# Chapter 1: Diphtheria

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## I. Disease Description

Diphtheria is a rare disease in the United States. Infection with toxin-producing strains of a Gram-positive bacterium, *Corynebacterium diphtheriae*, causes the disease. Sites of infection are primarily the respiratory mucosa (respiratory diphtheria) and the skin (cutaneous diphtheria). Rarely, extra-respiratory mucosal sites (e.g., eye, ear, genitals) may be affected. Humans are the only known reservoir of *C. diphtheriae*. The disease is transmitted from person to person by respiratory droplets or direct contact with respiratory secretions, discharges from skin lesions or, rarely, fomites.

The onset of respiratory diphtheria is insidious and begins after an incubation period of 2–5 days (range 1–10 days). Initial symptoms of illness include a sore throat, difficulty in swallowing, malaise, and low-grade fever. The hallmark of respiratory diphtheria is the presence of a tough, grayish-white pseudomembrane over the tonsils, nasopharynx, or larynx. The pseudomembrane is strongly adherent to the underlying tissue, and attempts to dislodge it usually result in bleeding. Inflammation of the cervical lymph nodes and swelling of the surrounding soft tissue of the neck can give rise to a "bull-neck" appearance, which is a sign of severe disease. The pseudomembrane may progressively extend into the larynx and trachea and cause airway obstruction, which can be fatal if left untreated. Diphtheria toxin may be absorbed from the site of infection and result in systemic complications, including damage to the myocardium, nervous system, and kidneys. Untreated respiratory diphtheria usually lasts for 1 to 2 weeks, but complications can persist for months. Before treatment was available, the case-fatality rate was approximately 50%; with treatment and vaccination more widely available, the case-fatality rate has declined significantly and remains approximately 10%.

Non–toxin-producing strains of *C. diphtheriae* can also cause disease. It is generally less severe, potentially causing a mild sore throat and, rarely, a membranous pharyngitis, although invasive disease, including bacteremia and endocarditis, has been reported.[1] Isolation of non–toxin-producing strains of *C. diphtheriae* from the throat does not necessarily indicate a pathogenic role in the illness. Vaccination is highly protective against disease caused by toxin-producing strains but does not prevent carriage of *C. diphtheriae*, regardless of toxin production status. A small percentage of the population may be carriers of non–toxin-producing or toxin-producing strains of *C. diphtheriae*, but population carriage rates in the current era of high vaccine coverage are unknown.

Cutaneous diphtheria, caused by toxin-producing or non–toxin-producing strains of *C. diphtheriae*, is usually mild, typically consisting of indistinct sores or shallow ulcers. While rarely developing into invasive or systemic disease, cutaneous diphtheria may act as a reservoir for transmission and result in respiratory or cutaneous infections in other susceptible hosts.[2]

Rarely, two other *Corynebacterium* species (*C. ulcerans* and *C. pseudotuberculosis*) may produce diphtheria toxin. Both species are zoonotic; such infections have been documented in pigs, cattle, dogs, and cats. Toxin-producing *C. ulcerans* may cause classic respiratory diphtheria-like illness in humans[3,4] but person-to-person spread has not been documented. *C. pseudotuberculosis* can cause lymphadenitis in humans.

## II. Background

Diphtheria is now rarely reported in the United States; however, in the pre-vaccine era, the disease was one of the most common and feared causes of illness and death among children. The United States introduced vaccines containing diphtheria toxoid (formalin-inactivated diphtheria toxin) in the 1920s, and the implementation of universal childhood immunization occurred in the late 1940s. Widespread use of diphtheria toxoid-containing vaccines has contributed to control of diphtheria in the United States, with the last major outbreak occurring in the 1970s in Seattle, Washington.[5] From 1996 through 2017, 13 cases of respiratory diphtheria were reported to CDC's National Notifiable Diseases Surveillance System (NNDSS); five cases were confirmed as *C. diphtheriae* (only one was known to be toxin-producing), and eight were probable as culture was not done or available.[6,7, unpublished CDC data] Among these 13 persons with reported diphtheria, the median age was 28 years (range: 8 months–86 years) and the majority of cases (92%) were among persons 15 years of age or older. Five cases were adequately vaccinated, one was inadequately vaccinated, one was unvaccinated, and vaccination status was unknown for six cases. One fatal case occurred in a 63-year-old male returning to the United States from a country with endemic disease.[8]

Diphtheria remains endemic in some low and middle-income countries having suboptimal vaccination coverage of the diphtheria- and tetanus-toxoid and whole-cell pertussis (DTP) primary series.[9] In the 1990s, a large epidemic of diphtheria occurred in the former Soviet Union where diphtheria had previously been well controlled; multiple factors, including insufficient population immunity, weakened socioeconomic infrastructure, and delayed public health response, contributed to this epidemic.[10,11] Displacement of large populations due to political or economic instability and civil conflicts has also resulted in diphtheria outbreaks, largely due to non-hygienic, crowded living conditions coupled with limited access to healthcare and vaccinations. Recent outbreaks in the past five years have occurred in the Americas (Haiti, Brazil, Venezuela, Colombia), Asia (Indonesia, Bangladesh [among Rohingya refugees from Myanmar], India, Nepal, Pakistan, Laos), Africa (South Africa, Nigeria), and Europe (Yemen, Ukraine).[12]

Like the United States, many low and middle-income countries have achieved high childhood vaccination coverage with diphtheria- and tetanus toxoids- and pertussis-containing vaccines (DTP/DTaP), resulting in significant reduction in diphtheria incidence. However, sporadic cases and outbreaks still occur among population subgroups.[10,11,13,14] A feature of these outbreaks is that the majority of cases occur among adolescents and adults, many of whom are unvaccinated or incompletely vaccinated against diphtheria. Rarely, outbreaks occur in well-vaccinated populations with intense exposure to toxin-producing *C. diphtheriae*, but disease among vaccinated individuals is usually mild, with fewer complications, and no fatalities.[14]

## III. Importance of Rapid Identification

Prompt recognition and reporting of the disease is important to ensure early, appropriate treatment with diphtheria antitoxin (DAT) and antibiotics when indicated. Early recognition is also important to obtain necessary laboratory specimens before treatment. Timely identification of close contacts is critical to monitor for development of respiratory or cutaneous illness; assess bacterial carriage through nasal and throat swabs; assess vaccination status and offer age-appropriate diphtheria toxoid-containing vaccines; and provide post-exposure antimicrobial prophylaxis.

## IV. Importance of Surveillance

Data from the National Health and Nutrition Examination Survey (NHANES) III serosurvey (1988–1994) indicated that 60.5% of the U.S. population had protective immunity against diphtheria, but the level of protection declined from about 80% among persons 12–19 years of age to about 30% among persons 60–69 years of age.[15] This may be because immunity to diphtheria wanes with time after vaccination, and many older adults may not have received either a primary vaccination series or the recommended decennial tetanus-diphtheria toxoid (Td) booster.

Potential sources of diphtheria infection include persons traveling to the United States from countries where diphtheria is endemic and from asymptomatic carriers (persons with *C. diphtheriae* bacteria present in the nose and/or throat who do not have disease symptoms). Persons with cutaneous diphtheria infection may also transmit the bacteria to others, resulting in skin or respiratory infection. To ensure timely

detection and appropriate management of these cases, clinicians need continued awareness of diphtheria. Surveillance, prompt treatment of diphtheria patients and investigation of close contacts help to halt the spread of disease. Public health officials use information obtained through surveillance to characterize infected persons so that additional intervention efforts can be focused to reduce disease incidence.

## V. Disease Reduction Goals

Since 1997, no case of culture-confirmed respiratory diphtheria caused by toxin-producing *C. diphtheriae* has been reported in the United States. *Healthy People 2020* does not include specific objectives for diphtheria elimination.[16]

## VI. Case Definition

The Council of State and Territorial Epidemiologists (CSTE) approved the following surveillance case definition for diphtheria at their annual meeting during June 2018, to go into effect January 1, 2019.[17]

**Suspect:** In the absence of a more likely diagnosis, an upper respiratory tract illness with each of the following: an adherent membrane of the nose, pharynx, tonsils, or larynx, and absence of laboratory confirmation, and lack of epidemiologic linkage to a laboratory-confirmed case of diphtheria; or histopathologic diagnosis.

**Confirmed:** An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx, and any of the following: isolation of toxin-producing *C. diphtheriae* from the nose or throat; or epidemiologic linkage to a laboratory-confirmed case of diphtheria; or an infection at a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa) with isolation of toxin-producing *C. diphtheriae* from that site.

An epidemiologically linked case is one in which the patient has had contact with one or more persons who have or had the disease, and transmission of the agent by the usual modes of transmission is plausible. A case may be considered epidemiologically linked to a laboratory-confirmed case if at least one case in the chain of transmission is laboratory confirmed.

## VII. Laboratory Testing

Early laboratory testing is critical for confirmation of diagnosis and prompt implementation of appropriate prevention and control measures.

Refer to the CDC web page Laboratory Information https://www.cdc.gov/diphtheria/laboratory.html and Chapter 22, "Laboratory Support for the Surveillance of Vaccine-Preventable Diseases https://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.html for detailed information on laboratory testing for diphtheria, and for specific information on specimen collection and shipment.

### *Specimen collection and shipment*

Specimen collection and shipping are important steps in obtaining laboratory diagnosis or confirmation for vaccine preventable diseases. Guidelines have been published for specimen collection and handling for microbiologic agents.[18] Information is also available on using CDC laboratories as support for reference and disease surveillance;[19] this includes

- a central website (https://www.cdc.gov/laboratory/specimen-submission/index.html) for requesting lab testing;
- the CDC Infectious Diseases Laboratories Test Directory; (https://www.cdc.gov/laboratory/specimen-submission/form.html)
- the form[2 pages, 2.80 MB] (https://www.cdc.gov/laboratory/specimen-submission/pdf/form-50-34.pdf) required for submitting specimens to CDC (See Appendix 23, Form # CDC 50.34 https://www.cdc.gov/laboratory/specimen-submission/form.html); and
- information on general requirements for shipment of etiologic agents [4 pages] https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix24-etiologic-agent.pdf.

The state public health laboratories and CDC provide an online test directory that contains not only a list of orderable tests (https://www.cdc.gov/laboratory/specimen-submission/list.html) for that institution, but also detailed information such as appropriate specimen types, collection methods, specimen volume, and points of contact.

## VIII. Reporting and Case Notification

### *Case reporting within a jurisdiction*

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[21] These regulations and laws list the diseases that are to be reported, and describe those persons or groups who are responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Persons reporting these conditions should contact their state health department for state-specific reporting requirements. Detailed information on reportable conditions in each state is available through CSTE.

The healthcare provider or clinical laboratory that detects *C. diphtheriae* should first promptly notify the state health department. The CDC *Diphtheria Worksheet* is used to collect information about a diphtheria case and is included as Appendix 3 [2 pages], https://www.cdc.gov/diphtheria/downloads/dip-wksht.pdf to serve as a guide for data collection during investigation of reported cases.

### *Case notification to CDC*

The state in which the patient resides at the time of diagnosis should submit the case notification to CDC. State health departments should send notifications for suspect and confirmed cases of diphtheria to CDC using the event code 10040 in NNDSS[22] via the National Electronic Telecommunications System for Surveillance (NETSS) or National Electronic Disease Surveillance System (NEDSS).

Cases of laboratory-confirmed, non–toxin-producing *C. diphtheriae* (respiratory or non-respiratory) do not meet the surveillance case definition requirements and should not be reported to CDC as part of NNDSS. Rarely, respiratory diphtheria-like illness may result from infection with other *Corynebacterium* species (e.g., *C. ulcerans*, *C. pseudotuberculosis*). While not reportable, if a non-diphtheria *Corynebacterium* species is identified, jurisdictions are asked to submit available specimens or isolates to the CDC Pertussis and Diphtheria Laboratory for further characterization.

### *Information to collect*

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may also be collected at the direction of the state health department.

- Patient demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
- Reporting Source
  - County
  - Earliest date reported
- Clinical
  - Hospitalizations: dates and duration of stay
  - Date of illness onset
  - Site of infection (e.g., nose, throat, larynx, skin, other anatomic site)
  - Symptoms (e.g., fever, sore throat)

- Signs (e.g., pseudomembrane, neck edema, stridor, tachycardia)
- Complications (e.g., myocarditis, polyneuropathy)
- Outcome (patient survived or died)
- Date of death
- Postmortem examination results
- Death certificate diagnoses

- Treatment
  - Date of administration of antitoxin
  - Number of units of antitoxin given
  - Antibiotics given
  - Antibiotic dosage given
  - Duration of antibiotic therapy
- Laboratory
  - Culture
  - Biotype test
  - PCR for diphtheria *tox* gene
  - Elek test for diphtheria toxin production
- Vaccine information
  - Dates and types of diphtheria vaccination
  - Number of doses of diphtheria toxoid received
  - Manufacturer name
  - Vaccine lot number
  - If not vaccinated, reason
- Epidemiologic
  - Contact with a suspect or confirmed case
  - Contact with a person who was recently (past 6 weeks) in an endemic-disease area
  - Number of contacts cultured
  - Results of contact cultures
  - Local or international travel history: 6-week period before illness onset or date of presentation
  - Contact with domestic pets, horses, or dairy farm animals

## IX. Vaccination

For specific information about diphtheria vaccination, refer to the Pink Book [https://www.cdc.gov/vaccines/pubs/pinkbook/index.html], which provides general recommendations, including vaccine scheduling and use, immunization strategies for providers, vaccine contents, adverse events and reactions, vaccine storage and handling, and contraindications and precautions.

## X. Enhancing Surveillance

Because diphtheria has occurred only rarely in the United States in recent years, many clinicians may not include diphtheria in their differential diagnoses. Clinicians are reminded to consider the diagnosis of respiratory diphtheria in patients with membranous pharyngitis and who are not up-to-date with vaccination against diphtheria. Clinicians should also be aware that diphtheria could present as a cutaneous infection, particularly in persons with recent travel to diphtheria-endemic countries. If diphtheria is suspected, clinicians should obtain a pre-antibiotic treatment specimen in order to increase the probability of isolating the organism. Although appropriate laboratory confirmation may not be feasible locally, state public health laboratories may act as a local reference, and should maintain capacity for isolation of *C. diphtheriae*, if possible. Reference testing capacity for culture, biotyping and toxin production testing will remain available at CDC.

## XI. Streamlining reporting using electronic methods

Although many surveillance systems still rely on paper and pencil for data collection, use of data from sources such as electronic medical records, electronic case reporting, and clinical laboratory information systems (LIMS) can significantly improve reporting speed, enhance data quality, and reduce workload.[23–29]

## XII. Case and Close Contacts Investigation

Health department officials should initiate a case investigation for all suspected respiratory diphtheria cases (Figure 1); in particular, investigations of patients in which there is a high clinical suspicion of diphtheria and their close contacts should not be delayed pending laboratory confirmation or toxin production results.

Non-respiratory diphtheria may not be clinically suspected and may only be detected through incidental laboratory testing; thus, a non-respiratory case investigation can be initiated upon notification from a clinical laboratory of detection of *C. diphtheriae*. If, during a case investigation, a patient with non-respiratory diphtheria reports recent travel history to a country with endemic diphtheria, then an investigation of close contacts should be initiated while awaiting toxin production results. If the organism is non–toxin-producing, the health department can discontinue the contact investigation. CDC recommends consultation with its subject matter experts for all case investigations and investigations of close contacts.

A case investigation for any suspected respiratory and non-respiratory diphtheria cases should include obtaining nasal and throat cultures, collecting preliminary epidemiologic and clinical information, and identifying close contacts. Close contacts include all household members, persons with a history of habitual, close contact with the patient, or persons directly exposed to secretions from the suspected infection site of the patient. Management of close contacts of persons with suspect or confirmed cases should include monitoring for possible respiratory or cutaneous diphtheria for 7–10 days from the time of the last exposure to the index patient, obtaining nasal and throat cultures for *C. diphtheriae*, administering prophylactic antibiotics (a 7- or 10-day course of penicillin or erythromycin, respectively), assessing diphtheria vaccination status, and administering any necessary vaccinations. All diphtheria patients and close contacts should receive a dose of diphtheria toxoid-containing vaccine, if not up to date. Health department officials may use the CDC diphtheria worksheet as a guide for data collection in conducting a case investigation used for both respiratory and non-respiratory diphtheria (see Appendix 3 [2 pages] https://www.cdc.gov/diphtheria/downloads/dip-wksht.pdf).

### *Diphtheria antitoxin (DAT)*

The mainstay of treatment of a case of suspected respiratory diphtheria is prompt administration of DAT. DAT is generally not administered in cases of non-respiratory diphtheria. Clinicians should give DAT early in the course of illness and without waiting for laboratory confirmation of a diagnosis. The recommended dosage and route of administration depend on the extent and duration of disease. While a U.S. Food and Drug Administration-licensed DAT product is no longer available commercially in the United States, it is available from CDC under an Investigational New Drug (IND) protocol.[30] Healthcare providers should first discuss the suspected diphtheria case with their respective state health department before requesting diphtheria antitoxin from CDC.

### *Contacting CDC for diphtheria antitoxin*

After consultation with their respective state health departments, healthcare providers should contact the CDC Emergency Operations Center (770-488-7100) to request DAT and assistance for its transport. If unable to make contact with the state health department, healthcare providers may contact the CDC Emergency Operations Center first. Once DAT is requested, additional epidemiologic and clinical data are needed as requirements under the IND. Additional details and documentation related to DAT release can be found on CDC's diphtheria website (https://www.cdc.gov/diphtheria/dat.html).

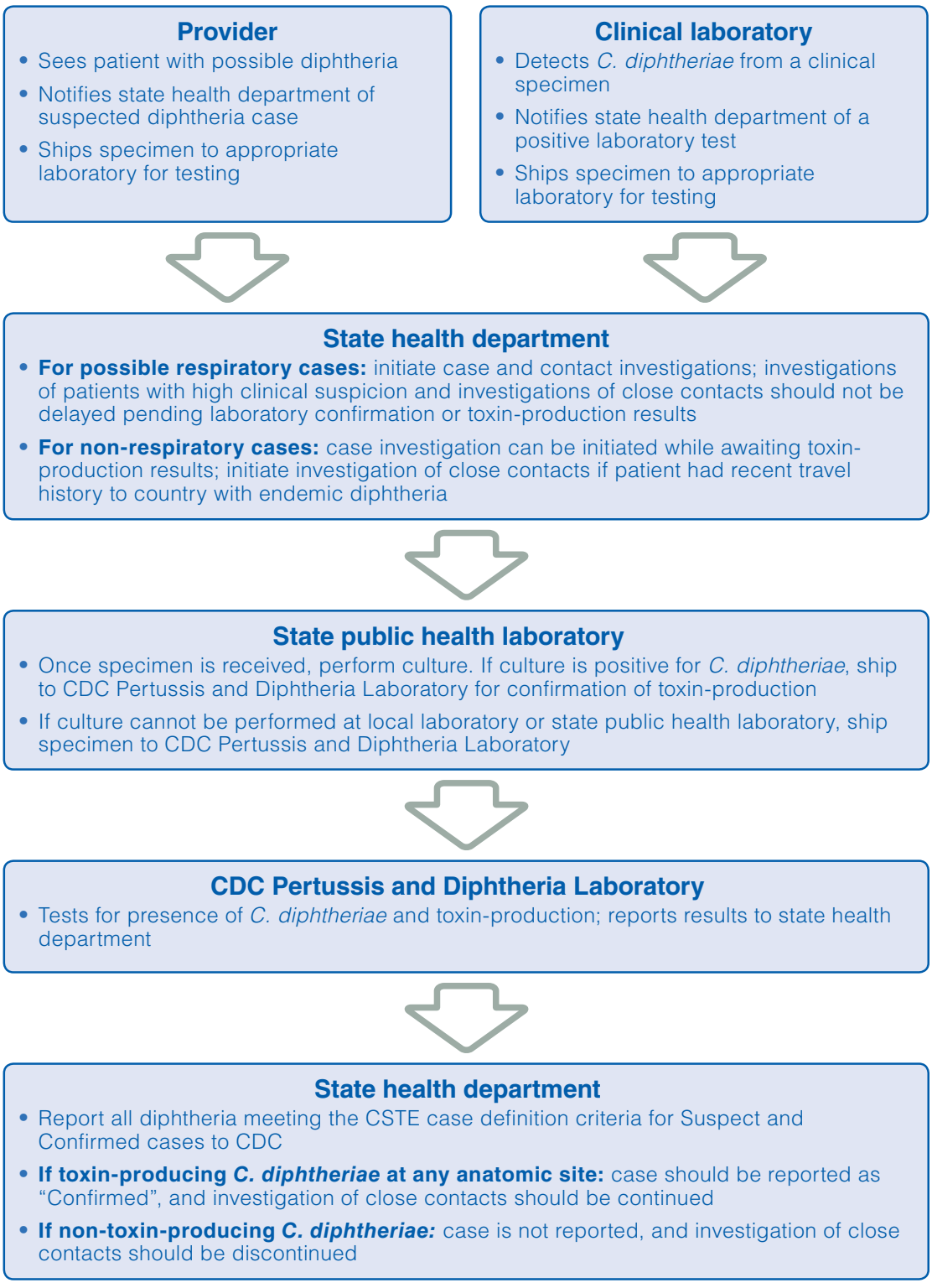
### *Antibiotics*

Diphtheria patients should also receive antibiotics to eradicate carriage of *C. diphtheriae*, limit transmission, and halt further production of diphtheria toxin.[31] Treatment with erythromycin or penicillin is administered as a 14-day course.[32]

### *Vaccination*

Because diphtheria disease does not always confer immunity, an age-appropriate vaccine containing diphtheria toxoid should be administered during convalescence.

**Figure 1: Schematic of diphtheria case detection, reporting to state health department, testing, and notification of case to CDC**



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