



Diphtheria

Colorado Communicable Disease Manual

Issued: 04/2013

Revised:

The Disease and Its Epidemiology

A. Etiologic Agent

Diphtheria is caused by toxigenic strains of gram-positive bacterium *Corynebacterium diphtheria*. If isolated, the organism must be distinguished in the laboratory from other *Corynebacterium* species that normally inhabit the nasopharynx and skin (e.g., diphtheroids).

B. Clinical Description

Diphtheria can involve almost any mucous membrane including 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. Diphtheria is classified into a number of manifestations, depending on the site of disease.

Respiratory diphtheria usually manifests as sore throat, difficulty in swallowing, malaise, and low-grade fever. Within 2 to 3 days, a tough, bluish-white pseudomembrane forms and extends over the tonsils, pharynx, or larynx. The pseudomembrane may vary in size from covering a small patch on the tonsils to covering most of the soft palate. Attempts to dislodge the membrane usually result in bleeding which may cause the membrane to appear black by the time a physician has been contacted. 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. Life-threatening complications include airway obstruction caused by extensive membrane formation and damage to the myocardium, nervous system and kidneys. Untreated respiratory diphtheria usually lasts for one to 2 weeks, but complications can persist for months. The case-fatality rate is about 10%.

Cutaneous diphtheria, caused by either toxigenic or nontoxigenic strains of *C. diphtheriae*, is usually mild and typically consists of a scaling rash or ulcers with clearly demarcated edges and membrane. Most cases of cutaneous diphtheria in the United States are associated with homeless persons and are nontoxigenic.

Rarely, other *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*) produce diphtheria toxin.

C. Reservoirs

Humans are the only known natural hosts.

D. Modes of Transmission

Diphtheria is transmitted most often person-to-person through respiratory secretions and by contact with discharges from skin lesions.

E. Incubation Period

Incubation period is usually 2 to 7 days, but occasionally is longer.

F. Period of Communicability or Infectious Period

Diphtheria can be present in discharges from the nose and throat and from eye and skin lesions for 2 to 6 weeks after infection. Patients treated with an appropriate antimicrobial agent usually are communicable for less than 4 days.

G. Epidemiology

Once a common cause of illness and death among children, diphtheria is now rare in the United States. In the post-vaccine era, cases in the United States are more likely to occur among unvaccinated or inadequately vaccinated persons who travel to countries where diphtheria is endemic.

Diphtheria remains endemic in many parts of the developing world, including some countries of the Caribbean and Latin America, Eastern Europe, Southeast Asia, the Middle East, and Africa. In the 1990s, a large epidemic of diphtheria occurred in the newly independent countries of the former Soviet Union with case fatality rates ranging from 3% to 23%. The epidemic was attributed to several factors, including a lack of routine immunization of adults in these countries.

Case Definition

Laboratory Criteria for Diagnosis

	In the absence of a more likely diagnosis, an upper respiratory tract illness with:
Probable:	<ul style="list-style-type: none"> 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.
	An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils or larynx; and any of the following:
Confirmed:	<ul style="list-style-type: none"> Isolation of <i>Corynebacterium diphtheriae</i> from the nose or throat; OR Histopathologic diagnosis of diphtheria; OR Epidemiologic linkage to a laboratory-confirmed case of diphtheria.

Reporting Criteria

What to Report to the Colorado Department of Public Health and Environment (CDPHE) or local health agency

- Suspect, confirmed, and probable cases of diphtheria.
- Cases should be reported using telephone, fax or the Colorado Electronic Disease Reporting System (CEDRS) to CDPHE or the local health department. See below for phone and fax numbers.
- All diphtheria cases should be reported within 7 days of clinical or laboratory diagnosis.
- Only confirmed and probable cases are reported to CDC.

Purpose of Surveillance and Reporting

- To identify cases for investigation and ensure laboratory testing if necessary.
- To promptly identify clusters and potential outbreaks of disease.
- To recommend vaccination and post-exposure antibiotic prophylaxis in certain situations.
- To monitor trends in disease incidence.

Important Telephone and Fax Numbers

CDPHE Communicable Disease Epidemiology Branch

- Phone: 303-692-2700 or 800-866-2759
- Fax: 303-782-0338
- After hours: 303-370-9395

CDPHE Microbiology laboratory: 303-692-3480

Communicable Disease (CD) Manual website: <https://www.colorado.gov/pacific/cdphe/communicable-disease-manual>

State Laboratory Services

Laboratory Testing Services Available

Diagnostic tests used to confirm the diagnosis of diphtheria include isolation of *C. diphtheriae* by culture and toxigenicity testing. A polymerase chain reaction (PCR) test is also available at CDC but is only used if diphtheria anti-toxin (DAT) has been requested to treat the patient. Other pathogens can cause a membrane in the throat and over the tonsils, including *Streptococcus spp.*, Epstein-Barr virus, cytomegalovirus, *Arcanobacter hemolyticum*, *Candida albicans*, fusiform bacteria and some viruses. The patient's healthcare provider should be encouraged to perform appropriate laboratory tests to rule out these conditions and organisms.

Culture

Specimens for culture should be obtained from the nose or throat or any mucosal or cutaneous lesion. Material should be obtained from beneath the membrane using polyester, rayon or nylon swabs. The swabs should be placed in transport media such as Amies or Stuart and shipped overnight with ice packs. Dry swabs submitted in silica gel sachets are also acceptable. Pieces of membrane may also be submitted for culture. Pseudo-membrane should be placed in sterile saline (not formalin) and shipped overnight with ice packs.

The laboratory should be alerted to the suspicion of diphtheria because isolation of *C. diphtheriae* requires special culture media containing tellurite.

Toxigenicity Testing

After *C. diphtheriae* has been isolated, toxigenicity testing at CDC using the Elek test should be done to determine whether the organisms produce diphtheria toxin. Demonstration of toxin production confirms a case as diphtheria. Pure isolates should be cultured on tryptic soy agar slants (TSA), blood agar slants, or other common agar slants. Isolates should be sent overnight at ambient temperature.

Polymerase Chain Reaction (PCR)

Note: CDC does not perform PCR to rule out diphtheria unless diphtheria anti-toxin (DAT) has been requested to treat the patient.

Although not commercially available, PCR testing at CDC can provide supportive evidence for the diagnosis if isolation of *C. diphtheriae* is not possible. PCR allows for detection of the regulatory gene for toxin production (dtxR) and the diphtheria toxin gene (tox) on nonviable organisms but 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 epidemiologic linkage to a laboratory-confirmed case should be classified as a probable case. Clinical specimens (nasal and throat swabs, pieces of membrane, biopsy tissue) can be transported to CDC with cold packs in a sterile empty container or in silica gel sachets.

State Laboratory Testing Services

Diphtheria culture is available at the CDPHE Lab on a fee-for-service basis.

If indicated, specimens may be submitted to the CDC Lab through the CDPHE Lab for diphtheria PCR and/or toxigenicity testing.

For more information, see CDC's [Instructions for specimen collection and transport for laboratory testing of *Corynebacterium diphtheriae* and *C. ulcerans*](#)

Case Investigation

Investigate all reports of *respiratory* diphtheria, including suspect cases.

A. Case Investigation / Forms

Organized health departments have primary responsibility for investigating cases in their jurisdiction.

Public health nursing services should consult their CDPHE Field Epidemiologist to establish primary responsibility for investigating cases in their jurisdiction.

- Interview the case's health care provider.
 - ▶ Determine whether the case had clinical symptoms compatible with respiratory diphtheria, including an adherent membrane of the nose, pharynx, tonsils, or larynx.
 - ▶ Ask about demographic information, other symptoms, vaccine history (including vaccination date, type of vaccine, vaccine manufacturer, and lot number), travel history (including dates, location, and activities while traveling), occupation, and whether specimens were collected for diphtheria testing.
 - ▶ If indicated, discuss the need for diphtheria antitoxin with the case's health care provider. See Disease Control Measures, section A (Treatment).
 - ▶ If specimens were not collected for testing and diphtheria is likely, recommend specimen collection. See Laboratory Testing, above, for details regarding laboratory testing.
- If case's symptoms, vaccination history, and travel history are compatible with diphtheria, institute strict isolation and maintain isolation until elimination of the organism is demonstrated by negative cultures of two samples obtained at least 24 hours apart after completion of antimicrobial therapy.
- If multiple attempts to obtain case information are unsuccessful (e.g., the case, case's guardian, or health care provider does not return your calls, or the person refuses to divulge information), contact your CDPHE Field Epidemiologist to discuss the situation.
- Provide immunization with diphtheria toxoid during convalescence. Vaccination is required because clinical diphtheria does not necessarily confer immunity.
- Enter all information from the worksheet into CEDRS or mail or fax the completed worksheet to CDPHE.

B. Identify and Evaluate Contacts

- Identify close contacts of respiratory diphtheria cases. Close contacts include household members and other persons with a history of direct, habitual close contact with a case-patient (e.g., sexual or kissing contacts, caretakers, relatives, or friends who regularly visit the home) as well as medical staff exposed to oral or respiratory secretions of a case-patient.
- Record names, ages, county (city or address) and phone numbers of all close contacts.
- For close contacts, the following measures should be taken regardless of immunization status:
 - ▶ Assess and monitor contacts for signs and symptoms of diphtheria for at least 7 days.
 - ▶ Obtain cultures for *C. diphtheria*. Any contacts with a positive culture should avoid close contact with inadequately vaccinated persons and if symptomatic, treated like a confirmed case of diphtheria. Repeat cultures of pharyngeal specimens should be performed for contacts proven to be carriers a minimum of 2 weeks after completion of antimicrobials to assure eradication of the organism. Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of oral erythromycin and should submit samples for follow-up cultures.
 - ▶ Recommend antimicrobial post exposure prophylaxis with oral erythromycin (40-50mg/kg per day for 10 days, maximum 2 g/day) or a single dose of intramuscular benzathine penicillin G (600,000 units for children weighing less than 30 kg and 1.2 million U for children weighing 30 kg or more and adults). Preventative measures may be extended to close contacts of carriers but should be considered a lower priority than control measures for contacts of each case.
- Assess the immunization status of close contacts and recommend vaccination if they are not up-to-date:
 - ▶ >3 doses, last dose <5 years ago: Children in need of their 4th primary dose or booster dose should be vaccinated; otherwise vaccination not required.
 - ▶ >3 doses, last dose >5 years ago: Administer immediate booster dose of diphtheria toxoid (DTaP, DT, Tdap, or Td, as appropriate for age).

- ▶ < 3 doses or unknown: Administer immediate dose of diphtheria toxoid (DTaP, DT, Tdap, or Td, as appropriate for age) and complete primary series according to schedule.

C. Reported Incidence Is Higher than Usual/Outbreak Suspected

Call the CDPHE Communicable Disease Program if there are a higher number of cases in your area than usual or an outbreak is suspected.

Disease Control Measures

A. Treatment

Antitoxin

Because the condition of patients with diphtheria may deteriorate rapidly, if diphtheria is likely, a single dose of equine antitoxin should be administered before culture results are available. If equine diphtheria antitoxin is needed, contact your State Health Department to request antitoxin from CDC. Before administration, patients should be tested for sensitivity to horse serum and, if necessary, desensitized. The recommended dosage and route of administration depend on the extent and duration of disease. Detailed recommendations can be obtained from the package insert and other publications.

Antimicrobial Therapy

Antimicrobial therapy is not a substitute for antitoxin treatment. Acceptable therapies for respiratory diphtheria are penicillin G procaine administered intramuscularly for 14 days, penicillin G administered intramuscularly or intravenously for 14 days, or erythromycin administered parenterally or orally for 14 days.

Cases of cutaneous diphtheria are treated with thorough cleansing of the lesion with soap and water and administration of an appropriate antibiotic for 10 days.

B. Vaccination

Clinical diphtheria does not necessarily confer immunity. Cases and close contacts should have their immunization statuses assessed and receive vaccination if not up-to-date:

- > 3 doses, last dose < 5 years ago: Children in need of their 4th primary dose or booster dose should be vaccinated; otherwise vaccination not required.
- > 3 doses, last dose > 5 years ago: Administer immediate booster dose of diphtheria toxoid (DTaP, DT, Tdap, or Td, as appropriate for age).
- < 3 doses or unknown: Administer immediate dose of diphtheria toxoid (DTaP, DT, Tdap, or Td, as appropriate for age) and complete primary series according to schedule.

C. Prophylaxis

Antimicrobial post exposure prophylaxis is recommended for close contacts of diphtheria cases. See Case Investigation, section B (Identify and Evaluate Contacts).

D. Education

- Advise contacts of signs and symptoms of diphtheria and to contact a health care provider if they develop symptoms.
- Recommend contacts review their vaccination status and receive diphtheria vaccine (DTaP, DT, Tdap, or Td, as appropriate for age), if susceptible.
- Additional educational materials are available from CDC at <http://www.cdc.gov/diphtheria/clinicians.html>.
- A Health Alert Network (HAN) Advisory about diphtheria may be sent to health care providers. Sending a HAN should be discussed with your CDPHE Field Epidemiologist, who may assist you in developing the notice.

E. Managing Special Situations

Patients and Staff in Health Care Facilities (Hospitals and Long Term Care Facilities)

Hospitals and long term care facilities generally have written infection control policies and procedures for handling cases of communicable disease among patients and staff members. If a facility does not have such policies in place, provide the following recommendations:

- Standard and droplet precautions are recommended for patients and carriers with respiratory diphtheria until two cultures from both the nose and throat collected 24 hours after completing antimicrobial treatment are negative for *C. diphtheria*.
- Contact precautions are recommended for patients with cutaneous diphtheria until two cultures of skin lesions take at least 24 hours apart and 24 hours after cessation of antimicrobial therapy are negative.
- Identify health care workers and staff having close contact with the case while the person was infectious and not in droplet isolation (or staff not following respiratory precautions).
- Refer to Case Investigation, section B (Identify and Evaluate Contacts) for details on how to follow-up with close contacts.

F. Environmental Measures

No specific environmental measures are recommended.

References

American Academy of Pediatrics. *Red Book 2012: Report of the Committee on Infectious Diseases, 29th Edition*. Illinois, American Academy of Pediatrics, 2012.

CDC. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Atkinson W, Wolfe S, Hamborsky J, McIntyre L, eds. 12th ed. Washington DC: Public Health Foundation, 2011 or <http://www.cdc.gov/vaccines/pubs/pinkbook/index.html>.

CDC. *Manual for the Surveillance of Vaccine-Preventable Diseases, 5th Edition*. Roush S, McIntyre L, Baldy L, eds. 5th ed. Atlanta, GA, 2011 or <http://www.cdc.gov/vaccines/pubs/surv-manual/index.html>

CDC Website: Disease Listing, Diphtheria, Technical Information
<http://www.cdc.gov/diphtheria/clinicians.html>

Heymann, David, editor, *Control of Communicable Diseases Manual, 18th Edition*. Washington, DC, American Public Health Association, 2004.