

SURVEILLANCE REPORT

Annual Epidemiological Report for 2021

Diphtheria

Key facts

- Sixty cases of diphtheria due to toxigenic *Corynebacterium diphtheriae* (n=29) or *C. ulcerans* (n=31), and one case with unknown pathogen were reported to ECDC in 2021.
- The highest proportion of *C. ulcerans* cases was among adults aged 65 years and above. *C. diphtheriae* cases were more common in younger age groups.
- Among *C. diphtheriae* cases, 31% were reported as imported.
- Vaccination status was available for 44% of all cases. Seventy 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, the severe consequences of 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].

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Methods

This report is based on data for 2021 retrieved from The European Surveillance System (TESSy) on 1 August 2023. 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 2021, 30 European Union/European Economic Area (EU/EEA) Member States reported data on diphtheria and related toxigenic pathogens. Of these, nine countries reported cases of *Corynebacterium diphtheriae* or *C. ulcerans* or with unknown pathogen.

The majority of Member States reported data on diphtheria according to the 2008 (n=6), 2012 (n=8) or 2018 (n=10) EU case definition. Six countries used an alternative or unspecified 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].

The majority of countries reported data from a comprehensive (n=29) and compulsory (n=30) case-based surveillance system [5].

Epidemiology

Sixty cases of laboratory-confirmed diphtheria and related toxigenic pathogens, and one possible case of diphtheria were reported in 2021 (Table 1, Figure 1). Twenty-nine confirmed cases were reported as *C. diphtheriae*, 31 confirmed cases as *C. ulcerans* and one possible case with unknown pathogen was reported (Table 2). The overall notification rate was 0.01 per 100 000 population.

Diphtheria caused by *C. diphtheriae* was reported by seven countries (Table 2). Among these countries, France (n=9) and Germany (n=9) reported the highest number of cases, followed by Slovakia (n=4).

Diphtheria caused by *C. ulcerans* was reported by four countries. More than 80% of these cases were reported in France (n=13) and in Germany (n=13).

Between 2017 and 2021, 280 cases of diphtheria were reported in the EU/EEA (Table 1), of which 136 cases were due to *C. diphtheriae*.

Table 1. Distribution of diphtheria cases by country and year, EU/EEA, 2017–2021

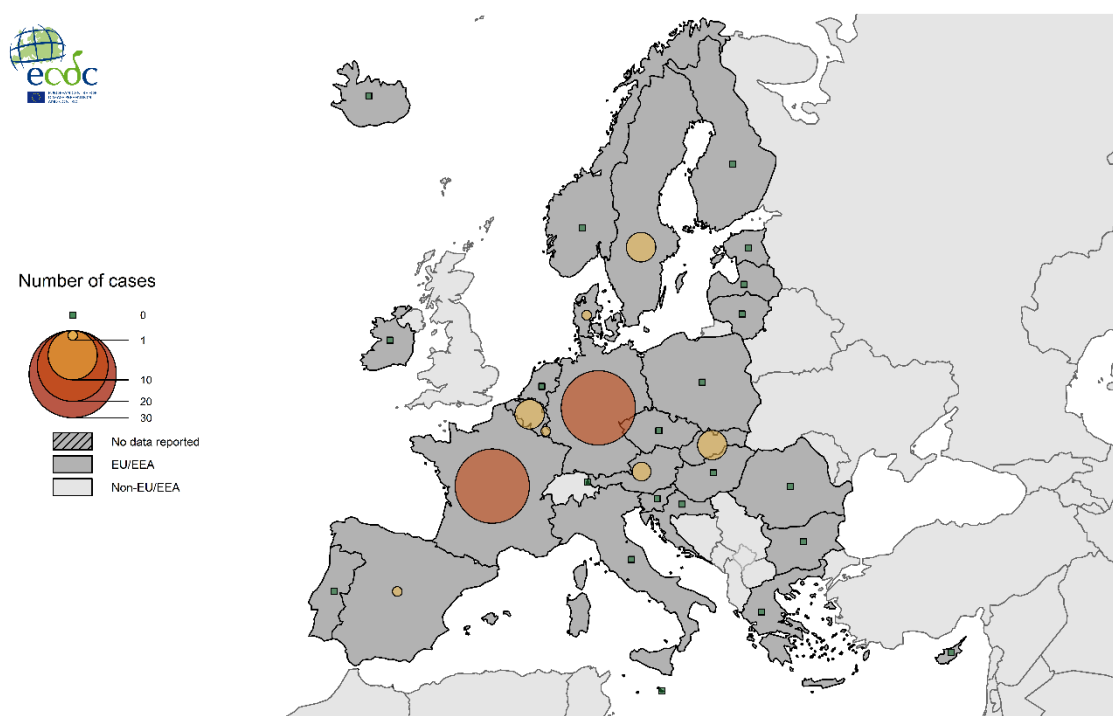
Country	2017	2018	2019	2020	2021
	Number	Number	Number	Number	Number
Austria	0	0	0	2	2
Belgium	1	2	6	3	4
Bulgaria	0	0	0	0	0
Croatia	0	0	0	0	0
Cyprus	0	0	0	0	0
Czechia	0	0	0	0	0
Denmark	0	0	0	0	1
Estonia	0	0	0	0	0
Finland	0	0	0	0	0
France	7	9	19	18	22
Germany	10	26	15	24	22
Greece	0	0	1	0	0
Hungary	0	0	0	0	0
Iceland	0	0	0	0	0
Ireland	0	0	0	0	0
Italy	1	1	0	0	0
Latvia	3	4	3	0	0
Liechtenstein	ND	ND	ND	ND	0
Lithuania	0	0	0	0	0
Luxembourg	0	0	0	0	1
Malta	0	0	0	0	0
Netherlands	4	2	0	3	0
Norway	1	1	2	0	0

Country	2017	2018	2019	2020	2021
	Number	Number	Number	Number	Number
Poland	0	0	0	0	0
Portugal	0	0	0	0	0
Romania	0	0	0	0	0
Slovakia	0	1	2	0	4
Slovenia	0	0	0	0	0
Spain	0	1	2	1	1
Sweden	4	5	4	0	4
United Kingdom	8	11	12	ND	ND
EU-EEA	39	63	66	51	61

Source: Country reports

ND: no data reported.

Figure 1. Distribution of diphtheria cases by country, EU/EEA, 2021



Administration boundaries: © Eurographics
The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. ECDC. Map produced on 2 August 2023.

Table 2. Number of reported cases of diphtheria by country and species, EU/EEA, 2021

Country	<i>C. diphtheriae</i>	<i>C. ulcerans</i>	Unknown
Austria	2	0	0
Belgium	0	4	0
Bulgaria	0	0	0
Croatia	0	0	0
Cyprus	0	0	0
Czechia	0	0	0
Denmark	0	0	1
Estonia	0	0	0
Finland	0	0	0
France	9	13	0
Germany	9	13	0
Greece	0	0	0
Hungary	0	0	0
Iceland	0	0	0
Ireland	0	0	0
Italy	0	0	0
Latvia	0	0	0
Liechtenstein	0	0	0
Lithuania	0	0	0
Luxembourg	1	0	0

Country	<i>C. diphtheriae</i>	<i>C. ulcerans</i>	Unknown
Malta	0	0	0
Netherlands	0	0	0
Norway	0	0	0
Poland	0	0	0
Portugal	0	0	0
Romania	0	0	0
Slovakia	4	0	0
Slovenia	0	0	0
Spain	1	0	0
Sweden	3	1	0
EU/EEA	29	31	1

Source: Country reports.

Age and gender distribution

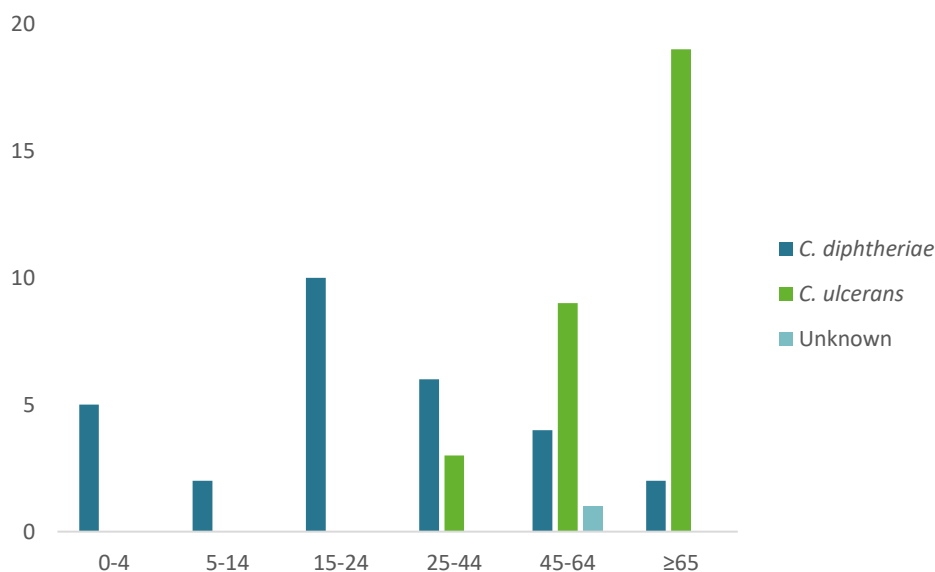
In 2021, cases were reported among all age groups, with a preponderance among those aged 45–64 years (23%) and 65 years or older (34%) (Figure 2). Forty-five (74%) of the 61 cases were reported in males.

Of the 29 *C. diphtheriae* cases, seven (24%) were below 15 years, ten (35%) were reported in teenagers and young adults from 15–24 years and 12 (41%) were reported in adults 25 years and over. Twenty-one (72%) of the 29 cases were reported in males.

Of the 31 *C. ulcerans* cases with known age, three (10%) were reported in adults 25–44 years and 28 (90%) cases were reported in adults 45 years and over. Twenty-three (74%) of the *C. ulcerans* cases with known gender were reported in males.

One case with unknown species was reported in a 47-year-old male.

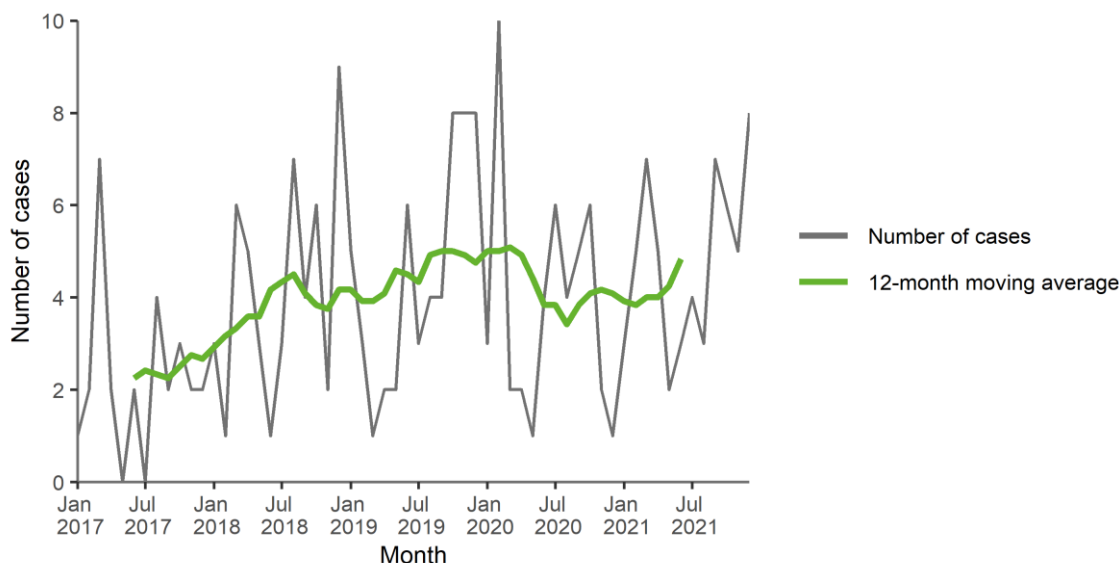
Figure 2. Age distribution of diphtheria cases by species, EU/EEA, 2021



Seasonality

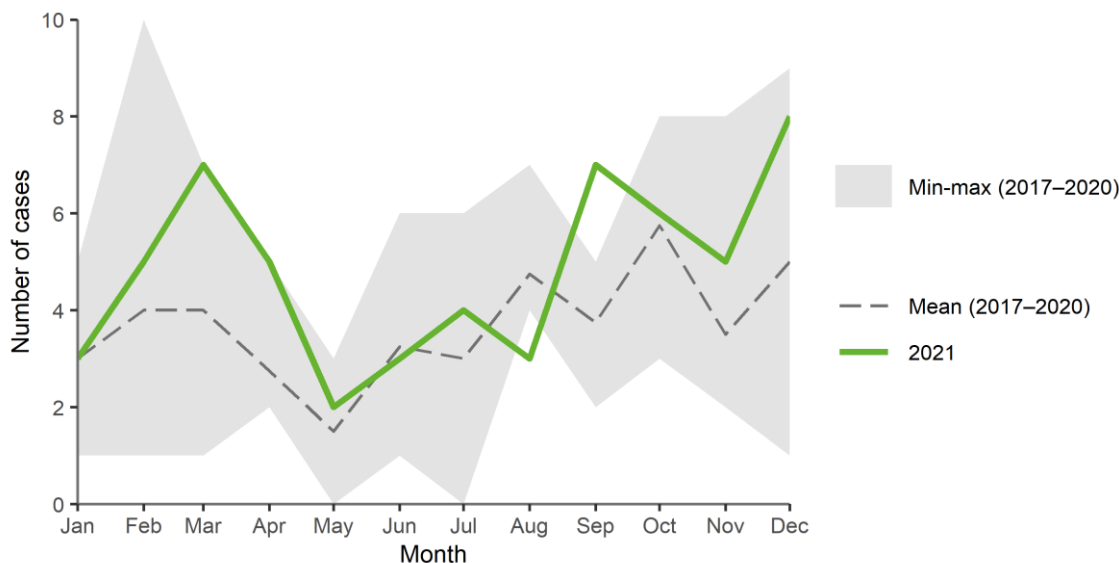
The low number of cases reported does not allow for analysis of seasonal variation (Figure 3). Similar to previous years, cases in 2021 were reported throughout the year and peaked during the last quarter (Figure 4).

Figure 3. Distribution of diphtheria cases by month, EU/EEA, 2017–2021



Source: Country reports from Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden.

Figure 4. Distribution of diphtheria cases by month, EU/EEA, 2021 and 2017–2020



Source: Country reports from Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden.

Clinical presentation, biotype and outcome

Nineteen *C. diphtheriae* cases were reported with known clinical presentation. Two of these cases were reported by Slovakia as classical respiratory diphtheria. Germany (8), Sweden (3), Austria (2), and Spain (1) reported 14 *C. diphtheriae* cases with cutaneous infections. Luxembourg reported one case with genital infection, Germany reported one case with nasal infection, and Slovakia reported one case with 'other' clinical presentation. Nine cases from France and one case from Slovakia were reported with unknown clinical presentation.

Of the reported *C. ulcerans* cases, 17 had cutaneous infection. These were reported from Germany (13), Belgium (3), and Sweden (1). Of these, Belgium reported one case of respiratory and cutaneous diphtheria and in 13 cases the clinical presentation was reported as 'unknown'.

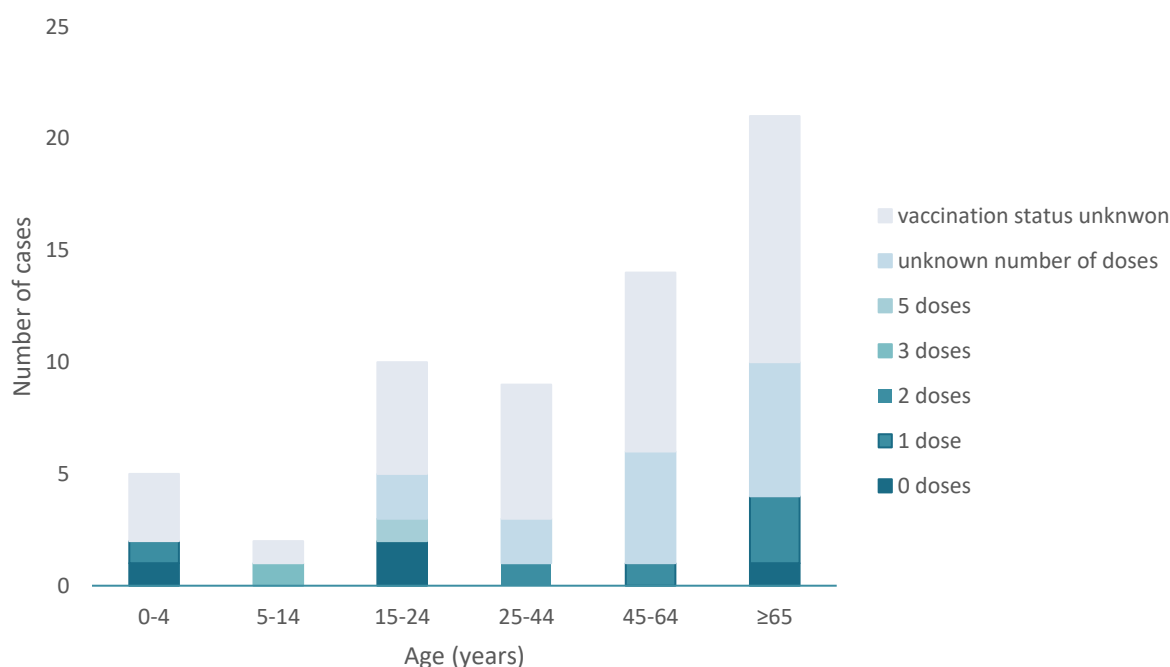
Three *C. diphtheriae* cases were due to biotype Var *gravis*, three *C. diphtheriae* cases were due to biotype Var *mitis* and one *C. diphtheriae* case was due to biotype Var *intermedius*. For twelve *C. diphtheriae* cases, the biotype was unknown, and it was not available for ten *C. diphtheriae* cases.

Information on eventual outcome was available for all cases. One death was reported due to *C. diphtheriae* in a four-year-old female in France.

Vaccination status

Vaccination status was available for 27 cases. Four *C. diphtheriae* cases were reported to have been vaccinated with a known number of doses: one received one dose, one received two doses, one received three doses and one received five doses (Figure 5). Four *C. ulcerans* cases were reported to have been vaccinated with a known number of doses: they received one dose. Fifteen cases (four *C. diphtheriae* cases, 10 *C. ulcerans* cases, one case with unknown pathogen) were reported as vaccinated with an unknown number of doses. Three *C. diphtheriae* cases and one *C. ulcerans* case were reported as not vaccinated at all. Thirty-four additional cases had unknown vaccination status.

Figure 5. Percentage of vaccination status among diphtheria cases by age group, EU/EEA countries, 2021



Source: Country reports from Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden.

Importation status

In 2021, nine cases were reported as imported cases. All imported cases were caused by *C. diphtheriae*. Six of the cases presented with cutaneous disease while the clinical presentation was unknown for three cases. The probable country of origin was known for seven cases. They were imported from Cameroon (1), Côte d'Ivoire (1), Gambia (1), Mali (1), Philippines (1), Somalia (1) and Sri Lanka (1). Thirteen *C. diphtheriae* cases were reported as indigenous: France (5), Germany (4) and Slovakia (4). No case due to *C. ulcerans* was imported.

Discussion

This report includes cases due to *C. diphtheriae* and *C. ulcerans*. While all Member States had surveillance in place for *C. diphtheriae*, few countries reported cases to ECDC from 2017–2021. It is likely that countries with reported cases of all species causing diphtheria in consecutive years have a higher awareness of these pathogens [8].

Diphtheria case detection is strongly influenced by the availability of laboratory resources, expertise and surveillance systems [9,10]. This varies across Europe, and in the past, few countries have performed toxigenicity testing [9-11]. Therefore, under-ascertainment and under-reporting are possible.

The majority of *C. diphtheriae* cases with known clinical presentation were reported as cutaneous. The imported *C. diphtheriae* cases with known probable country of infection were imported from endemic geographical areas. The increased number of susceptible individuals in the EU, such as travellers and migrant populations, are likely to have contributed to distribution [12,13]. 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 [3,13-16].

During the second half of 2022, a substantial increase of cutaneous diphtheria was observed in EU/EEA countries. ECDC monitored this event through event based surveillance and enhanced indicator based surveillance [13,17].

Communication with Member States 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. Thus, timely mobilisation of available DAT stocks in individual countries should be ensured. This may require support from other countries if domestic DAT stocks are depleted.

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