Diphtheria

Summary

Diphtheria is caused by toxin-producing *Corynebacterium diphtheriae* bacteria. Toxigenic diphtheria primarily manifests as a respiratory infection which can cause death in 5-10% of cases, but can also present as milder infections in non-respiratory sites (cutaneous diphtheria). People can also be infected or colonized with non-toxigenic diphtheria bacteria in a respiratory or non-respiratory site, although these are not counted as cases for surveillance purposes.

Thanks to vaccines that protect against diphtheria toxin, toxigenic respiratory diphtheria is now extremely rare in the United States. The disease remains endemic in many parts of the world, with cutaneous diphtheria being relatively common in tropical areas.

There has been an increasing recognition of cutaneous diphtheria. Five toxigenic cases were identified in the United States from 2019-2023, with four among travelers to areas with endemic diphtheria. Both respiratory and non-respiratory disease require public health follow-up, and all *C. diphtheriae* isolates should be sent to the Centers for Disease Control and Prevention (CDC) for toxigenicity testing.

Travel-related exposures should be considered for any suspected or confirmed case of diphtheria.

Disease control requires maintaining high immunization coverage, and promptly isolating cases and exposed contacts until they are culture negative.

See here for Surveillance Worksheet.

Agent

Corynebacterium diphtheriae is an aerobic gram-positive pleomorphic bacillus. Toxin production occurs only when the bacillus is itself infected (lysogenized) by a virus (corynebacteriophage) carrying genetic information for the toxin (*tox* gene). There are four biotypes of the bacteria (gravis, intermedius, mitis, and belfanti), all of which can become toxigenic and cause severe disease.

Rarely, two other *Corynebacterium* species, *C. ulcerans* and *C. pseudotuberculosis*, can also produce diphtheria toxin. Both species are zoonotic, with infections documented in pigs, cattle, dogs, and cats.

Transmission

Reservoir:

Humans

Mode of transmission:

Person-to-person by contact with infected respiratory secretions, discharges from skin lesions, or rarely, fomites (contaminated surfaces or objects), or coming into contact with the mucous membranes of a susceptible person.

Period of communicability:

If left untreated, people can remain infectious for 2-6 weeks. Rarely, carriers may shed the organism for six months or longer. Effective antibiotic therapy promptly terminates shedding, and people are usually not infectious 48 hours after treatment is initiated.

Clinical Disease

Incubation period:

Usually 2-5 days (range: 1-10 days).

Illness:

Diphtheria infection is classified by the site of disease: respiratory (affecting the pharyngeal, tonsillar, laryngeal, or nasal areas), or non-respiratory (affecting cutaneous (skin) and non-respiratory mucus membranes). Most complications and serious outcomes are associated with diphtheria toxin, which not all diphtheria bacteria carry. Toxigenic diphtheria bacteria may be found in both respiratory and non-respiratory sites, although the highest risk of death is associated with toxigenic respiratory diphtheria.

The most common sites of respiratory diphtheria are the pharynx and/or tonsils. Illness can begin with early symptoms of malaise, sore throat, loss of appetite, and low-grade fever (less than 101°F). Within 2-3 days, a bluish-white or gray membrane forms, ranging in size from a small patch on the tonsils to covering most of the soft palate. The pseudomembrane may be greyish-green or even black if bleeding has occurred, and it is firmly adhered to underlying tissue. Attempting to remove the pseudomembrane is likely to cause bleeding. Extensive membrane formation may obstruct breathing.

Some patients may develop edema (swelling) around the front of the neck and under the jaw, creating a “bull neck” appearance. Some patients recover without treatment, but an estimated 5-10% of cases are fatal. The fatality rate is higher (up to 20%) in children younger than 5 years, and adults older than 40 years. Death can occur within 6-10 days.

Cutaneous diphtheria may present as a scaling rash, or as one or more ulcers with clearly demarcated edges, with or without an overlying membrane; these are sometimes described as “punch-out” ulcers. Cutaneous diphtheria is relatively common in tropical areas.

Rarely, diphtheria has been found in other (non-respiratory) mucous membranes including the conjunctiva or vulvovaginal area. Involvement of the palate or uvula suggests diphtheria may be more likely, as strep throat and infectious mononucleosis usually do not affect the palate or uvula. Both toxigenic and non-toxigenic forms of diphtheria have been associated with endocarditis or myocarditis. Exposed persons may also become carriers.

Laboratory Diagnosis

Specimen for culture should be collected from the nose, throat, or any mucosal or cutaneous lesion. Notify the laboratory of suspicion of diphtheria.

In order to confirm a diagnosis, laboratories must:

1) Identify and isolate *Corynebacterium diphtheriae.*
    a. This can be done at most clinical labs.
2) Detect the *tox* gene.
    a. This is done at CDC, and should be submitted through the Scientific Laboratory Division (SLD).
3) Demonstrate that toxin is being produced.

a. This is done at CDC, using an Elek test. Specimen should be submitted through SLD.

All three steps are necessary to confirm the diagnosis, because not all strains of *C. diphtheriae* possess the *tox* gene, and not all strains that possess the *tox* gene actually produce toxin.

Note: Some investigations for suspected diphtheria cases are prompted when *C. diphtheriae* is unexpectedly grown out on a culture plate, often alongside other bacteria such as *Streptococcus* or *Staphylococcus* species. Labs and clinicians sometimes interpret unexpected *C. diphtheriae* as a contaminant, especially if only one out of multiple culture plates grows it out, and the patient has no compatible symptoms or exposure history.

Treatment

Treatment should occur based on the clinical diagnosis, without waiting for culture confirmation.

Antitoxin:

Diphtheria Antitoxin (DAT), an equine antitoxin, is not available commercially and can only be obtained from the CDC. Patients who have probable or confirmed respiratory diphtheria are eligible to receive DAT, but providers seeking DAT for their patient must consult with and order it from CDC. DAT neutralizes unbound toxin, and therefore is most effective the earlier it is given; clinicians should not wait for toxigenicity testing or culture results to begin administering DAT to patients with probable or confirmed respiratory diphtheria. Antitoxin is usually not necessary for cutaneous diphtheria cases.

As of spring 2025, the global supply of diphtheria antitoxin is limited, and providers who order DAT and do not use it will be asked to promptly return it to CDC. Side effects are common, with allergic reactions varying from anaphylaxis to rash occurring in 5-20% of patients.

Physicians caring for patients with suspected respiratory diphtheria can request DAT by contacting the CDC's Emergency Operations Center at (**770) 488-7100**.

Antibiotics:

Persons with *C. diphtheriae* infections should be treated with antibiotics, regardless of infection site, presence of symptoms, or toxin-producing status. A 14-day course of erythromycin or penicillin is recommended for treatment. Close contacts of diphtheria patients should receive a course of antimicrobial prophylaxis in the form of a 7- or 10-day course of erythromycin or a single intramuscular injection of penicillin G benzathine. Antibiotic treatment is required to interrupt new toxin production, clear C. *diphtheriae* infection, and prevent transmission, but is not a substitute for antitoxin. Successful treatment should be confirmed with two consecutive negative cultures taken 24 hours apart, and started at least 24 hours after completion of antibiotic therapy.

Vaccination:

Patients should be immunized or boosted with a diphtheria toxoid vaccine (e.g., DTaP, Tdap, Td) during convalescence as diphtheria disease does not necessarily confer immunity. Unimmunized or under-immunized carriers should complete the series (as age-appropriate).

Cutaneous Diphtheria – Lesions should be thoroughly cleaned with soap and water; antibiotic treatment administered for 10 days is recommended to clear the infection. Antitoxin is usually not necessary for cutaneous diphtheria, but consult with CDC for especially severe or invasive cases.

Surveillance

Case Definition (2019):

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 *Corynebacterium 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

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

Case Classification Comments:

- Cases of laboratory-confirmed, non-toxin-producing *C. diphtheriae* (respiratory or non-respiratory) should not be reported to CDC as confirmed diphtheria cases. (i.e., case status will be Not a Case when investigation is completed.)
- Negative laboratory results may be sufficient to rule out a diagnosis of diphtheria; however, clinicians should carefully consider all lab results in the context of the patient's vaccination status, antimicrobial treatment, and other risk factors.
- PCR and MALDI-TOF diagnostics for *C. diphtheriae*, when used alone, do not confirm toxin production. These tests, when used, should always be combined with a test that confirms toxin production, such as the Elek test.

Reporting:

Report all suspected or confirmed cases of diphtheria immediately to the Infectious Disease Epidemiology Bureau (IDEB) at 1-833-SWNURSE (1-833-796-8773). Information needed includes: patient's name, age, sex, race, ethnicity, home address, home phone number, occupation, and health care provider.

Case Investigation:

Complete the CDC Diphtheria Surveillance Worksheet and mail to the Infectious Disease Epidemiology Bureau, P.O. Box 26110, Santa Fe, New Mexico 87502-6110, or (preferably) fax to (505) 827-0013. Investigation information should also be entered into NMEDSS by an NMDOH epidemiologist per established procedures.

Control Measures

1. Case management
    a. *Isolation:*
        i. For respiratory diphtheria, droplet precaution in addition to standard precautions should be instituted (Appendix 4) until two sets of cultures from both nose and throat taken at least 24 hours apart, and started at least 24 hours after completion of antibiotic therapy, are negative.
        ii. For cutaneous diphtheria, contact isolation (Appendix 4) until two cutaneous cultures taken at least 24 hours apart, and started at least 24 hours after completion of antibiotic therapy, are negative.
2. Contact management
    a. *Contacts of Toxigenic Cases:* Contact tracing and post-exposure prophylaxis is only done for toxigenic cases. Contact tracing can usually be limited to:
        i. Household members
        ii. People with direct, habitual close contact
        iii. Healthcare personnel exposed to nasopharyngeal secretions
        iv. People sharing kitchen facilities
        v. People caring for infected children
    b. *Prophylaxis:* **Regardless of immunization status,** the following measures should be taken for close contacts of toxigenic cases:
        i. Monitor for symptoms in untreated patient(s) for 7 days from last exposure.
        ii. Obtain nasal and throat specimens for *C. diphtheriae* culture.
        iii. Antimicrobial prophylaxis with a 7-10 day course of erythromycin or a single intramuscular injection of penicillin G benzathine (preferred if contact is likely to become lost to follow-up).
            1. Follow-up cultures of pharyngeal specimens should be performed after completion of therapy for contacts proven to be carriers. If cultures are positive, an additional 10-day course of erythromycin should be administered, and follow-up cultures of pharyngeal specimens should be performed again.

iv. Assess diphtheria vaccination status.

1. Administer vaccine if patient is: 1) eligible, 2) never previously vaccinated, 3) not up-to-date, 4) last dose was administered ≥5 years prior, or 5) status is unknown.

v. Use of diphtheria antitoxin in exposed contacts is not recommended, due to no evidence of additional benefit.

vi. Isolation: Contacts who are food handlers and adults who have contact with incompletely immunized children should be excluded until nose and throat cultures are negative for *C. diphtheriae* and they have received appropriate antibiotic prophylaxis.

vii. For more, see CDC Worksheet on Information to Collect on Close Contacts of Diphtheria Cases.

c. *Contacts of Non-Toxigenic Cases:* Cases of non-toxigenic diphtheria do not require contact tracing or prophylaxis; however, in the period between when a *C. diphtheriae* isolate is first identified and toxigenicity test results are ready from CDC, contact investigations should be considered for those with clinical presentations concerning for respiratory diphtheria (e.g., pseudomembrane, bull neck, cardiomyopathy, neuritis), or those with *C. diphtheriae* infection who lack signs of respiratory diphtheria but have recently traveled to a country with endemic diphtheria. Persons who initiate post-exposure antibiotic prophylaxis before results are ready may discontinue if the isolate is determined to be non-toxigenic.

3. Prevention

a. Immunization: Active immunization with diphtheria toxoid (combined with tetanus toxoid and acellular pertussis, DTaP) is routinely given as five doses between the ages of 2 months and 6 years. A booster dose of Tdap is recommended at age 11-12 years. Among adults, a booster of either Tdap or Td is recommended every 10 years.

b. Vaccination does not prevent colonization of diphtheria bacteria; it only protects against the effects of the diphtheria toxin.

Management of Diphtheria in Healthcare Settings

The definition of close contact to diphtheria in healthcare settings may include, but is not limited to, performing a physical examination on, feeding, or bathing a patient; bronchoscopy; intubation; or administration of bronchodilators. Exposure to cutaneous diphtheria lesions may include unprotected contact with lesions or lesion drainage, such as when changing lesion dressings; or handling potentially infectious secretions without wearing appropriate personal protective equipment (i.e., gown and gloves).

For healthcare personnel who have been exposed to diphtheria, regardless of immunization status:

- Administer post-exposure prophylaxis as noted above in “Control Measures.”
- Exclude from work and obtain nasal and pharyngeal swabs for diphtheria culture.
    - If nasal and pharyngeal cultures are negative for toxin-producing *C. diphtheriae*, healthcare personnel may return to work while completing post-exposure antibiotic therapy.

- If nasal or pharyngeal cultures are positive for toxin-producing *C. diphtheriae*:
  - Complete post-exposure antibiotic therapy
  - Healthcare personnel may return to work when:
    - Post-exposure antibiotic therapy is completed, and
    - At least 24 hours after completion of post-exposure antibiotic therapy, two consecutive pairs of nasal and pharyngeal cultures, taken at least 24 hours apart, are both negative for toxin-producing *C. diphtheriae.*

- Implement daily monitoring for signs/symptoms of diphtheria for 7 days after the last exposure.

Management of Diphtheria in Child Care Centers

A case of diphtheria in a childcare center should be managed in conjunction with the NMDOH's Infectious Disease Epidemiology Bureau. Isolation and contact tracing measures apply to childcare as noted above in "Control Measures." Diphtheria immunization records of children in school and childcare should be reviewed and readily available to identify those at highest risk.

References

American Academy of Pediatrics. "Diphtheria." In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:304-307.

Acosta AM, Moro PL, Hariri S, Tiwari TSP. "Diphtheria." *Epidemiology and Prevention of Vaccine-Preventable Diseases.* https://www.cdc.gov/pinkbook/hcp/table-of-contents/chapter-7-diphtheria.html.

Tobolowsky FA, Pawlowski LC, Tromble E. "Diphtheria." *Manual for the Surveillance of Vaccine-Preventable Diseases.* https://www.cdc.gov/surv-manual/php/table-of-contents/chapter-1-diphtheria.html.

Centers for Disease Control and Prevention. "Diphtheria." *Infection Control in Healthcare Personnel: Epidemiology and Control of Selected Infections Transmitted Among Healthcare Personnel and Patients.* https://www.cdc.gov/infection-control/hcp/healthcare-personnel-epidemiology-control/diphtheria.html.

Centers for Disease Control and Prevention. "Diphtheria Antitoxin (DAT)." https://www.cdc.gov/diphtheria/hcp/dat/index.html.

Heymann, DL, ed. Control of Communicable Diseases Manual. 19th edition. Washington, DC: American Public Health Association; 2008.

See Diphtheria Fact Sheets (English) (Spanish).