Training session

European surveillance of diphtheria

Jordi Borrell Pique

GenEpi-BioTrain - Virtual training 15 - Focus on the Agents of Diphtheria, 7 March 2025

Diphtheria: key considerations

- ✓ Is an acute infectious disease caused by **toxin-producing** Corynebacterium species (mainly *Corynebacterium (C.) diphtheriae and also* by *C. ulcerans* and *C. pseudotuberculosis* strains)

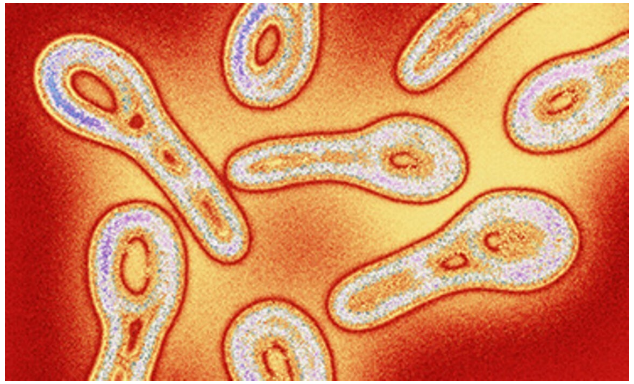
- ✓ It can present in two main clinical forms:
  - ✓ Respiratory diphtheria (severe disease that produces a membrane in the upper respiratory tract and damages other organs. Life threatening)
  - ✓ Cutaneous diphtheria (less severe, skin lesions)

- ✓ Diphtheria is a rare disease in the EU/EEA countries.

- ✓ Vaccination is the only effective method of preventing the toxin-mediated disease and the occurrence of disease in fully vaccinated individuals is very rare.

- ✓ Can be treated with antibiotics and antitoxin (DAT) .

- ✓ In non-vaccinated individuals, and especially if proper treatment is delayed, death can occur in up to 10% of clinical cases despite the administration of antibiotics and antitoxin (DAT).



Diphtheria: key considerations

- ✓ Humans are the only significant reservoir for *C. diphtheriae.*
- ✓ Transmission of *C. diphtheriae* occurs via airborne respiratory droplets, direct contact with respiratory secretions or direct contact with exudate from infected cutaneous lesions.
- ✓ The incubation period ranges from two to five days but can be as long as 10 days.
- ✓ Transmission from cutaneous lesions can cause both respiratory and cutaneous disease in susceptible contacts.
- ✓ The other two Corynebacterium species, *C. ulcerans* and *C. pseudotuberculosis* (very rarely), may also cause diphtheria disease. These infections are mainly zoonotic.

cutaneous presentation

respiratory presentation

Image source: CDC Public Health Image Library and The New England journal of medicine (Images in clinical medicine, Lindsey R. Baden).

Prevention through vaccination programmes

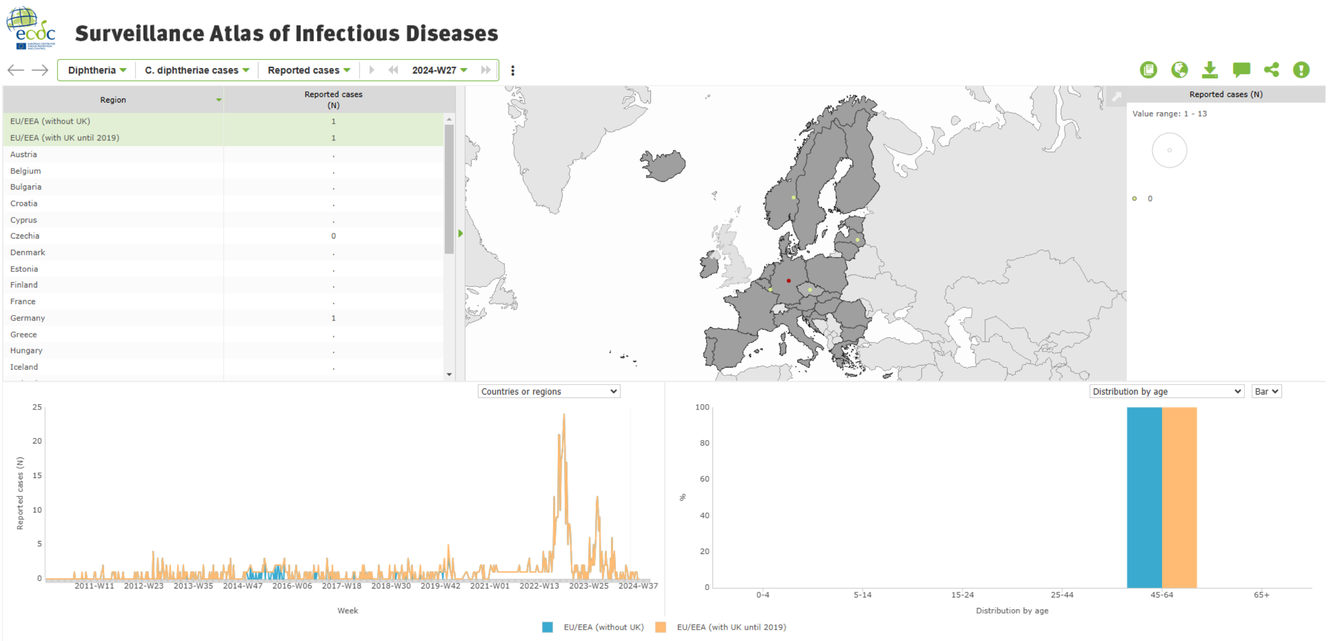
- Different vaccine products against tetanus (T), diphtheria (D), and pertussis (P) are available. While the vaccine for young children contains a full dose of diphtheria toxoid (DTP), the vaccine for older children with completed primary vaccination, adolescents and adults contains a reduced diphtheria component (dTP).

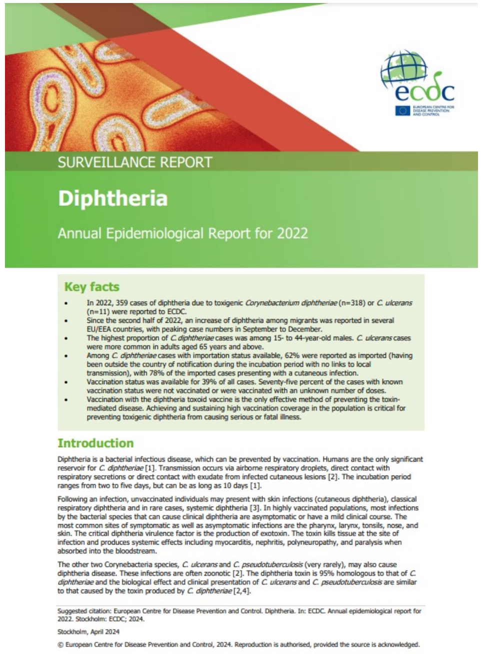
- The **European vaccine action plan 2015/2020** set a **target of ≥95%** vaccine **coverage for DTP3** in the WHO European region Member States.

- WHO recommends a **3-dose primary vaccination series** with diphtheria containing vaccine **followed by 3 booster doses**.
  - The primary series should begin as early as 6-week of age with subsequent doses given with a minimum interval of 4 weeks between doses.
  - The 3 booster doses should preferably be given during the second year of life (12-23 months), at 4-7 years and at 9-15 years of age. Ideally, there should be at least 4 years between booster doses.

Current surveillance in place at the EU/EEA level

- **Monthly reporting** by the last day of the month to EpiPulse cases. **Possible, probable and confirmed cases** should be reported. More timely reporting is also encouraged to countries.
- An **annual data call** will still be carried out in order to finalise datasets for the previous year. Mandatory to report "**zero cases**" if no cases have occurred.
- **Monthly** updates are **published in ECDC atlas**, providing data on cases disaggregated by country, week, species, gender and age. **Annually**, ECDC publishes the related **annual epidemiological report**.





SURVEILLANCE REPORT

Diphtheria

Annual Epidemiological Report for 2022

Key facts

- In 2022, 359 cases of diphtheria due to toxigenic *Corynebacterium diphtheriae* (n=318) or *C. ulcerans* (n=11) were reported to ECDC.
- Since the second half of 2022, an increase of diphtheria among migrants was reported in several EU/EEA countries, with peaking case numbers in September to December.
- The highest proportion of *C. diphtheriae* cases was among 15- to 44-year-old males. *C. ulcerans* cases were more common in adults aged 65 years and above.
- Among *C. diphtheriae* cases with importation status available, 62% were reported as imported (having been outside the country of notification during the incubation period with no links to local transmission), with 78% of the imported cases presenting with a cutaneous infection.
- Vaccination status was available for 39% of all cases. Seventy-five percent of the cases with known vaccination status were not vaccinated or were vaccinated with an unknown number of doses.
- Vaccination with the diphtheria toxoid vaccine is the only effective method of preventing the toxin-mediated disease. Achieving and sustaining high vaccination coverage in the population is critical for preventing toxigenic diphtheria from causing serious or fatal illness.

Introduction

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

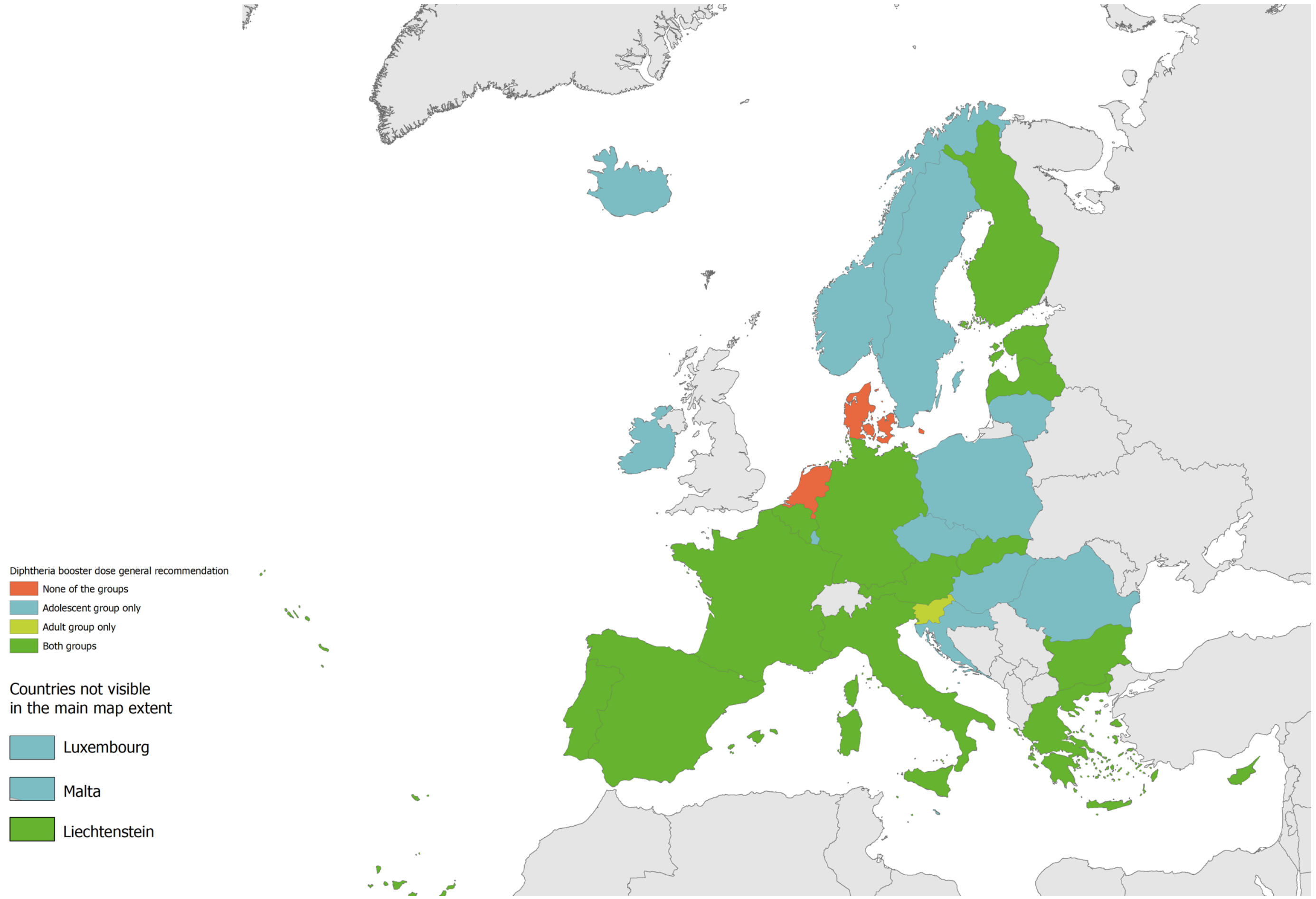
Following an infection, unvaccinated individuals may present with skin infections (cutaneous diphtheria), classical respiratory diphtheria and in rare cases, systemic diphtheria [3]. In highly vaccinated populations, most infections by the bacterial species that can cause clinical diphtheria are asymptomatic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

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

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

Stockholm, April 2024

Diphtheria booster dose recommendation in adolescents and adults in the EU/EEA



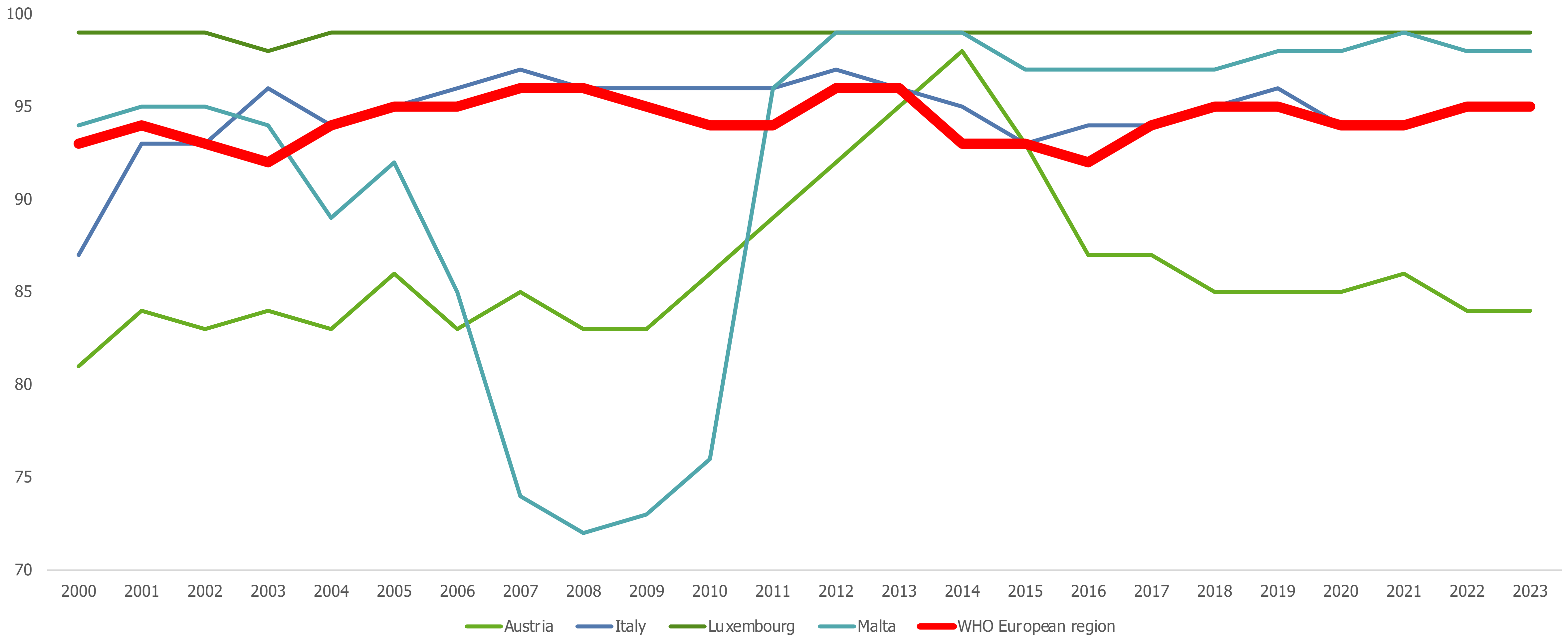
- **General diphtheria booster dose recommendation** excludes any specific recommendations for specific groups (e.g.: pregnant women).

- Excludes catch-up recommendations.

- **In the EU/EEA**:
    - One country recommends booster doses in adults only.
    - 12 countries recommends booster doses in adolescents only.
    - 15 countries recommends booster doses in both adolescents and adults.
    - Two countries do not recommend booster doses in any of these groups.

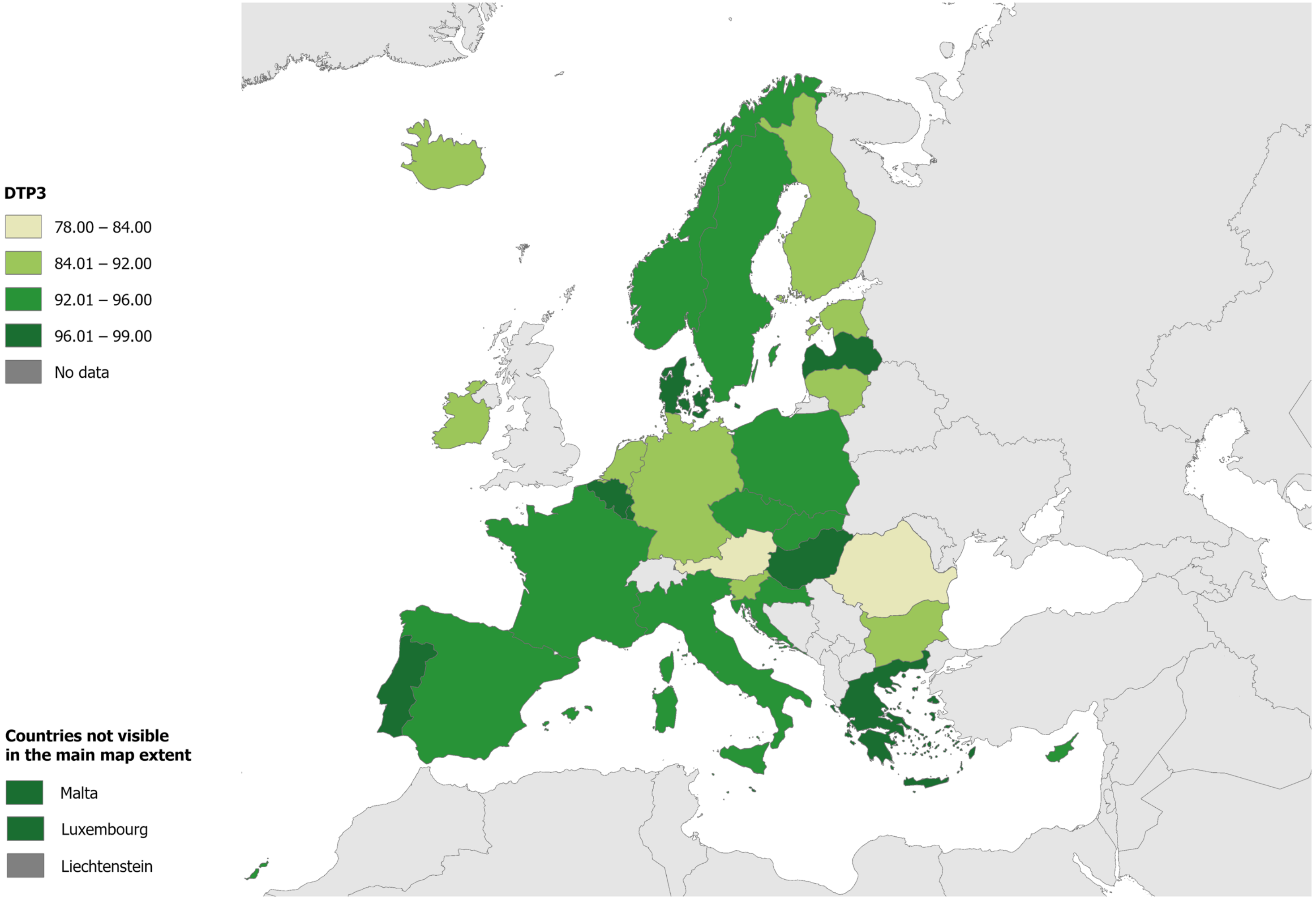
Data source: ECDC vaccine scheduler https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=1&SelectedCountryIdByDisease=-1

DTP3 vaccine coverage of selected EU/EEA countries for 2000 to 2023 period



Data source: WHO Immunisation data portal, WUENIC estimates for DTP3

DTP3 vaccine coverage in the EU/EEA in 2023



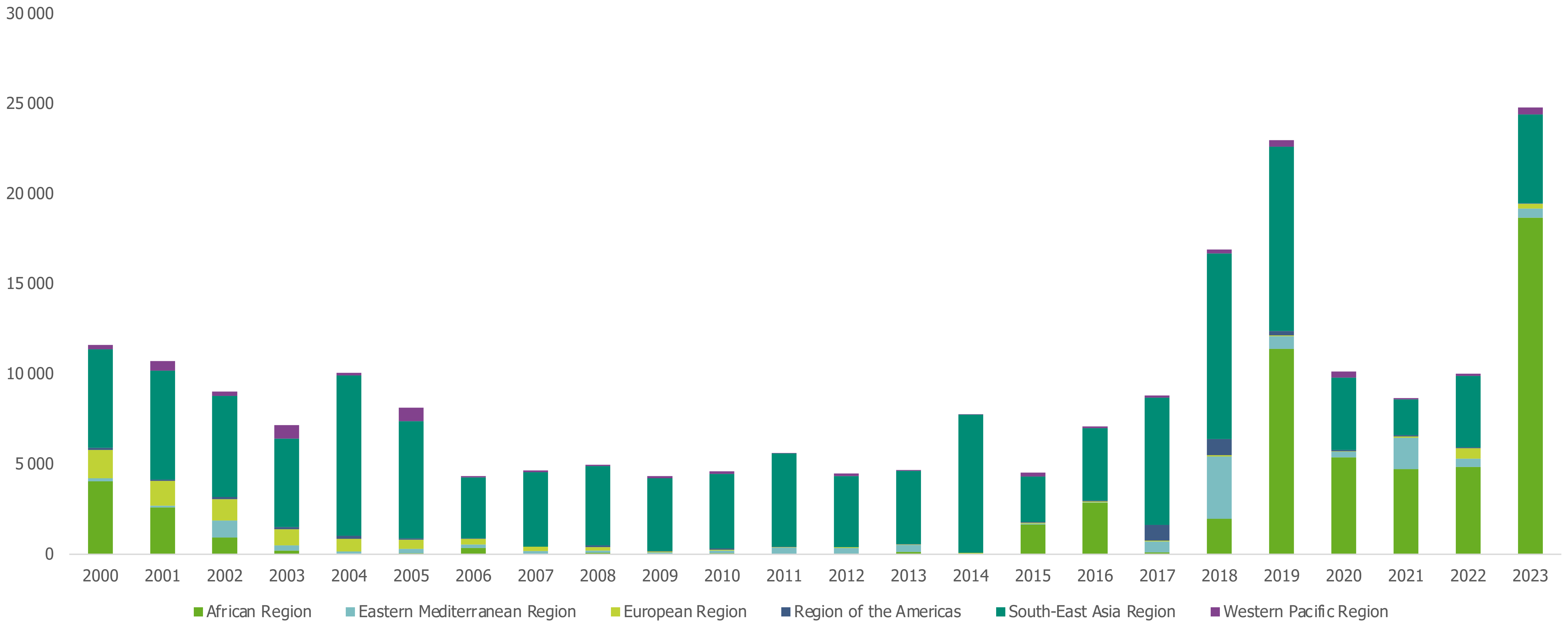
Thirteen EU/EEA countries reached the goal of ≥95% DTP3 in 2023:

Belgium
Cyprus
Denmark
France
Greece
Hungary
Italy
Latvia
Luxembourg
Malta
Norway
Portugal
Slovakia

Map produced on: 4 Dec 2024. Administrative boundaries: © EuroGeographics © UN–FAO © Turkstat.The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union.

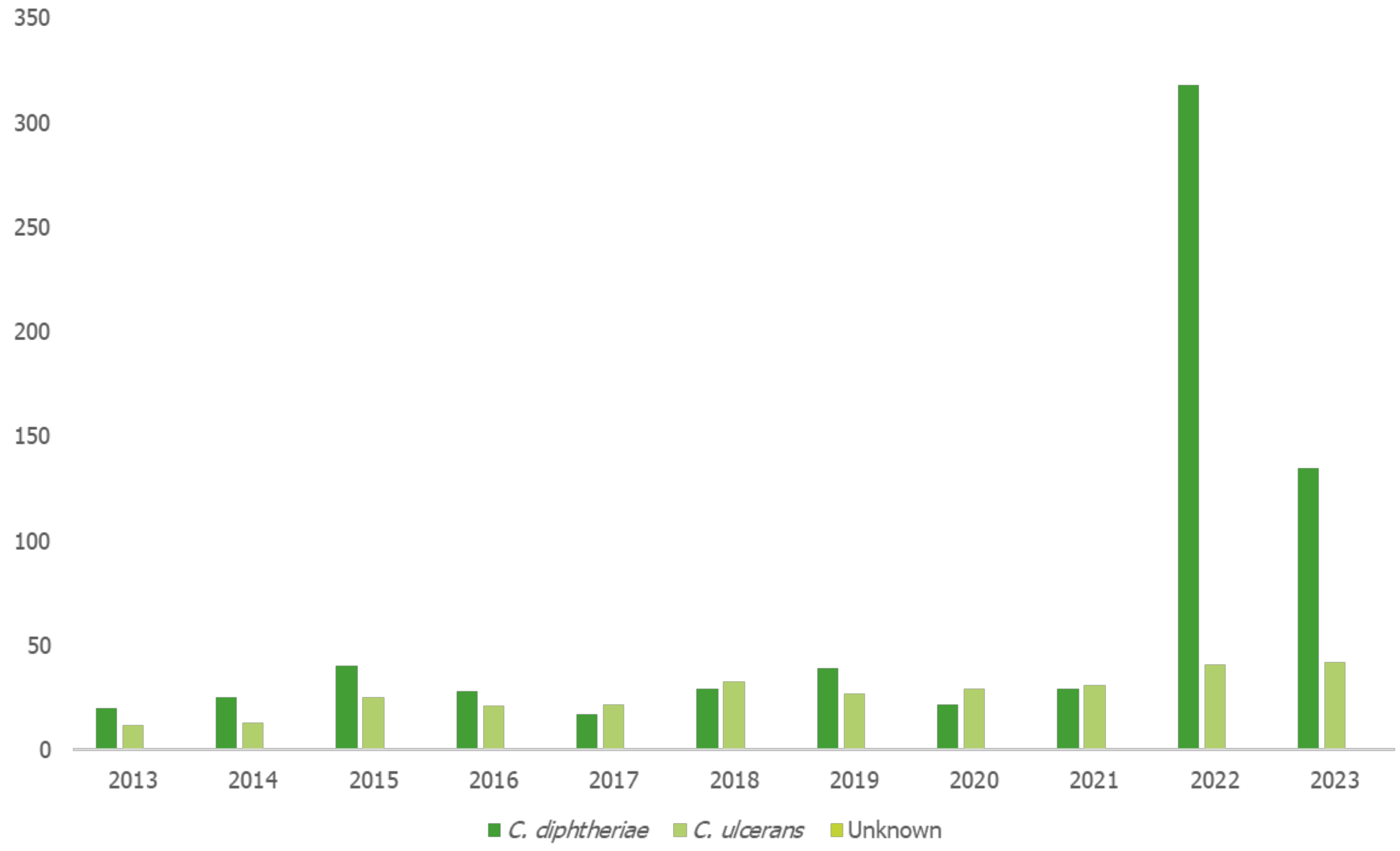
Source: WHO Immunisation data portal, WUENIC estimates for DTP3

Diphtheria confirmed cases reported worldwide in the 2000 to 2023 period



N= 216 166 confirmed diphtheria cases worldwide for the 2000-2023 period.
Source: WHO/UNICEF Joint Reporting Form on Immunization (JRF)

Diphtheria confirmed cases reported in the EU/EEA in the 2013 to 2024 period

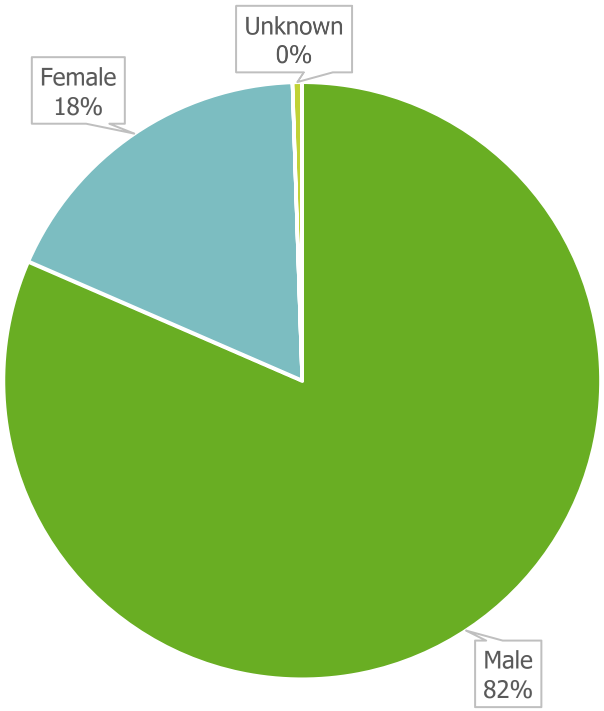


- In the period under analysis, **1 051 confirmed diphtheria cases** were reported in all the EU/EEA.
- Among these cases, **731** were attributable to ***C. diphtheriae*** (69.6% of the total) and **317** were attributable to ***C. ulcerans*** (30.2% of the total).

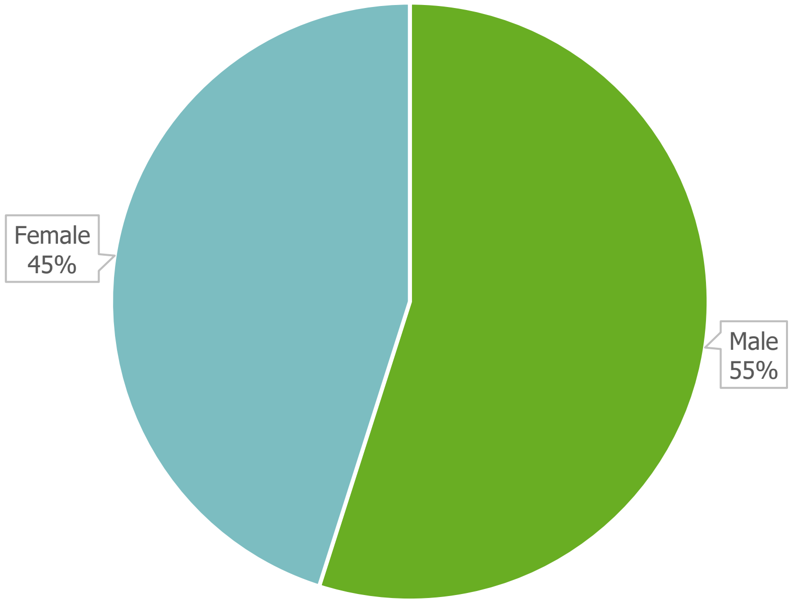
*Data as of November 2024.
Source: The European Surveillance System (TESSy)
Cases reported in the United Kingdom included only in the 2010-2019 period.

Gender distribution of confirmed cases reported in the EU/EEA in the 2010 to 2024* period

C. diphtheriae

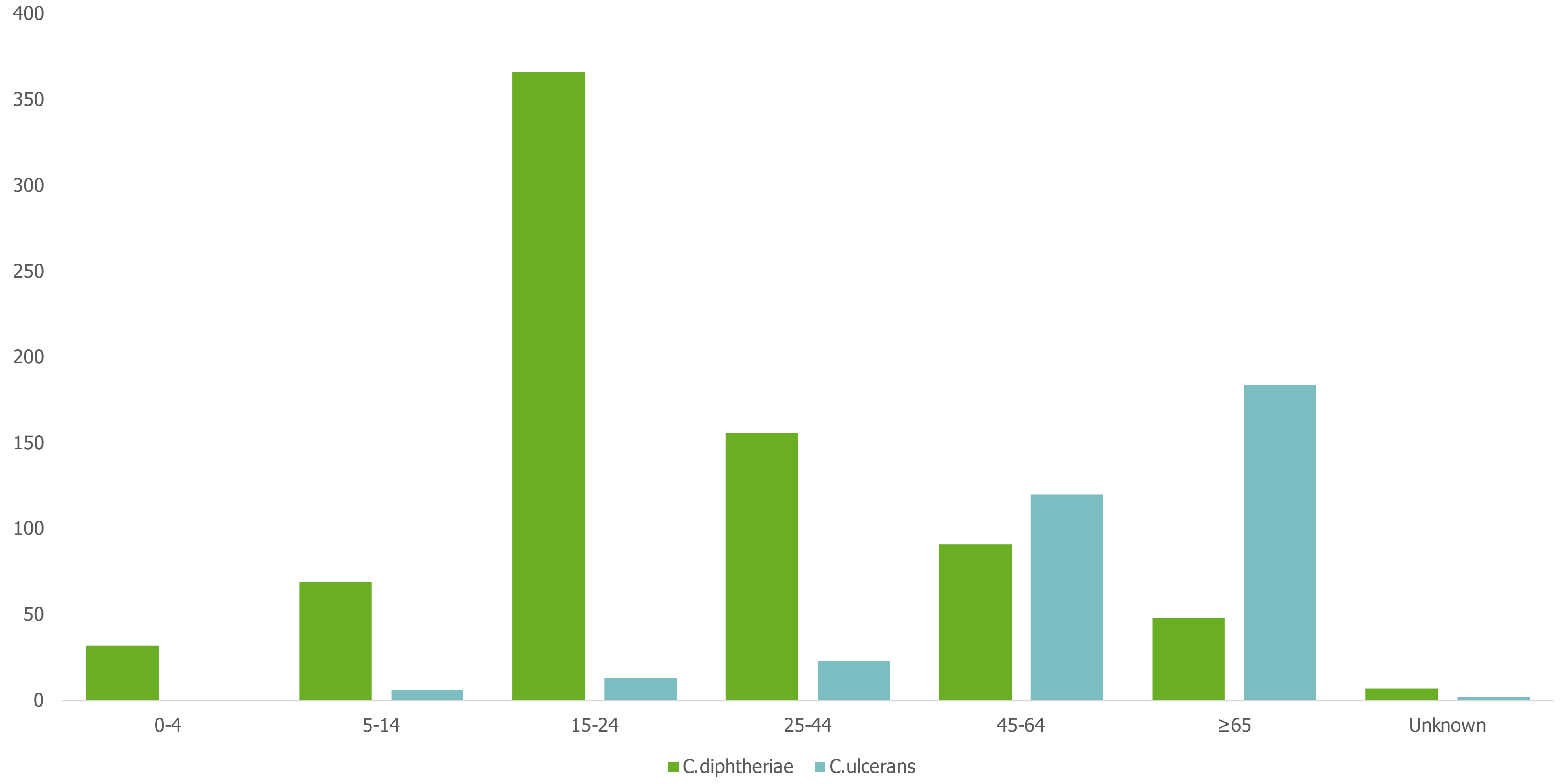


C. ulcerans



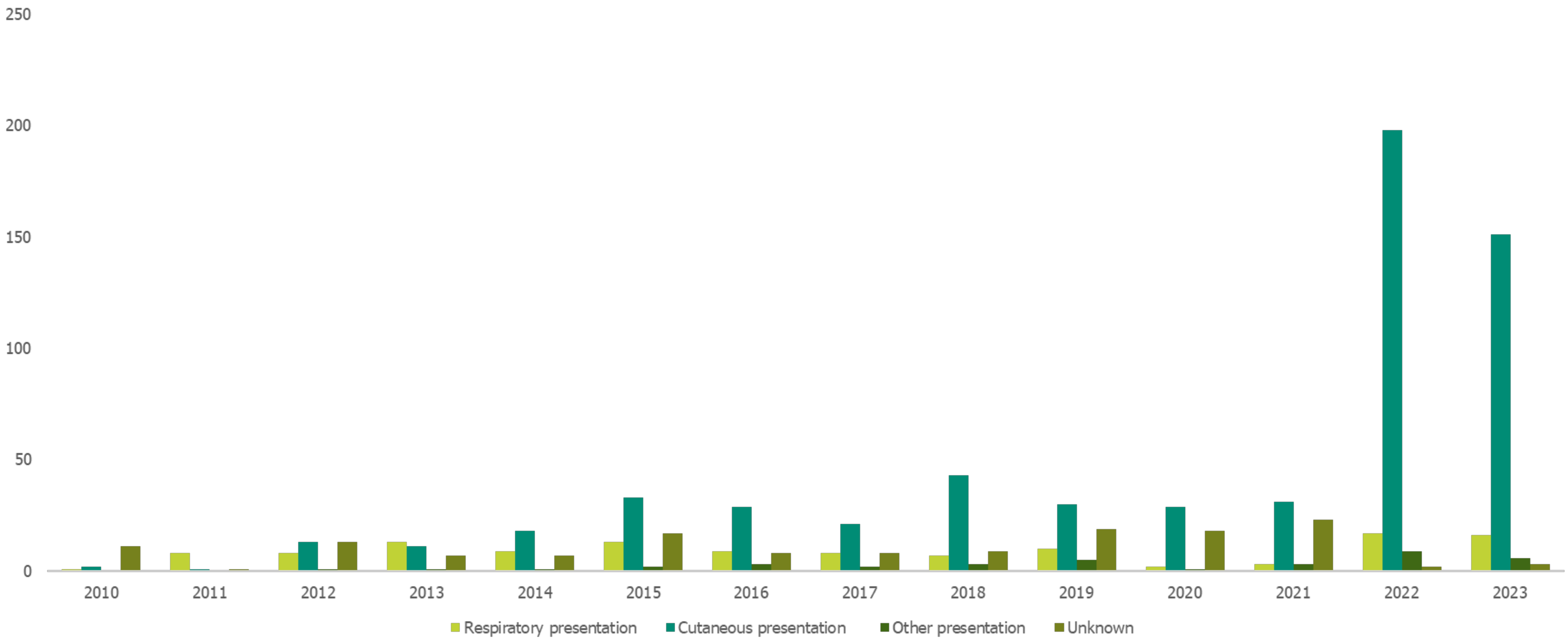
*DATA as of November 2024; Source: TESSy
Cases reported in the United Kingdom included only in the 2010-2019 period.

Age distribution of confirmed diphtheria cases in the EU/EEA for the 2010-2024* period



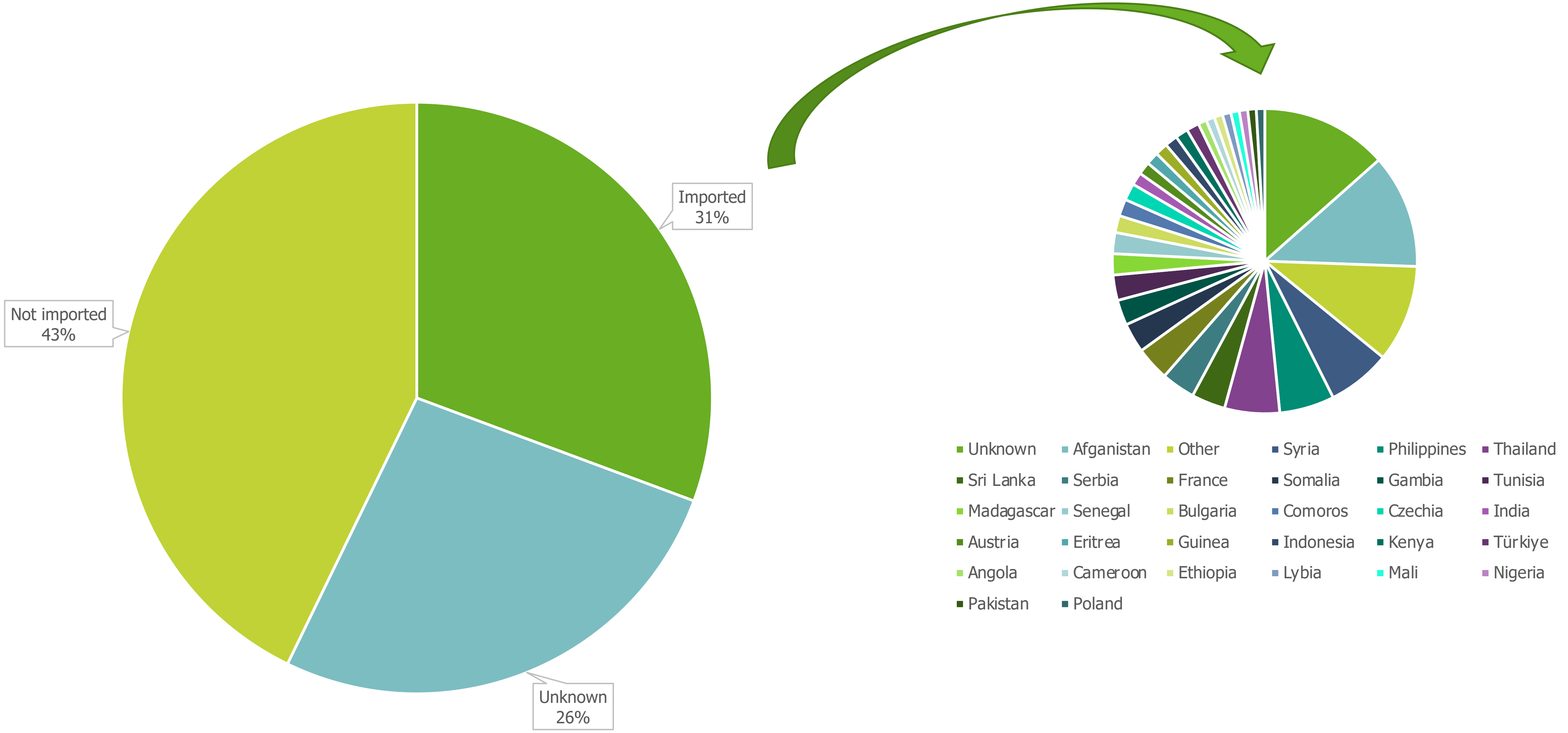
*DATA as of November 2024; Source: TESSy
Cases reported in the United Kingdom included only in the 2010-2019 period.

Clinical presentation of confirmed diphtheria cases in the EU/EEA for the 2010-2023 period



*DATA as of November 2024; Source: TESSy
Cases reported in the United Kingdom included only in the 2010-2019 period.

Importation status of confirmed diphtheria cases in the EU/EEA for the 2010-2024* period



*DATA as of November 2024; Source: TESSy
Cases reported in the United Kingdom included only in the 2010-2019 period.

Seroprevalence of diphtheria antibodies in the EU/EEA population

Study: Circulation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries.

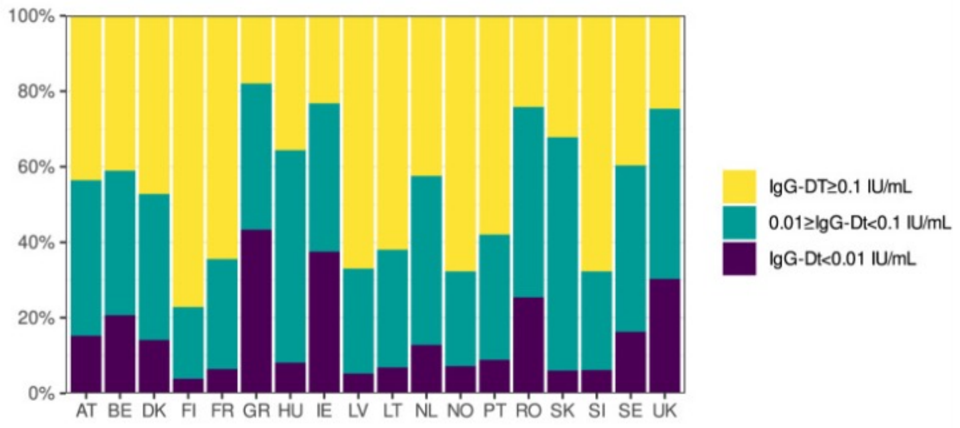
Publication: May 2021; NATURE COMMUNICATIONS

Aim: To determine the seroprevalence of DTP antibodies in two middle age groups in selected EU/EEA countries.

Methods:

- A cross-sectional seroprevalence study with a random sample of retrospective collections of leftover serum samples from diagnostics or samples from nationwide serosurveillance studies.
- Eighteen countries collected around 500 samples each (250 per age group) between 2015 and 2018 (N = 10 302 samples included in the analysis) which were analysed for IgG-DTP specific antibodies.
- Two age groups (40–49 and 50–59 years) were chosen for this study.
- An equal distribution of sera from male and female donors was preferred.

Conclusion: For diphtheria, the proportion of sera with non-protective and inadequate protective IgG levels ranged between 23 and 82% of the middle-aged population analysed in this study.



Source: Image taken from "Circulation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries" by Berbers G, et al published in Nat Commun. 2021 May 17.

IgG ≥ 0.1 IU/mL → protective level (yellow bar in the graph)

Source: Berbers G, van Gageldonk P, Kassteele JV, Wiedermann U, Desombere I, Dalby T, Toubiana J, Tsiodras S, Ferencz IP, Mullan K, Griskevicius A, Kolupajeva T, Vestrheim DF, Palminha P, Popovici O, Wehlin L, Kastrin T, Maďarová L, Campbell H, Ködmön C, Bacci S, Barkoff AM, He Q; Serosurveillance Study Team. Circulation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nat Commun. 2021 May 17;12(1):2871. doi: 10.1038/s41467-021-23114-y. PMID: 34001895; PMCID: PMC8128873.

Large outbreaks of diphtheria in the EU/EEA

A returning threat?

2022: large outbreaks of diphtheria reported across Europe

- First diphtheria cases among migrants reported in Austria on 1 June 2022 (through EWRS) and Switzerland (detected through EBS) over the summer.
- Item launched in EpiPulse by Austria on 22 August 2022.
- ECDC encouraged all EU/EEA countries to report recent detections of diphtheria cases through EpiPulse and through TESSy at a later stage.

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CORYNEBAKTERIUM DIPHTHERIAE

Zwei Diphtherie-Fälle in Österreich gemeldet, eine Person in Wien gestorben

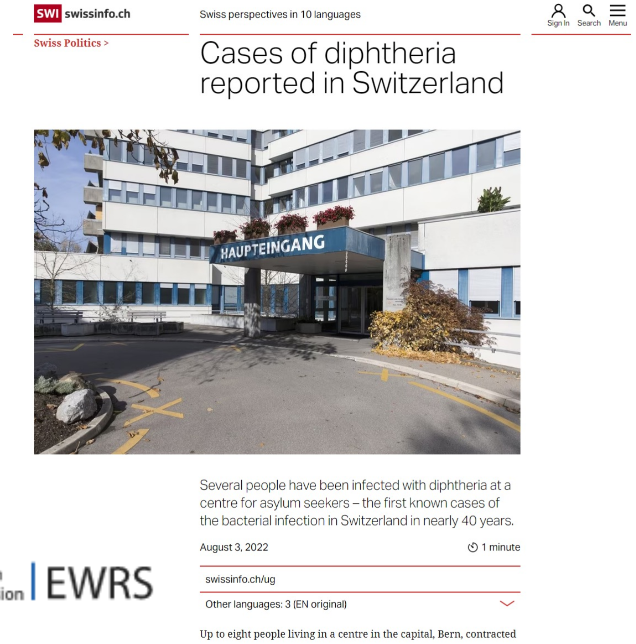
Laut Gesundheitsministerium sind seit 2014 einzelne Fälle aufgetreten. Eine Impfauffrischung alle zehn Jahre wird empfohlen

9. Juni 2022, 16:37, 184 Postings

Wien – In Österreich sind zwei Diphtherie-Fälle aufgetreten, eine Person ist in einem Wiener Krankenhaus daran gestorben. Der zweite Erkrankungsfall wird ebenfalls in einem Spital in Wien behandelt, teilte das Gesundheitsministerium am Donnerstag mit. Aufgrund einer Impfung samt Auffrischung tritt die meldepflichtige Krankheit hierzulande kaum auf, seit 2014 wurden aber einzelne Fälle gemeldet, heißt es auf der Website des Ministeriums.

Diphtherie wird durch Gifte von Bakterien – Corynebakterium diphtheriae – verursacht. Die Bakterien werden durch Tröpfchen und engen Kontakt übertragen. Die Inkubationszeit beträgt in der Regel zwei bis fünf Tage. Das Krankheitsbild kann von einer lokalen Infektion (Nase, Rachen, Kehlkopfdiphtherie) über eine Infektion der Atemwege bis zu einer schweren toxischen Form (Herzmuskel-, Nieren-, Leberschäden) variieren. Ausreichend geimpfte Personen können C. diphtheriae im Nase-Rachen-Raum tragen und dieses übertragen, ohne selbst zu erkranken. Behandelt wird die Erkrankung mit Antibiotika und Antitoxin.

Die zwei Fälle in Österreich wurden laut dem Gesundheitsministerium "in den vergangenen Tagen" gemeldet.
Foto: imago/Jochen Tack/stock&people



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Cases of diphtheria reported in Switzerland

Several people have been infected with diphtheria at a centre for asylum seekers – the first known cases of the bacterial infection in Switzerland in nearly 40 years.

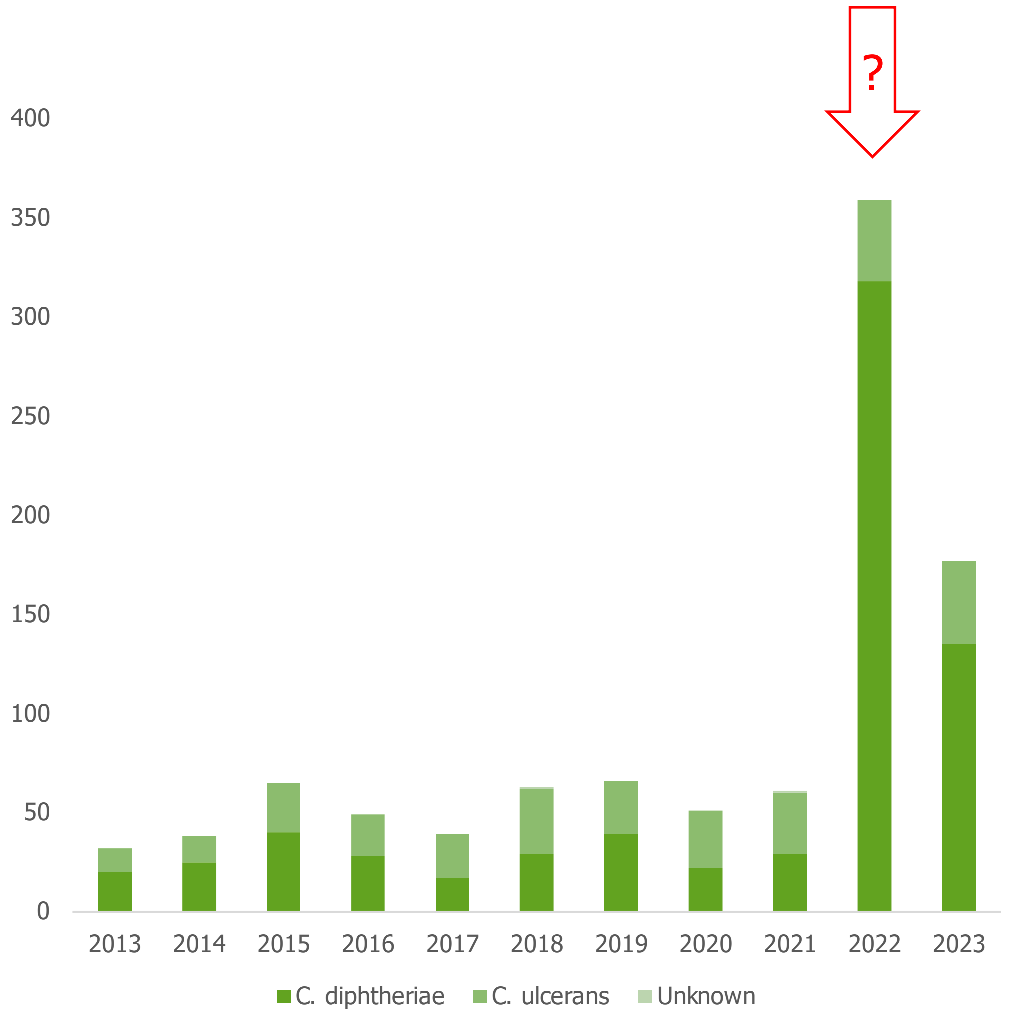
August 3, 2022 | 1 minute

swissinfo.ch/ug

Other languages: 3 (EN original)

Up to eight people living in a centre in the capital, Bern, contracted

European Commission | EWRS



Event summary

- ✓ ECDC conducted a RRA assessing the risks associated with a current increase of diphtheria cases observed among migrants in Europe in 2022, caused by toxigenic Corynebacterium diphtheriae. Published on 6 October 2022. On 5 December 2022, ECDC published an epidemiological update.

- ✓ Currently reporting through weekly restricted CDTR and daily CDTR on a monthly frequency basis (audience: NFPs for threat detection and key stakeholders: WHO, EC, EC agencies), public weekly CDTR and through EpiPulse.

RAPID RISK ASSESSMENT

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.

Suggested citation: European Centre for Disease Prevention and Control. Increase of reported diphtheria cases due to *Corynebacterium diphtheriae* among migrants in Europe – 6 October 2022. ECDC: Stockholm; 2022.

Other sites: ECDC European Antibiotic Awareness Day ESCAIDE - Scientific conference Eurosurveillance journal EVIP - Vaccination portal

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Media centre

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

Epidemiological update

5 Dec 2022

Diphtheria is an infectious bacterial disease, which can be prevented by vaccination. Transmission occurs via airborne respiratory droplets, direct contact with respiratory secretions, or direct contact with exudate from infected cutaneous lesions. Diphtheria can present with respiratory or cutaneous (skin) symptoms, and, in some cases can affect the heart, kidneys and the nervous system.

On 6 October 2022, ECDC published a Rapid Risk Assessment, 'Increase of reported diphtheria cases among migrants in Europe due to *Corynebacterium diphtheriae*, 2022'. The conclusions and options for response suggested in this publication remain valid for the present event. Currently, an increased number of diphtheria cases among migrants is still being observed in the EU/EEA, and an unusually broad predicted resistance of *Corynebacterium (C.) diphtheriae* isolates to common oral and parenteral antibiotics has been reported.

Since the beginning of 2022, and as of 2 December 2022, 154 cases of diphtheria have been reported by eight EU/EEA countries: Germany (64), Austria (42), Belgium (18), France (14), Norway (7), the Netherlands (5), Italy (3), and Spain (1). Diphtheria cases linked to migrants have also been reported in Switzerland (25) and the United Kingdom (53), bringing the overall number for Europe to 232 cases. The majority of cases have been diagnosed among migrants residing in or exposed to reception centres for migrants. This is an increase of 140 cases since the publication of the Rapid Risk Assessment on 6 October 2022, when 92 cases of diphtheria among migrants were reported by seven European countries and one fatal case was identified. *C. diphtheriae* has been detected in all cases, and the majority of them have presented with the cutaneous form of the disease.

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

Risk for the general population

- ✓ Increased number of diphtheria cases observed in most Member States is driven by multiple importations from diphtheria endemic countries.
- ✓ As of 15 September 2022, ECDC is not aware of any evidence indicating outbreaks in the general population linked to the importation of these diphtheria cases from endemic countries.
- ✓ High immunisation coverage in the community prevents outbreaks in the general population.
- ✓ Nevertheless, presentation with severe clinical diphtheria is possible in unvaccinated, immunosuppressed or under immunised individuals

→ The risk assessed for the general population in the EU/EEA is considered to be **VERY LOW**

Risk for specific populations in migrant centres

- ✓ Most of these cases are being reported among migrants residing in settings susceptible to crowd and where some individuals may be lacking a complete diphtheria vaccine scheme.
- ✓ It is expected that individuals residing, working or volunteering in these centres may be exposed to the pathogen
- ✓ In unvaccinated or immunosuppressed individuals exposed to these settings, a severe outcome following a diphtheria infection is possible.

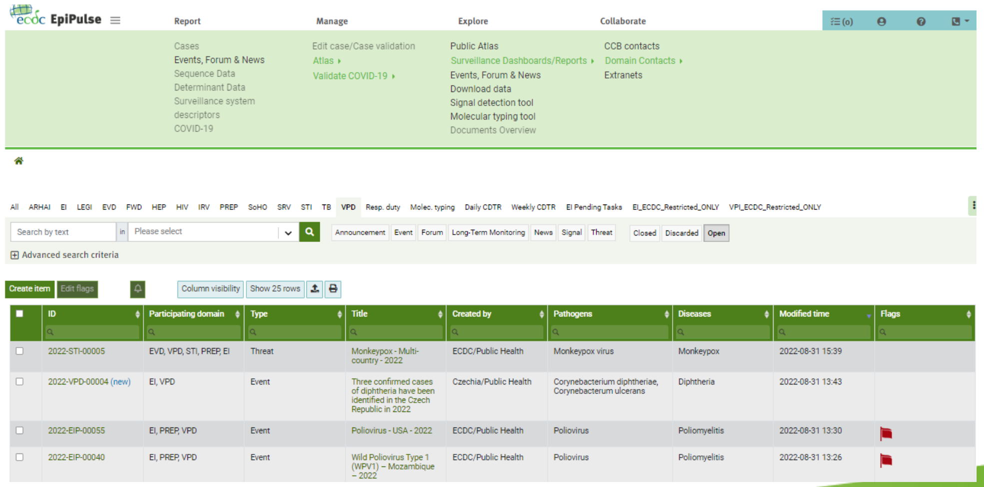
→ The risk assessed for the specific population in asylum centres in the EU/EEA is considered to be **MODERATE**

Main options for response for these events

- **Check vaccination status of newly arrived migrants** and consider all migrants who lack evidence of vaccination against diphtheria as unprotected; **provide vaccinations** with diphtheria-toxoid-containing vaccines in accordance with national guidelines.
- Ensure **all personnel working in reception centres** for migrants **have their vaccination status up to date** according to their national vaccination calendars.
- **Alert clinicians** to the possibility of cutaneous and/or respiratory diphtheria among migrants and travellers returning from endemic areas, provide them with all support needed.
- **Include diphtheria into the differential diagnosis in skin ulcers of individuals and returning travellers from endemic countries. Timely laboratory confirmation** of cases is vital for implementing control measures.
- **Identify close contacts**. Monitor the clinical conditions of contacts and swab, regardless of immunisation status.
- Provide **antibiotic treatment to close contacts**.
- Ensure **timely reporting to competent authorities** adhering to the EU case definition for diphtheria.
- Perform **enhanced surveillance, molecular typing and whole genome sequencing of patient isolates**.

ECDC tools available online to support Member States in outbreak investigation in refugee settings

- Handbook on implementing syndromic surveillance in migrant reception/detention centres and other refugee settings
- Handbook on using the ECDC preparedness checklist tool to strengthen preparedness against communicable disease outbreaks at migrant reception/detention centres
- Expert Opinion on the public health needs of irregular migrants, refugees or asylum seekers across the EU's southern and south-eastern borders
- EpiPulse, the European surveillance portal for infectious diseases



Conclusions

Take home message:

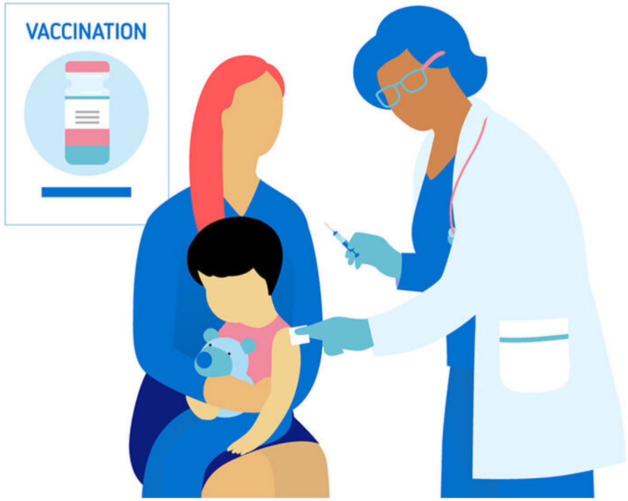
- **Diphtheria is a rare disease in the EU/EEA** countries, **still** its **occurrence** across EU/EEA countries **persists and large outbreaks in Europe have been recently reported.**

- **It can be a life-threatening disease**, especially in non-vaccinated individuals and if proper treatment is delayed. Under-immunised and immunosuppressed individuals remain at risk too.

- **Vaccination is the only effective method of preventing the toxin-mediated disease**.

- **Europe** adheres to the WHO European Vaccine action plan 2015/2020 setting a **target of ≥95% vaccine coverage for DTP3** in the WHO European region Member States.

- Is in all our hands to contribute achieving this goal, by keeping in mind diphtheria and **ensure at the possible extend vaccination to all the individuals not vaccinated or under-vaccinated** (extensive to all vaccine preventable diseases).



Thank you very much

Q&A