC internal decision, 9 September 2022.

Consulted experts

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All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 853/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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