Vaccine-preventable disease update: reported diphtheria cases in the WHO European Region, 2022

19 January 2023
Contents

Abbreviations ................................................................................................................................. 3
Status update summary .................................................................................................................... 4
Background .................................................................................................................................. 4
Diphtheria in the WHO European Region 2012–2021 ................................................................... 5
Diphtheria in the Region in 2022 ................................................................................................... 6
Recommended actions .................................................................................................................... 7
WHO guidance on diphtheria surveillance, case definition and final classification ..................... 8
References ....................................................................................................................................... 10
Abbreviations

DTP1  diphtheria, tetanus, pertussis vaccine, first dose
DTP3  diphtheria, tetanus, pertussis vaccine, third dose
IHR   International Health Regulations
JRF   WHO/UNICEF Joint Reporting Form
UNHCR United Nations High Commissioner for Refugees
UNICEF United Nations Children’s Fund
WUENIC WHO/UNICEF estimates of immunization coverage
Status update summary

- An unusually large number of diphtheria cases have been reported for 2022 to date, most of which occurred in the period June–October.
- 391 cases of diphtheria have been reported by nine countries (Austria, Czechia, France, Germany, Italy, Netherlands, Norway, Switzerland and the United Kingdom).
- Of the 391 cases, 119 (30%) were classified as clinically compatible and 272 (70%) were laboratory confirmed as toxigenic diphtheria cases.
- Of the 272 toxigenic diphtheria cases: 241 were caused by *C. diphtheriae* and 31 were caused by *C. ulcerans*.
- 202 of the toxigenic cases (74%) were classified as cutaneous diphtheria and in another 6 toxigenic cases the diagnosis was classic respiratory diphtheria.
- 4 cases resulted in death and in another case post-mortem results are still pending.
- 317 of the 391 cases (81%) were among asylum seekers, refugees or other newly arriving migrants in the countries reporting cases, primarily originating from Afghanistan (169 cases). 74 cases (19%) were local residents, 7 of whom were reportedly travel-related (infections were acquired abroad).
- There were no reports of transmission of diphtheria between local residents and newly arriving migrants.

WHO recommended actions

- Clinicians examining or caring for patients presenting with a sore throat or skin lesions such as ulcers are encouraged to consider the possibility of diphtheria; and in the current context in the WHO European Region to be particularly alert for possible infection among newly arriving migrants.
- Clinicians are encouraged to send clinical specimens for laboratory confirmation of toxigenic diphtheria.
- Health authorities are reminded that consistently high coverage with 3 doses of a diphtheria-containing vaccine and with recommended booster doses in all populations is needed to prevent diphtheria cases and outbreaks.

Background

Diphtheria is an acute bacterial disease caused by *Corynebacterium* species. The commonest type of diphtheria is classic respiratory diphtheria, caused by toxin-producing *C. diphtheriae*. The disease is characterized by a membranous inflammation of the upper respiratory tract, with widespread damage to other organs, primarily the myocardium and peripheral nerves. The infection can also affect the skin (cutaneous diphtheria) and rarely, it can affect mucous membranes at other non-respiratory sites, such as genitalia and conjunctivae.

The pathogen is transmitted by contact with a patient or carrier and less commonly by contact with articles soiled with discharges from lesions of infected persons. Most diphtheria-related deaths result from the effects of the toxin and include acute systemic toxicity, myocarditis and neurologic complications. The case fatality of respiratory diphtheria is 5–10% even with treatment (1). Non-toxigenic strains may cause a sore throat but do not produce membranous lesions.

Two other potentially toxigenic species, *Corynebacterium ulcerans* and *Corynebacterium pseudotuberculosis*, are primarily zoonotic infections but can also cause disease in humans. *C. ulcerans* infection is associated with disease indistinguishable from that caused by toxigenic strains of *C. diphtheriae*.

---

1 Referred to further in this document collectively as newly arriving migrants.
Diphtheria in the WHO European Region 2012–2021

Diphtheria is considered uncommon in the WHO European Region; of the over 96,000 diphtheria cases reported globally in 2012–2021 (2) only 452 cases were reported in the Region. Although sporadic cases may have been missed due to suboptimal surveillance systems and lack of specialized laboratory diagnostic capacity in some countries. The relatively low number of cases in the Region is considered to be the result of overall long-standing high coverage with the third dose of diphtheria, tetanus, pertussis vaccine (DTP3) at regional level.

For 2012–2021, 452 diphtheria cases were reported in the Region through the WHO/United Nations International Children’s Emergency Fund (UNICEF) Joint Reporting Form (JRF) (3) submitted by each country to the WHO Regional Office for Europe (Fig.1).² From 2018, the JRF specifically included a request for reporting of toxigenic diphtheria cases only. For 2021, 41 cases were reported by 11 of 49 countries that submitted reports (including zero reporting). For 2012–2021, based on WHO/UNICEF Estimates of National Immunization Coverage (WUENC) (4), coverage in the Region with the first dose of diphtheria, tetanus, pertussis vaccine (DTP1) and DTP3 was 95–97% and 92–96%, respectively.

**Fig. 1.** Number of diphtheria cases* (n=452) and DTP1 and DTP3 coverage in the WHO European Region, 2011–2021

![Diagram showing number of diphtheria cases and DTP1 and DTP3 coverage](image)

DTP1: first dose of diphtheria, tetanus and pertussis vaccine; DTP3: third dose of diphtheria, tetanus and pertussis vaccine.

*The number of countries that submitted reports (including zero reporting) on diphtheria cases are shown in parentheses below the year.

² For further reading on diphtheria in the European Region during the period 2010–2019 and 2020, see:

Diphtheria in the Region in 2022

In the period 1 January to 20 December 2022, 391 diphtheria cases detected in the Region were reported to the WHO Regional Office for Europe through the International Health Regulations (IHR) system or directly to the Regional Office’s Vaccine-preventable Diseases and Immunization programme. Most of the cases were detected in June through October. The cases were reported by Austria, Czechia, France, Germany, Italy, Norway, Switzerland and the United Kingdom. Vaccination status of these cases was either not reported or reported as unknown except for one case that had been vaccinated with two doses of a diphtheria-containing vaccine.

Populations affected

317 cases (81%) were among asylum seekers, refugees or other newly arrived migrants in the countries reporting cases, who came primarily from Afghanistan (169 cases) or other countries including Albania, Algeria, Bangladesh, Cameroon, Iran, Iraq, Morocco, Pakistan, Russian Federation, Syria, Tunisia and Türkiye. Gender was known in 193 of these cases, of which 190 cases (98%) were males. 185 cases had data on age, which ranged from 3 years to 41 years with a median age of 17 years.

Of the 74 cases reported among local residents (19%), 7 were reportedly travel-related (infection was acquired abroad). There were no reports of transmission of diphtheria between local residents and newly arriving migrants or returning residents.

Toxigenic diphtheria cases and clinical sub-classification

272 cases (70%) were laboratory confirmed with a confirmatory toxigenic test result (Elek test) and classified as such according to the WHO case classification for diphtheria (5). Of these, 202 cases were clinically classified as cutaneous diphtheria (one of which resulted in death); 58 cases as mild/asymptomatic (including 6 cases classified as ‘asymptomatic’ and 4 cases as ‘respiratory’); 3 cases had features of both respiratory and cutaneous (one of which resulted in death); and in 3 other cases the clinical presentation was not specified. Classic respiratory diphtheria was reported in 6 cases, one of which resulted in death and in another case post-mortem results are still pending.

Other case classifications

In addition to the 272 laboratory-confirmed as toxigenic cases, 119 cases (30%) were classified as clinically compatible since although the pathogen was identified, neither confirmatory toxigenic test results nor epidemiologic linkage to a laboratory-confirmed case were reported. Of these, 105 cases were caused by Corynebacterium diphtheriae, 9 cases by C. ulcerans, and 1 case by C. pseudotuberculosis. In 4 cases the Corynebacterium species was not reported. One diphtheria-related death was among the clinically compatible cases.

Comments

The information presented in this update is derived from reports received by the WHO Regional Office for Europe through the IHR system and through direct communications from countries with the Regional Office’s Vaccine-preventable Diseases and Immunization programme. Cases of diphtheria in the Region are seldom spontaneously reported in these ways but the unusually large number of reports of diphtheria cases starting in early summer 2022 triggered such reporting. These cases were mostly among newly arriving migrants from outside the Region, notably from Afghanistan but also from other countries. Cutaneous diphtheria among asylum seekers and refugees has also been reported in recent years (5,6) but in smaller numbers.

Not all countries applied the same criteria for the final classification and clinical sub-classification of diphtheria cases. For the purposes of this report, based on the available data or lack of it, some cases were
re-classified to adhere to the WHO-recommended surveillance standards for diphtheria (7). The case definition of a suspected case of diphtheria and final case classification are provided in the annex.

Comparisons to the previous years’ data on diphtheria (as obtained through the JRF) and data for 2022 reported here (as obtained though the IHR system or directly from countries) have to be made with caution as the number of reporting countries for 2022 is only nine and the data cover only part of the year. In addition, data collected in the JRF do not distinguish between locally acquired infections and imported infections.

Recommended actions

**Increased awareness**
The WHO Regional Office for Europe would like to alert all clinicians, particularly those responsible for the health of asylum seekers, refugees and other newly arriving migrants, to the potential presence of cutaneous and respiratory diphtheria. Clinicians examining or caring for patients presenting with skin lesions such as ulcers or a sore throat are encouraged to consider the possibility of diphtheria. The risk of spread of the disease is higher in closed and crowded spaces as is often the case in asylum seeker centres. In contrast, the risk of spread to the general community is low primarily because of high vaccination coverage against diphtheria.

**Improved surveillance**
Surveillance systems for diphtheria, including laboratory diagnostic capacity, need to be adequate to ensure that cases are not missed. Clinicians are encouraged to collect and send clinical specimens of suspected cases for laboratory confirmation of toxigenic diphtheria. In addition, antimicrobial susceptibility testing of all *C. diphtheriae* isolates is encouraged especially in view of the recently noted unusually broad resistance to many common antibiotics (8).

An adequate surveillance of diphtheria requires that laboratories are equipped with the appropriate materials and that all isolates of potentially toxigenic *Corynebacterium spp.* should ideally be submitted to a reference/specialist laboratory for confirmation of identification and toxigenicity testing. A revised WHO manual for laboratory diagnosis of diphtheria and related infections has recently been published to assist laboratory workers in the correct procedures to diagnose diphtheria cases and to guide clinicians in treatment options (9). Where confirmatory tests for toxigenic *Corynebacterium spp.* are limited, arrangements with the WHO Collaborating Centre for Diphtheria based at the United Kingdom Health Security Agency in London, England, can be made for further laboratory investigation. Countries are also encouraged to adhere to the WHO-recommended surveillance standards for diphtheria that serve as a guide to good practice and may help to harmonize surveillance activities (7).

**Optimized vaccination coverage**
Diphtheria cases and outbreaks can only be prevented by attaining high coverage with 3 doses of a diphtheria-containing vaccine and recommended booster doses. Countries should strive to ensure strong national immunization programmes that address inequities in vaccination uptake in all populations. Asylum seekers and refugees should be vaccinated without unnecessary delay according to the national immunization schedules of the country where they are envisioned to reside for more than a week. General principles on vaccination of asylum seekers, refugees and other migrants in the WHO European Region are outlined in a WHO-UNICEF-United Nations High Commissioner for Refugees (UNHCR) joint technical guidance document (10).
WHO guidance on diphtheria surveillance, case definition and final classification

WHO recommended actions for diphtheria surveillance
Surveillance for diphtheria should be national and facility based; and because the disease is relatively rare in the European Region, surveillance should also be case based. All health care providers identifying cases should be required to report those cases. Ideally, laboratory testing of all suspected cases should be conducted for case confirmation. Case-based surveillance may not be possible during large outbreaks, when laboratory testing of all suspected cases becomes logistically challenging. Below are the suspected case definition and final case classification as per WHO Surveillance Standards for diphtheria (7).

Suspected case definition for case finding
For case finding, the definition of a suspected case of diphtheria is an illness of the upper respiratory tract characterized by the following:

➢ pharyngitis, nasopharyngitis, tonsillitis or laryngitis

AND

➢ adherent pseudomembrane of the pharynx, tonsils, larynx and/or nose. A diphtheria pseudomembrane is an exudate that is greyish, thick, firmly adherent and patchy to confluent. Dislodging the pseudomembrane is likely to cause profuse bleeding.

Some countries can choose to expand the suspected case definition to include the following:

➢ mild cases without a pseudomembrane
➢ non-healing ulcers in a person with a travel history to countries with endemic disease or countries with diphtheria outbreaks.

Final case classification
➢ Laboratory-confirmed case. A laboratory-confirmed case is a person with Corynebacterium spp. isolated by culture and positive for toxin production, regardless of symptoms. Toxigenicity must be confirmed by the phenotypic Elek test in all instances. Polymerase chain reaction (PCR) can complement surveillance and may qualify as laboratory-confirmed after reviewing the epidemiology and clinical manifestations of the case. Laboratory-confirmed cases may be further classified into three subcategories based on the type of surveillance occurring in the country.

» Laboratory-confirmed classic respiratory diphtheria cases meet the suspected case definition and are laboratory-confirmed as defined above.

» Laboratory-confirmed mild respiratory/asymptomatic diphtheria cases have some respiratory symptoms such as pharyngitis and tonsillitis, but no pseudomembrane, or no symptoms (usually identified via contact tracing).

» Non-respiratory laboratory-confirmed diphtheria cases have a skin lesion or non-respiratory mucosal infection (for example, eye, ear or genitalia) from which Corynebacterium spp. is isolated by culture and tests positive for toxin production.

➢ Epidemiologically linked case. An epidemiologically linked case meets the definition of a suspected case and is linked epidemiologically to a laboratory-confirmed case. In this situation, a person has had intimate respiratory or physical contact with a laboratory-confirmed case within the 14 days prior to onset of sore throat.
 Clinically compatible case. This type of case meets the definition of a suspected case and lacks both a confirmatory laboratory test result and epidemiologic linkage to a laboratory-confirmed case.

 Discarded case. A discarded case is a suspected case that meets either of these criteria:
» Corynebacterium spp. but negative Elek test (non-toxigenic Corynebacterium)
OR
» negative PCR for the diphtheria toxin (tox) gene.

 Classifying asymptomatic or mild cases. Sometimes during outbreak investigations in which household contacts are investigated, a person may be identified with Corynebacterium and have evidence of toxigenicity but does not meet the suspected case definition because the person is asymptomatic or has only mild disease. These persons should still be reported as laboratory-confirmed cases, as their treatment and public health response is the same as other laboratory-confirmed cases.
References


Related publications


Document number: WHO/EURO:2023-6208-45973-68002

© World Health Organization 2023. Some rights reserved. This work is available under the CC BY-NC-SA 3.0 IGO license.