Chapter 1: Diphtheria

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I. Disease Description

Diphtheria, which is rare disease in the United States, is caused by infection with toxigenic strains of Gram-positive Corynebacterium diphtheriae. Important sites of infection are the respiratory mucosa (respiratory diphtheria) and the skin (cutaneous diphtheria). Rarely, extra-respiratory mucosal sites—e.g., the eye, ear, or 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, the pharynx, or larynx. The pseudomembrane is strongly adherent to the underlying tissue, and attempts to dislodge it usually result in bleeding. Accompanying inflammation of the cervical lymph nodes and surrounding soft-tissue swelling of the neck give rise to a “bull-neck” appearance and are signs of moderate to severe disease. The pseudomembrane may progressively extend into the larynx and trachea and cause airway obstruction, which, if left untreated, can be fatal. Absorption of diphtheria toxin from the site of infection can cause 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 remained approximately 10%. Nontoxigenic strains of C. diphtheriae may cause a mild sore throat and, rarely, a membranous pharyngitis, but these strains can be invasive and cause bacteremia and endocarditis. Isolation of nontoxigenic strains of C. diphtheriae from the throat does not necessarily indicate a pathogenic role in the illness. A small percentage of the population may be carriers of nontoxigenic or toxigenic strains of C. diphtheriae during outbreaks but population carriage rates in the current high vaccine coverage era are unknown.

Cutaneous diphtheria, caused by either toxigenic or nontoxigenic strains of C. diphtheriae, is usually mild, typically consisting of nondistinctive sores or shallow ulcers. While rarely developing into invasive or systemic disease, cutaneous diphtheria may act as a reservoir and result in respiratory or cutaneous infections in other susceptible hosts.

Rarely, other Corynebacterium species (C. ulcerans or C. pseudotuberculosis) may produce diphtheria toxin. Both species may cause disease in animals. Toxigenic C. ulcerans is zoonotic and may cause classic respiratory diphtheria-like illness in humans. Person-to-person spread has not been documented. C. pseudotuberculosis can cause lymphadenitis in humans.

II. Background

Although diphtheria is now rarely reported in the United States, in the pre-vaccine era, the disease was one of the most common and feared causes of illness and death among children. Widespread use of vaccines containing diphtheria toxoid (formalin-inactivated diphtheria toxin) beginning in the 1920s and the introduction of universal childhood immunization in the late 1940s have contributed to diphtheria being well controlled in the United States. In the 1970s, diphtheria was endemic in the Southwest, the Northern Plains, and the Pacific Northwest. The last major outbreak was in Seattle, Washington, in the 1970s. From 1995 through 2015, 14 cases of diphtheria were reported to CDC’s National Notifiable Diseases Surveillance System (NNDSS), unpublished CDC data. Among 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. 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 many parts of the developing world.9 In the 1990s, a large epidemic of diphtheria occurred in the former Soviet Union where diphtheria had previously been well controlled; the cause for the epidemic was multifactorial, and included insufficient population immunity.10, 11 Recently, cases have been reported in the Western hemisphere (Haiti, the Dominican Republic, and Venezuela), and in a number of countries in Asia and Africa.12 Displacement of large populations due to political or economic instability have also resulted in diphtheria outbreaks, largely due to non-hygienic, crowded living conditions coupled with limited access to healthcare and vaccinations.

Like the United States, many developing countries have achieved high childhood immunization coverage with diphtheria and tetanus toxoids and pertussis vaccine (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 have occurred among adolescents and adults instead of children. Many of these adolescents and adults had not received routine childhood vaccination or booster doses of diphtheria toxoid. Rarely, outbreaks occur in well-vaccinated populations with intense exposure to toxigenic C. diphtheriae, but disease 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; to obtain necessary laboratory specimens before antibiotic or antitoxin treatment; to identify and evaluate contacts; and to provide necessary antimicrobial prophylaxis to prevent further spread. The outcome of diphtheria infection improves with early, appropriate treatment.

**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 through 19 years old to about 30% among persons 60 through 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 a recommended tetanus-diphtheria toxoid (Td) booster every 10 years.

Potential sources of diphtheria infection may include persons traveling to the United States from countries where diphtheria is endemic or from asymptomatic carriers (persons infected with C. diphtheriae bacteria in the nose and/or throat but who do not have disease symptoms). Persons with cutaneous diphtheria infections may also transmit the bacteria to others, resulting in skin or respiratory infection. For these reasons, continued awareness of diphtheria is needed. Surveillance, prompt investigation, and treatment of case-patients and close contacts help to halt the spread of disease. Information obtained through surveillance is used to characterize infected persons or areas so that additional intervention efforts can be focused to reduce disease incidence.

**V. Disease Reduction Goals**

Since 1997, no culture-confirmed respiratory diphtheria caused by toxigenic C. diphtheriae has been reported in the United States, achieving the Healthy People 2010 goal to eliminate indigenous diphtheria among persons younger than 35 years of age in the United States.16 Healthy People 2020 does not include specific objectives for diphtheria elimination.17

This document can be found at: www.cdc.gov/vaccines/pubs/surv-manual/chpt01-dip.html
VI. Case Definition
The following case definition for diphtheria was revised by the Council of State and Territorial Epidemiologists (CSTE) and published in 2010.18

**Probable:** In the absence of a more likely diagnosis, an upper respiratory tract illness with 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.

**Confirmed:** An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx; and any of the following: isolation of *Corynebacterium diphtheriae* from the nose or throat; or histopathologic diagnosis of diphtheria; or epidemiologic linkage to a laboratory-confirmed case of diphtheria.

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
Diagnostic tests used to confirm infection include isolation of *C. diphtheriae* by culture and Elek testing of isolates for diphtheria toxin production. Although no other tests for confirming diphtheria are commercially available, CDC can perform a PCR test on clinical specimens to confirm an infection with a potentially toxigenic strain. While this PCR assay allows for detection of the diphtheria toxin gene (tox), it does not confirm whether the organism is producing the toxin.19 PCR is particularly useful if nonviable *C. diphtheriae* organisms are present in clinical specimens that are obtained from a patient after antibiotic therapy has been initiated. The state health department should be contacted to report a suspected case and to arrange for laboratory testing.

Although, PCR (as performed by the CDC Pertussis and Diphtheria Laboratory) provides supportive evidence for the diagnosis, data are not yet sufficient for PCR to be accepted as a criterion for laboratory confirmation. A case that is PCR positive without isolation of the organism or histopathologic diagnosis and without epidemiologic linkage to a laboratory-confirmed case should be classified as a probable case.

For additional information on laboratory testing for confirmation of diphtheria, see Chapter 22, “Laboratory Support for the Surveillance of Vaccine-Preventable Diseases.”

*Note:* Other pathogens can cause a membrane in the throat and over the tonsils, including Streptococcus spp., Epstein-Barr virus and cytomegalovirus (both of which cause infectious mononucleosis syndrome), *Arcanobacter hemolyticum*, *Candida albicans*, fusiform bacteria (which can cause Vincent’s angina), and some viruses. The patient’s healthcare provider should be encouraged to perform appropriate laboratory tests to rule out these conditions and organisms.

**Specimen collection**
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.19 Information is also available on using CDC laboratories as support for reference and disease surveillance;20,21 this includes:

- a central website ([https://www.cdc.gov/laboratory/specimen-submission/index.html](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](https://www.cdc.gov/laboratory/specimen-submission/form.html));
- the form required for submitting specimens ([https://www.cdc.gov/laboratory/specimen-submission/form.html](https://www.cdc.gov/laboratory/specimen-submission/form.html)) to CDC (See Appendix 23, Form # CDC 50.34}; and

This document can be found at: www.cdc.gov/vaccines/pubs/surv-manual/chpt01-dip.html
The state laboratories and CDC provide an online test directory that contains not only a list (https://www.cdc.gov/laboratory/specimen-submission/list.html) of orderable tests for that institution, but also detailed information such as appropriate specimen types, collection methods, specimen volume, and points of contact. Although written to guide specimen submission to CDC, this information may be applicable to submission of specimens to other laboratories.

**Isolation of C. diphtheriae by culture**

Isolation of *C. diphtheriae* by culture is essential for confirming diphtheria. However, in a situation where there is increased risk of infection, even if the patient’s culture is negative—as could occur if the patient has been treated with antibiotics—isolation of *C. diphtheriae* from close contacts may help confirm the diagnosis of the case. Clinical specimens for culture should be taken from the nose or nasopharynx, and throat from all persons with suspected cases and their close contacts. If possible, swabs also should be taken from beneath the membrane, or a piece of the membrane should be removed. Specimens for culture should be obtained as soon as diphtheria (involving any site) is suspected, even if treatment with antibiotics has already begun. For more information on collection of clinical specimens, see Appendix 1 or Chapter 22, “Laboratory Support for the Surveillance of Vaccine-Preventable Diseases.” The laboratory should be alerted to the suspicion of diphtheria because isolation and identification of *C. diphtheriae* is aided by special culture media containing tellurite.

**Toxigenicity testing and biotyping**

After *C. diphtheriae* has been isolated, biotyping should be performed to determine the biotype (intermedius, belfanti, mitis, or gravis). Toxigenicity testing using the Elek test should be done to determine whether the organisms produce diphtheria toxin: demonstration of toxin production confirms a case as diphtheria. Elek and PCR tests are not readily available in many clinical microbiology laboratories; isolates should be sent to a reference laboratory, such as CDC, which is proficient in performing biotyping and the Elek test.

**PCR testing**

Isolation of *C. diphtheriae* may not always be possible because many patients will have received antibiotics before a diagnosis of diphtheria is considered. PCR allows for detection of the diphtheria toxin gene in nonviable organisms. Note that PCR does not demonstrate production of diphtheria toxin but only detection of the diphtheria toxin gene. A positive PCR test in the absence of a positive culture does not meet the laboratory criteria for classifying a case as confirmed diphtheria. Additional clinical specimens for PCR testing at CDC should be collected when specimens are being collected for culture. Swabs (nasal and throat) can be transported to CDC with cold packs in Amies transport, a sterile empty container or in silica gel sachets while pieces of membrane and biopsy tissue should be transported cold in sterile saline without formalin. For detailed information on collection and shipping of specimens, and for arranging PCR testing, the state health department may contact the CDC Pertussis and Diphtheria Laboratory (404-639-1231).

**MALDI-Tof**

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-Tof) is an additional technology that can be used to rapidly identify bacterial species such as *C. diphtheriae*. The technique requires an isolate in order to identify the protein composition of microbial cells. However, this form of testing only confirms the bacterial species, does not confirm diphtheria toxin production, and is not available at the CDC Pertussis and Diphtheria Laboratory.

**Serologic testing**

Measurement of the patient’s serum antibodies to diphtheria toxin before administration of antitoxin may help in assessing the probability of the diagnosis of diphtheria. The state health department can provide information on laboratories that offer this test (few laboratories have the capability to accurately test antibody levels). If antibody levels are less than 0.01 IU/ml, immunity is likely to be absent, but a level of greater than 0.1 IU/ml is considered protective and diphtheria is unlikely to be the cause of the patient’s illness. Diphtheria antibody levels between 0.01 IU/ml and 0.09 IU/ml indicate the presence of some or limited immunity.
Submission of *C. diphtheriae* isolates

All isolates of *C. diphtheriae*, whether toxigenic or nontoxigenic, regardless of association with disease, and from any anatomic site (respiratory, cutaneous, or other) should be sent to the CDC Pertussis and Diphtheria Laboratory for reference testing. To arrange specimen shipping, the state health department should be contacted.

Submission of isolates of other *Corynebacterium* species

Infrequently, other diphtheria toxin-producing *Corynebacterium* species (e.g., *C. ulcerans* or *C. pseudotuberculosis*) may be isolated from patients. Such isolates should also be sent to the CDC Pertussis and Diphtheria Laboratory (404-639-1231).

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. 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 health-care 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 the CSTE. The CDC *Diphtheria Worksheet* is included as Appendix 1, to serve as a guide for data collection during investigation of reported cases.

Case notification to CDC

The healthcare provider should first notify the state health department promptly so that epidemiologic investigation can be initiated. The state in which the patient resides at the time of diagnosis should submit the case notification to CDC. Notifications for probable and confirmed cases of diphtheria should be sent to CDC by the state health department using the event code 10040 in the National Notifiable Disease Surveillance System NNDSS via the National Electronic Telecommunications System for Surveillance (NETSS) or National Electronic Disease Surveillance System (NEDSS). Case notifications should not be delayed because of incomplete information or lack of laboratory confirmation; data can be updated electronically as more information becomes available. The CDC *Diphtheria Worksheet* is included as Appendix 1, to serve as a guide for data collection to be included in case investigations and case notification to CDC.

Respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria. Rarely, respiratory diphtheria-like illness may result from infection with other *Corynebacterium* species (e.g., *C. ulcerans*, *C. pseudotuberculosis*). Such cases should also be reported to CDC.

Cutaneous diphtheria is not a notifiable disease, and these cases should not be reported to NNDSS.

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.

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
  - Length of time in United States
• 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)
  ◦ Symptoms (e.g., fever, sore throat)
  ◦ Signs (e.g., neck edema, stridor, tachycardia)
  ◦ Complications (e.g., myocarditis, neuritis)
  ◦ 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 therapy

• Laboratory
  ◦ Culture
  ◦ Biotype and toxigenicity test
  ◦ PCR
  ◦ Molecular typing

• 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 probable or confirmed case
  ◦ Contact with immigrants or returning travelers from endemic-disease areas
  ◦ 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

Primary diphtheria immunization with diphtheria-tetanus toxoids-acellular pertussis vaccine (DTaP) is recommended for all persons at least 6 weeks but less than 7 years of age and without a history of contraindications. DTaP is the preferred vaccine for all doses in the infant and childhood vaccination series (including completion of the series for children who have received 1 or more doses of whole-cell DTP). The primary vaccination with DTaP series consists of a 3-dose series, administered at ages 2, 4, and 6 months, with a minimum interval of 4 weeks between doses. The fourth (first booster) dose is recommended at 15 through 18 months of age to maintain adequate immunity during preschool years.
The fourth dose should be administered at least 6 months after the third. If the interval from the third dose is 6 months or greater and the child is unlikely to return for a visit at the recommended age, the fourth dose of DTaP may be administered as early as age 12 months. The fifth (second booster) dose is recommended for children 46 years of age to confer continued protection against disease during the early years of schooling. A fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.25

Adolescents and adults should receive a one-time booster dose of Tdap.26–28 Adolescents 11 through 18 years of age who have completed the recommended childhood DTP/DTaP vaccination series should receive a single dose of Tdap instead of Td vaccine, preferably at a preventive-care visit at age 11 or 12 years. For adolescents and adults who previously have not received a dose of Tdap, a single dose of Tdap should be given and can be administered regardless of interval since the last diphtheria-tetanus-toxoids-containing vaccine. After receipt of Tdap, persons should continue to receive Td for routine booster vaccination against tetanus and diphtheria at 10-year intervals. Adolescents and adults who have never been vaccinated against diphtheria should receive a primary series of 3 doses of Td. The first 2 doses should be administered at least 4 weeks apart, and the third dose 6–12 months after the second dose. For added protection against pertussis, Tdap can substitute for any 1 dose in the 3-dose primary series.

Regarding wound management, if the last dose of Td was received 5 or more years earlier, Tdap is preferred to Td for adults who have never received Tdap.28 Up-to-date vaccination against diphtheria is especially important for travelers who will be living or working with local populations in countries where diphtheria is endemic.27

Healthcare providers should ensure that travelers to all countries with endemic or epidemic diphtheria are up-to-date with diphtheria vaccination. Information on countries with diphtheria is summarized in a recent publication by the World Health Organization29 and updates can be found on the CDC website for travelers at http://www.cdc.gov/travel. Vaccine providers should carefully review the vaccine history of all travelers to areas with endemic and epidemic diphtheria to ensure that they are optimally protected according to the recommendations of the Advisory Committee on Immunization Practices.25–29

X. Treatment

Diphtheria antitoxin

The mainstay of treatment of a case of suspected diphtheria is prompt administration of diphtheria antitoxin. This should be given 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. A U.S. Food and Drug Administration-licensed diphtheria antitoxin product is no longer available commercially in the United States. However, healthcare providers requiring diphtheria antitoxin to treat suspected diphtheria can request diphtheria antitoxin from CDC under an Investigational New Drug (IND) protocol after discussing the need for antitoxin with their respective state health departments.31

Contacting CDC for diphtheria antitoxin

After consultation with their respective the state health departments, healthcare providers should contact the CDC Emergency Operations Center (770-488-7100) to request diphtheria antitoxin 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. Additional epidemiologic and clinical data are needed as requirements under the IND.

Antibiotics

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

Vaccination

Because diphtheria disease does not always confer immunity, an age-appropriate vaccine containing diphtheria toxoid should be administered during convalescence.
XI. 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. However, if diphtheria is suspected, appropriate laboratory confirmation may not be feasible locally because isolation of the organism requires selective media. Treatment with antibiotics before specimen collection may further decrease the probability of isolating the organism. State public health laboratories should maintain capacity for isolation of \( C. diphtheriae \), if possible. Reference capacity for biotyping and toxigenicity testing will remain available at CDC.

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.\(^{33–39}\)

XII. Case Investigation

Guidelines for investigating a suspected case and for managing contacts are published and are included in Appendix 2 (Figure 1.23).

Management of contacts of persons with suspected cases should include screening for possible respiratory or cutaneous diphtheria, obtaining nasopharyngeal cultures for \( C. diphtheriae \), administering prophylactic antibiotics, assessing diphtheria vaccination status, and administering any necessary vaccinations. The \textit{CDC Diphtheria Worksheet} may be used for guidelines in conducting a case investigation (see Appendix 3).

References


21. CDC. Infectious diseases laboratories. submitting specimens to CDC. [updated 2011 April 6; cited 2017 May 1]. https://www.cdc.gov/laboratory/specimen-submission


