

Diphtheria

1. DISEASE REPORTING

A. Purposes of Reporting and Surveillance

1. To assist in the diagnosis of cases.
2. To assure early and appropriate treatment with diphtheria antitoxin and antibiotics.
3. To identify and evaluate contacts and recommend appropriate antibiotic prophylaxis and/or immunization to prevent further spread of the disease.
4. To alert public health authorities to the presence of diphtheria cases and the possibility of additional cases developing in the area, a particular concern given the large number of susceptible adults.

B. Legal Reporting Requirements

1. Health care providers: **immediately notifiable to local health jurisdiction.**
2. Health care facilities: **immediately notifiable to local health jurisdiction.**
3. Laboratories: *Corynebacterium diphtheriae* **immediately notifiable to local health jurisdiction**, specimen submission required - culture (2 business days).
4. Local health jurisdictions: **immediately notifiable to the Washington State Department of Health (DOH) Communicable Disease Epidemiology Section (CDES).**

C. Local Health Jurisdiction Investigation Responsibilities

1. Begin case investigation immediately. Please inform CDES about possible cases. CDES will assist with release of antitoxin if necessary.
2. Facilitate the transport of specimens to assist with the diagnosis.
3. Recommend measures to prevent further spread from the case.
4. Identify and evaluate contacts; educate and recommend measures to prevent further spread from contacts.
5. Report all *confirmed* and *probable* cases (see Section 3C) to CDES. Complete the diphtheria case report form (<http://www.doh.wa.gov/notify/forms/diphtheria.pdf>) and enter the data into the Public Health Issues Management System (PHIMS).

2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic Agent

Diphtheria is caused by toxigenic strains of the bacteria *Corynebacterium diphtheriae*. Exotoxin production results when the bacteria are infected by a bacteriophage carrying the toxin-producing gene (tox gene). Only toxigenic strains can cause severe disease. (Rarely a diphtheria-like illness is caused by a toxigenic strain of *C. ulcerans* or *C. pseudotuberculosis*.) *C. diphtheriae* has three biotypes: *gravis*, *intermedius*, and *mitis*. The *gravis* biotype is associated with the most severe disease, but any strain may be

toxigenic. ALL clinical isolates of *C. diphtheriae* should be tested for toxigenicity. Nontoxigenic strains can cause sore throat and other invasive infections, and have been increasingly associated with endocarditis.

B. Description of Illness

Classic diphtheria is an upper-respiratory tract illness characterized by sore throat, low-grade fever, and an adherent pseudomembrane of the tonsil(s), pharynx, and/or nose. The disease can involve almost any mucous membrane. For clinical purposes, diphtheria can be classified according to the site of the infection:

1. Anterior nasal diphtheria

Anterior nasal diphtheria usually presents with mucopurulent discharge from the nose which may be bloody and a white pseudomembrane on the nasal septum.

2. Pharyngeal and tonsillar diphtheria

Pharyngeal and tonsillar diphtheria, the most common type of infection, initially presents with malaise, sore throat, anorexia, and low-grade fever. Within a few days, a bluish-white pseudomembrane forms on one or both tonsils which can extend to the tonsillar pillars, uvula, soft palate, pharynx and nasopharynx. Over time, the pseudomembrane evolves, assuming a dirty gray color with areas of green or black necrosis surrounded by a minimal amount of erythema. Attempts to remove the pseudomembrane cause bleeding. With severe disease patients can develop edema of the anterior neck, giving a characteristic “bullneck” appearance. If a significant amount of toxin is absorbed into the blood stream, patients may develop pallor, rapid pulse, coma and death.

The differential diagnosis of diphtheria includes streptococcal pharyngitis, viral pharyngitis, Vincent's angina, infectious mononucleosis, oral syphilis and candidiasis.

3. Laryngeal diphtheria

If the infection involves the larynx, it may occur either as an extension of the pharyngeal form, or as laryngeal involvement alone. Patients can present with fever, hoarseness and a barking cough. The pseudomembrane can cause potentially fatal airway obstruction.

4. Cutaneous (skin) diphtheria

Cutaneous diphtheria, caused by either toxigenic or nontoxigenic strains of *C. diphtheriae*, is usually mild, typically consisting of nondistinctive sores or shallow ulcers, and rarely causes toxic complications (cutaneous infections represent 1%–2% infections with toxigenic strains.) The disease may present as a scaling rash or as clearly demarcated ulcers. A chronic skin lesion may harbor *C. diphtheriae* along with other organisms. Skin infections with *C. diphtheriae* are common in tropical climates, and this is likely the reason for high levels of natural immunity seen among local populations in these regions. Since 1980, cutaneous diphtheria has not been a nationally reportable disease. Nevertheless, all *C. diphtheriae* isolates should be submitted for testing to determine whether the tox gene is present.

Other possible sites of infection include the conjunctiva, vulvovaginal area and external auditory canal. Severe disease is more likely to occur in people who are unimmunized or under immunized. Fully immunized people may be asymptomatic carriers or experience a mild sore throat. Complications of diphtheria include myocarditis, neuritis, airway obstruction, and death. The case-fatality rate for diphtheria is approximately 10%.

C. Diphtheria in the United States and Washington State

Diphtheria is rare in the United States with only 0–5 cases reported annually. The last major outbreaks in the United States occurred in Seattle, Washington. There were three outbreaks of cutaneous diphtheria in Seattle from 1972 through 1982. The first was due to a toxigenic strain while the later outbreaks were due to nontoxigenic strains. The last case of toxigenic diphtheria reported in Washington occurred in 1979. Cases would now likely be travel-associated since diphtheria is no longer endemic in Washington.

Between 1980 and 2005, 55 cases of diphtheria were reported in the United States. The majority of cases (77%) were in persons 15 years of age and older, and 4 of 5 fatal cases were in unvaccinated children. The fifth fatal case was in an adult traveler returning from a country where the disease is endemic. Enhanced surveillance has shown ongoing circulation of toxigenic *C. diphtheriae* in a Northern Plains Indian community, where the disease was previously endemic, and in some communities in Canada. Cutaneous diphtheria due to nontoxigenic strains is still known to occur, particularly among homeless persons.

D. Reservoir

Infected humans are the reservoir.

E. Modes of Transmission

Diphtheria is transmitted from person to person through respiratory droplets or less commonly, through contact with discharge from skin lesions. Historically, raw milk and fomites were known to have served as vehicles.

F. Incubation Period

The incubation period is usually 2–5 days (range 1–10 days).

G. Period of Communicability

Persons are communicable for up to 4 days after treatment with effective antibiotics has been initiated. Untreated persons generally shed bacteria from the respiratory tract or from skin lesions for 2–4 weeks after infection. A chronic carrier state is rare, but known to exist, and such a carrier may shed organisms for 6 months or more.

H. Treatment

The mainstay of treatment for diphtheria is prompt administration of diphtheria antitoxin. If diphtheria is strongly suspected on the basis of clinical findings, specimens for bacteriologic testing should be collected and then antitoxin should be given immediately after without waiting for results.

CDC stores diphtheria antitoxin (DAT) at quarantine stations around the country. DAT is currently available for treatment of respiratory diphtheria under an FDA-approved

Investigational New Drug (IND) protocol. Since the antitoxin is of equine origin, a test to rule out hypersensitivity should be performed before administration. Antitoxin may only be administered in an inpatient environment.

Healthcare providers who suspect diphtheria should contact their local health jurisdiction immediately. The local health jurisdiction in collaboration with DOH can assist with arranging consultation with CDC, and subsequent transport of antitoxin as needed. For additional information regarding DAT, see:

<http://www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/dat-main.htm>

In addition to diphtheria antitoxin which is the primary therapy, patients should also be treated with erythromycin (given orally or parenterally) for 14 days, penicillin G (intramuscularly or intravenously) for 14 days, or procaine penicillin G intramuscularly for 14 days. Antimicrobial therapy is necessary to stop toxin production, to eradicate *C. diphtheriae* and to prevent further spread, but antitoxin remains the **primary** therapy. Patients with suspected diphtheria should have appropriate (droplet) precautions in place until they have completed at least the first 4 days of treatment with an appropriate antibiotic or until diphtheria is ruled out.

I. Immunity

Lifelong immunity is usually, but not always, acquired after disease or inapparent infection. Immunization with diphtheria toxoid produces prolonged but not lifelong immunity. Serosurveys in the United States indicate that more than 40% of adults lack protective levels of circulating antitoxin. However, many of these older adults may have immunologic memory and would have some protection against disease if exposed.

3. CASE AND CONTACT DEFINITIONS

A. Clinical description

Classic diphtheria is an upper-respiratory tract illness characterized by sore throat, low-grade fever, and an adherent pseudomembrane on the tonsil(s), pharynx, and/or nose. However, disease can involve almost any mucous membrane. For clinical purposes it is convenient to classify diphtheria depending on the site of disease:

- anterior nasal diphtheria
- pharyngeal and tonsillar diphtheria
- laryngeal diphtheria
- cutaneous (skin) diphtheria

B. Laboratory criteria for diagnosis

- Isolation of *Corynebacterium diphtheriae* from a clinical specimen, or
- Histopathologic diagnosis of diphtheria

C. Case classification (2010)

1. *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.
2. *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.

D. Comment

Respiratory disease caused by either toxigenic or nontoxigenic *C. diphtheriae* should be reported as diphtheria. Cutaneous diphtheria should not be reported.

All *C. diphtheriae* isolates, regardless of association with disease, should be submitted to the Washington State Public Health Laboratories and will be sent to the Diphtheria Laboratory, National Center for Infectious Diseases, CDC. Rarely, respiratory diphtheria may result from infection with other *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*). These isolates should also be forwarded to CDC.

4. DIAGNOSIS AND LABORATORY SERVICES

A. Diagnosis

The initial diagnosis of diphtheria is usually based on the clinical presentation since it is imperative to begin presumptive therapy quickly.

Culture and toxigenicity testing: Diphtheria is confirmed by isolation of *Corynebacterium diphtheriae* on culture and by toxigenicity testing. Health care providers who suspect diphtheria should alert their laboratory that diphtheria is suspected. Culture medium containing tellurite is preferred because it provides a selective advantage for the growth of *C. diphtheriae*. However, since tellurite medium is not readily available in most laboratories, a blood agar plate can also be inoculated. If diphtheria bacilli are isolated they **must** be tested for the presence of the toxin-producing gene. A PCR assay is available at CDC for testing *C. diphtheriae* isolates for the presence of the toxin-producing gene at PHL. If the patient received antibiotics prior to specimen collection and is receiving diphtheria antitoxin (DAT), a clinical specimen can be also tested directly for the presence of the tox gene at CDC using PCR.

Serologic testing: Serum collected prior to the administration of DAT can assist with assessing the probability of the diagnosis. This may be especially helpful if antibiotics were administered prior to collection of specimens for culture. Persons with serum antibody levels less than 0.01 IU/ml are more likely to be susceptible to diphtheria while levels between 0.01–0.09 IU/ml indicate basic immunity. Testing for serum antibody levels is available at commercial laboratories.

Note: Other pathogens that can cause symptoms similar to those caused by infection with *C. diphtheriae* include other corynebacteria species, *Arcanobacterium haemolyticum*, as well as Streptococcus spp., Epstein-Barr virus and cytomegalovirus (both of which cause infectious mononucleosis syndrome). Candida albicans, bacterial anaerobes (such as the organisms associated with Vincent's angina), and some viruses may cause a membrane of

the throat and tonsils. Therefore, appropriate lab testing should be performed to rule out these conditions.

B. Tests Available at Washington State Public Health Laboratories (PHL)

PHL can culture clinical specimens for *C. diphtheriae*. All *C. diphtheriae* isolates will be forwarded to CDC. If the patient is receiving DAT, CDC will perform additional toxigenicity testing (i.e., ELEK test) to verify toxin expression.

PHL and CDC do not perform serologic testing for diphtheria.

All requests for diphtheria testing to be done at PHL or forwarded to CDC for testing must have approval from a Communicable Disease Epidemiology Section epidemiologist.

Note that PHL require all clinical specimens have two patient identifiers, a name **and** a second identifier (e.g., date of birth) both on the specimen label and on the submission form. Due to laboratory accreditation standards, specimens will be rejected for testing if not properly identified. Also include specimen source and collection date.

C. Specimen Collection

Culture specimens: Using respiratory precautions, health care providers should collect clinical specimens for culture from the nose or nasopharynx, and throat from all persons with suspected cases. If possible, swabs also should be taken from beneath the pseudomembrane, or collection of a portion of the adherent pseudomembrane in addition to the swabs is ideal. Specimens for culture should be obtained as soon as diphtheria (involving any site) is suspected, even if treatment with antibiotics has already begun.

Throat cultures should be obtained with a cotton or Dacron[®] swab and placed in Amies or similar transport media. Clinical specimens should reach the PHL as quickly as possible after collection.

If the patient received antibiotics prior to specimen collection and the patient is receiving DAT, a clinical specimen can be tested directly for the presence of the tox gene at CDC using PCR. Respiratory specimens for PCR testing should be collected using a Dacron[®] swab and placed in a dry sterile container transported at 4° C.

In addition, collection of clinical specimens for isolation of *C. diphtheriae* from close contacts of a suspect diphtheria case (potential carriers) can aid in the presumptive diagnosis of suspect diphtheria cases who have received antibiotic therapy prior to specimen collection.

Presumptive diphtheria isolates and clinical specimens should be submitted with a completed DOH microbiology form available at:

<http://www.doh.wa.gov/EHSPHL/PHL/Forms/Microbiology.pdf>

For additional information regarding laboratory testing for diphtheria, see:

<http://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.pdf>

5. ROUTINE CASE INVESTIGATION

Interview the case and/or others who might be able to provide pertinent information.

A. Evaluate the Diagnosis

Review the clinical presentation, risk factors for exposure, and immunization status to determine the likelihood of the diagnosis. Immediately consult with Communicable Disease Epidemiology Section (CDES) staff.

If diphtheria is highly suspected, do the following:

- Assure that the patient is in respiratory isolation with droplet precautions.
- Request that specimens are collected to confirm the diagnosis. Facilitate the transportation of specimens to the Washington State Public Health Laboratories.
- Collect serum to be held for serologic testing, as needed.
- Consult with CDES regarding the need for treatment with diphtheria antitoxin. CDES will facilitate CDC consultation as needed. Recommend the initiation of antibiotic treatment. Treatment should not be delayed pending laboratory confirmation when the diagnosis of diphtheria is strongly suspected.

If the suspicion of diphtheria is low, specimens can be sent to a commercial laboratory, but the laboratory staff should be alerted that diphtheria is included in the differential diagnosis.

B. Identify Source of Infection

Ask the patient about potential sources of infection in the 10 days prior to onset including:

- Travel out of the country, especially to an area where diphtheria is still endemic;
- Contact with persons from a country where diphtheria is still endemic; and
- Working or volunteering in a health care setting.

Searching for carriers by use of nose and throat cultures, other than among close contacts, is not ordinarily useful or indicated.

C. Identify Close Contacts

Identify all close contacts, particularly household members and others who were directly exposed to respiratory secretions of the case, and determine their immunization status. See section 6.B. for managing contacts.

D. Environmental evaluation

None

6. CONTROLLING FURTHER SPREAD

A. Infection Control Recommendations / Case Management

1. Hospitalized patients with confirmed pharyngeal diphtheria should be cared for using droplet precautions until they are off antimicrobial therapy and two cultures taken at least 24 hours apart, and at least 24 hours after cessation of antimicrobial therapy, fail to show diphtheria organisms.

2. Hospitalized patients with cutaneous diphtheria should be cared for using contact precautions until they are off antimicrobial therapy and two cultures taken at least 24 hours apart, and at least 24 hours after cessation of antimicrobial therapy, fail to show diphtheria organisms.
3. Persons with confirmed diphtheria should avoid close contact with others until two cultures taken 24 hours apart, and at least 24 hours after cessation of antimicrobial therapy, fail to show diphtheria organisms.
4. All articles soiled by respiratory or cutaneous discharges of a patient with diphtheria should be cleaned using contact precautions.
5. Persons with diphtheria should be vaccinated with diphtheria toxoid during convalescence since clinical disease does not necessarily confer immunity.

B. Contact Management

1. Close contacts with symptoms compatible with diphtheria should be referred to a health care provider for evaluation immediately.
2. All close contacts of a confirmed diphtheria case should have cultures taken from the nose and throat, regardless of their immunization status or whether symptoms are present.
3. After cultures have been collected, close contacts should receive a single dose of benzathine penicillin (IM) (600,000 units for persons less than 6 years of age and 1.2 million units for persons 6 years of age or older) or a 7–10 day course of oral erythromycin (40 mg/kg/d for children and 1 g/d for adults), regardless of their immunization status. Contacts found to have had positive cultures should have follow-up cultures done after completion of therapy to ensure that eradication of the organism has occurred.
4. Previously immunized close contacts should receive a booster dose of diphtheria toxoid if more than 5 years have elapsed since their last dose. Unimmunized contacts should initiate the primary series immediately.
5. Close contacts should watch for symptoms of diphtheria during the 7–10 days after exposure, particularly if they are unimmunized.
6. Close contacts that handle food or who work with school children should be excluded from work or school until bacteriologic examination proves them not to be carriers. (Transmission of diphtheria through raw milk has been documented.)

For additional information regarding case investigations, see the CDC VPD Surveillance Manual available at: <http://www.cdc.gov/vaccines/pubs/surv-manual/chpt01-dip.htm>

C. Environmental measures

None

7. MANAGING SPECIAL SITUATIONS

Special situations will be handled on a case by case basis. Consult with Communicable Disease Epidemiology Section.

8. ROUTINE PREVENTION

A. Immunization Recommendations

Routine immunization with diphtheria toxoid in combination with tetanus toxoid and acellular pertussis vaccine as DTaP is recommended for all children younger than 7 years of age according to the schedule below (Table). If a child has a contraindication to the pertussis vaccine, pediatric DT should be used to complete the childhood vaccination series.

Table 1: Routine Childhood DTaP Vaccination Schedule

Dose	Age	Minimal Interval
Primary 1	2 months	N/A
Primary 2	4 months	4 weeks
Primary 3	6 months	4 weeks
First Booster (1)	15–18 months	6 months
Second Booster (2)*	4–6 years	6 months
Tdap or Td Booster (3)	11–12 years	N/A**

* The booster dose is not required if the fourth dose is given on or after the fourth birthday

** Tdap can be administered regardless of interval since the last tetanus or diphtheria containing vaccine if necessary to prevent pertussis.

Booster doses of tetanus toxoid are recommended every 10 years. Tdap (which contains a pertussis antigen) is preferred over Td because adolescents and adults are susceptible to pertussis due to waning immunity; however, Td may be indicated rather than Tdap in special situations.

All adults < 65 years of age (regardless of age) should receive a single dose of Tdap instead of Td for booster immunization against tetanus, diphtheria and pertussis.

Tdap should be given as one dose in the catch-up schedule to children 7 through 18 years of age who:

- have received tetanus and diphtheria containing vaccines (DT or Td) instead of DTP/DTaP for some or all doses of the childhood series;
- have received fewer than 5 doses of DTP/DTaP or 4 doses if the fourth dose was administered at age 4 years or older; or
- have never been vaccinated against tetanus, diphtheria, or pertussis (no doses of pediatric DTP/DTaP/DT or Td).

A catch-up schedule is available in Appendix D at:

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5503a1.htm?s_cid=rr5503a1_e.

Note: In October, 2010 the Advisory Committee on Immunization Practices (ACIP) voted in favor of the following recommendation: The catch-up schedule, which was designed to provide catch up guidance for adolescents aged 11 through 18 years, now

applies to children aged 7 through 18 years. In addition, adults > 65 years of age may receive a single dose of Tdap instead of Td at the discretion of their health care provider for pertussis prevention. A provisional ACIP recommendation to this effect is pending.

For additional information regarding use of the diphtheria vaccines, adverse reactions and contraindications see the most recent Pink Book:

Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Atkinson W, Wolfe S, Hamborsky J, McIntyre L, eds. 11th ed. Washington DC: Public Health Foundation, 2009.

<http://www.cdc.gov/vaccines/pubs/pinkbook/pink-chapters.htm>

B. Prevention Recommendations

Immunization is the best way to prevent diphtheria.

ACKNOWLEDGEMENTS

This document is a revision of the Washington State Guidelines for Notifiable Condition Reporting and Surveillance published in 2002 which were originally based on the Control of Communicable Diseases Manual (CCDM), 17th Edition; James Chin, Ed. APHA 2000. We would like to acknowledge the Oregon Department of Human Services for developing the format and select content of this document.

UPDATES

January 2011:

The Legal Reporting Requirements section has been revised to reflect the 2011 Notifiable Conditions Rule revision.

Updated to include the 2010 CSTE case classification changes.