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

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Abbreviations

DTP1  diphtheria, tetanus, pertussis vaccine, first dose
DTP3  diphtheria, tetanus, pertussis vaccine, first 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

- So far, in 2022 an unusually large number of reported diphtheria cases have been submitted through the International Health Regulations (IHR) reporting mechanism, mostly during June-August.
- 144 cases of diphtheria have been reported by seven countries (Austria, France, Germany, Italy, Norway, Switzerland and the United Kingdom), many of which among asylum seekers.
- Of the 144 cases, 97 (69%) were classified as clinically compatible, 44 (31%) were laboratory confirmed as toxigenic diphtheria cases and 3 (2%) were suspected cases.
- Of the 44 cases known to be toxigenic: 43 were caused by *C. diphtheriae* and 1 case by *C. pseudotuberculosis*. The clinical sub-classification of these cases was: cutaneous diphtheria in 35 cases, mild/asymptomatic in 8 cases and classic respiratory diphtheria in one case that resulted in death.
- 90 of the 144 cases (63%) were among reported asylum seekers or refugees, primarily from Afghanistan (52 cases). 32 cases (23%) were local residents, three of whom were reportedly infected abroad. For 22 cases (16%) the population affected was not reported.
- There were no reports of transmission of diphtheria between the general population and asylum seeker/refugee populations.

WHO recommendations

- 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 asylum seekers and refugees from Afghanistan and other countries.
- Clinicians are encouraged to send clinical specimens for laboratory confirmation of toxigenic diphtheria.
- High coverage with 3 doses of a diphtheria-containing vaccine and 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*. 
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 from the Region. Nevertheless, sporadic cases, sometimes resulting in death, continue to be reported.

The relatively low number of cases reported annually in recent years is probably the result of overall long-standing high DTP3 coverage at regional level. However, this may be also partly attributed to suboptimal surveillance systems and inadequate or lack of specialized laboratory diagnostic capacity.

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).1 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 (WUENIC) (4), coverage in the Region with the first dose of diphtheria, tetanus, pertussis vaccine (DTP1) and the third dose of diphtheria, tetanus and pertussis vaccine (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

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of reported diphtheria cases</th>
<th>DTP1 coverage</th>
<th>DTP3 coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>36 (n=48)</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>2013</td>
<td>33 (n=45)</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>2014</td>
<td>35 (n=38)</td>
<td>96%</td>
<td>93%</td>
</tr>
<tr>
<td>2015</td>
<td>59 (n=45)</td>
<td>93%</td>
<td>96%</td>
</tr>
<tr>
<td>2016</td>
<td>47 (n=48)</td>
<td>94%</td>
<td>93%</td>
</tr>
<tr>
<td>2017</td>
<td>35 (n=52)</td>
<td>95%</td>
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<tr>
<td>2018</td>
<td>52 (n=53)</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>2019</td>
<td>32 (n=49)</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>2020</td>
<td>41 (n=49)</td>
<td>94%</td>
<td>94%</td>
</tr>
</tbody>
</table>

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.

1 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 31 August 2022, 144 diphtheria cases detected in the Region were reported to WHO through the IHR system. Most of the cases were detected in the summer months June through August. The cases were reported by Austria, 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. Gender was known in 71 cases (50%), of which 67 cases (94%) were males and 4 cases (6%) were females.

Populations affected

90 cases (63%) were reported to be among asylum seekers or refugees, primarily from Afghanistan (52 cases) but also from Algeria, Bangladesh, Cameroon, Mali, Morocco, Senegal, Syria or Türkiye. In 21 of these cases the country of origin was not established. 32 cases (23%) were local residents, three of whom were reportedly infected abroad. The origin of infection of the remaining 29 local residents was not reported. The population affected in 22 cases (16%) was not reported.

Clinical sub-classification

Of the 144 cases, 90 (63%) presented with cutaneous diphtheria: 81 of which were caused by *C. diphtheriae*, seven were caused by *C. ulcerans* and 1 by *C. pseudotuberculosis*. In another cutaneous diphtheria case the causative pathogen still needed to be identified. Classic respiratory diphtheria was reported in six cases; all caused by *C. diphtheriae*. Mild or asymptomatic diphtheria was identified in 26 cases, all caused by *C. diphtheriae*. For 22 cases the clinical presentation was not reported.

Toxigenic diphtheria cases

44 cases (31%) were laboratory confirmed as toxigenic diphtheria: 43 cases caused by *C. diphtheriae* and one case by *C. pseudotuberculosis*, according to the WHO case classification for diphtheria (5). The clinical sub-classification of these cases was: cutaneous diphtheria in 31 cases, mild/asymptomatic in 8 cases and classic respiratory diphtheria in 1 case. 43 cases were asylum seekers and 1 case was a local resident. The country of origin for most asylum seekers was Afghanistan (29 cases).

Other case classifications

There were 97 other reports (69%) of diphtheria: 71 cases caused by *C. diphtheriae*, seven cases by *C. ulcerans* and 19 cases by *Corynebacterium* species was not reported. These cases 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. Reports of the results of the definitive Elek test used to confirm toxigenic diphtheria are still pending in several cases. These cases would be re-classified according to these results. A further three cases were reported as suspected cases of diphtheria.

Comments

The information presented in this update is derived from communications through the IHR system. Cases of diphtheria in the Region are seldom reported through this system but during the summer months June through August there was an unusually large number of reports of diphtheria, many among asylum seekers from outside the Region, notably from Afghanistan but also from other countries. Cutaneous diphtheria among asylum seekers has also been reported in recent years (6,7).

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 (6). The case definition of a suspected case of diphtheria and final case classification are provided in the annex.
The number of reporting countries for 2022 is only seven and the data cover only part of the year. While the total number of cases is unusually high for the Region and occurred in a short period, many have not been tested for toxigenicity. In addition, data collected in the JRF do not distinguish between locally acquired infections and imported infections. Therefore, comparisons of these variables between previous years’ data (as obtained through the JRF) and data for 2022 reported here (as obtained through the IHR reporting system) cannot be made.

Recommendations

Increased awareness
The WHO Regional Office for Europe would like to alert all clinicians, particularly those responsible for the health of asylum seekers, migrants and refugees, to the potential presence of cutaneous and respiratory diphtheria in those who arrive from countries endemic for the disease. 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, and in the current context in the WHO European Region to be particularly alert for possible infection among asylum seekers and refugees from Afghanistan and other countries. 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.

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 (8). 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 (6).

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 refugees, asylum seekers and migrants in the WHO European Region are outlined in a WHO-UNICEF-United Nations High Commissioner for Refugees (UNHCR) joint technical guidance document (9).
WHO guidance on diphtheria surveillance, case definition and final classification

**WHO recommendations 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 (6).

**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


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