

Diphtheria !

PROTOCOL CHECKLIST

- Report immediately 24/7 by phone upon initial suspicion or laboratory test order.
- County Health Department (CHD) should notify the Bureau of Immunization (BOI) by telephone immediately at (850) 245-4342. For after-hours or weekend reporting, notify the Bureau of Epidemiology (BOE) at (850) 245-4401. BOE will notify BOI of the patient when reported directly to BOE.
- Enter available information into Merlin upon receipt of initial report.
- Review background on disease, case definition, and laboratory testing
- Contact provider
 - Is provider requesting anti-toxin?
- Facilitate laboratory collection and forwarding of isolate to Bureau of Public Health Laboratories (BPHL) and/or CDC, special media is necessary
 - Ensure testing for presence of toxin-producing gene
- Interview patient's family or guardian
 - Review disease facts
 - Modes of transmission
 - Incubation period
 - Symptoms/types of infection
 - Document prior vaccination history for Diphtheria and number of doses
 - Ask about risk factors for possible exposure
 - In the 10 days prior to onset, has patient traveled out of the country, especially to an area where diphtheria is still endemic; contact with persons from a country where diphtheria is still endemic; or worked or volunteered in a health care setting.
 - Is patient unvaccinated or partially vaccinated?
 - Is patient immunocompromised - HIV, sickle cell, asplenia, malignancy?
 - Determine if patient was hospitalized for this reported illness
 - Determine if patient is in respiratory distress
 - Document pertinent clinical symptoms and type of infection
 - Ensure appropriate antibiotic treatment and evaluate need for anti-toxin
- Identify possibly exposed contacts/family members who may be at risk
- Determine whether patient or symptomatic contact is in sensitive situation (daycare)
 - Recommend exclusion for patients or symptomatic contacts
 - Recommend prophylaxis and immunization for contacts as appropriate
- Provide education on prevention through vaccination and prophylaxis as indicated
- Address patient family's questions or concerns
- Follow-up on special situations, including exposed contacts or patient in sensitive situations
- Enter additional data obtained from interview into Merlin

Diphtheria

1. DISEASE REPORTING

A. Purposes of reporting and surveillance

1. To assist in the diagnosis of patients.
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 patient and the possibility of additional patients developing in the area, a particular concern given the large number of susceptible adults due to waning immunity.

B. Legal reporting requirements

Laboratories and physicians are required to report cases to the county health department (CHD) immediately upon suspicion or laboratory test/ order. Reports should not be delayed for laboratory confirmation. CHDs must contact the BOI immediately at (850) 245-4342 and BOI will contact the BOE. For after hours or weekend reporting, notify the Bureau of Epidemiology (BOE) at (850) 245-4401.

C. County health department investigation responsibilities

1. Begin investigation immediately. Inform BOE about possible patient/s. The BOE will assist with coordination with CDC for the 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 patient.
4. Identify and evaluate contacts; educate and recommend measures to prevent further spread from contacts. Report all confirmed and probable patients (see Section 3C) to BOE. Complete the diphtheria case form: (http://www.doh.state.fl.us/Disease_ctrl/epi/topics/crforms.html) and attach to patient's record in Merlin.

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. *C. diphtheriae* has three biotypes: gravis, intermedius, and mitis. The gravis biotype is associated with the most severe disease, but any strain may produce toxin. ALL clinical isolates of *C. diphtheriae* should be tested for toxigenicity. Nontoxigenic strains have been increasingly associated with infective 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. However, disease can involve almost any mucous membrane. Complications of diphtheria include myocarditis, neuritis, airway obstruction, and death. The fatality rate for diphtheria is

approximately 10%. 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 into 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. Progressive extension of the membrane can cause respiratory obstruction. 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, the patient can present with fever, hoarseness and a barking cough. Airway obstruction can result in coma and death.

4. **Cutaneous (skin) diphtheria**

Cutaneous diphtheria may present as a scaling rash or as clearly demarcated ulcers. Peripheral effects of the toxin are usually not evident. Since 1980, cutaneous diphtheria caused by either toxigenic or non-toxigenic strains of *C. diphtheriae* has not been reportable to the National Notifiable Disease Surveillance System (NNDSS) in the United States. Nevertheless, all *C. diphtheriae* isolates should be submitted for testing to determine whether the tox gene is present.

5. Other possible sites of infection include the conjunctiva, vulvovaginal area and external auditory canal.

Rarely, other *Corynebacterium* species (*C. ulcerans* and *C. pseudotuberculosis*) may produce diphtheria toxin and cause classic respiratory diphtheria-like illness.

C. Reservoir

Infected humans are the only reservoir.

D. Modes of transmission

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

E. Incubation period

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

F. Period of communicability

Persons are communicable for up to 48 hours after treatment with effective antibiotics. 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.

G. Treatment

The mainstay of treatment for diphtheria is prompt administration of diphtheria antitoxin. If diphtheria is strongly suspected on the basis of clinical findings, antitoxin should be given immediately after specimens for bacteriologic testing are collected 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.

Healthcare providers who suspect diphtheria should contact their CHD immediately. The CHD, in collaboration with the BOE, can assist with arranging consultation and transport of antitoxin as needed. For additional information regarding DAT, see: <http://www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/dat-main.htm>. U.S. physicians may contact the CDC's Emergency Operations Center at 770-488-7100 for consultation on the use of DAT.

In addition to diphtheria antitoxin, which is the primary therapy, patients should also be treated with erythromycin or procaine penicillin G for 14 days to stop toxin production, eradicate *C. diphtheriae* and prevent further spread.

H. Immunity

Since lifelong immunity may not be acquired after disease or inapparent infection, confirmed diphtheria patients should begin or complete an age appropriate diphtheria toxoid containing vaccination series during convalescence. Immunization with diphtheria toxoid produces prolonged but not lifelong immunity and persons should receive booster vaccination every ten years thereafter. 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.

I. Diphtheria in the United States

Diphtheria is rare in the U.S. with only 0–5 cases of infection reported annually. The last major outbreak in the U.S. occurred in Seattle, Washington. There were three outbreaks of cutaneous diphtheria in Seattle from 1972 through 1982. The first outbreak was due to a toxigenic strain while the later outbreaks were nontoxigenic strains. The last patient of toxigenic diphtheria reported in Washington occurred in 1979. Cases of infection now occur only rarely and are travel-associated since diphtheria is no longer endemic in Washington.

Between 1980 and 2005, 55 cases of diphtheria were reported in the U.S. The majority of infections (77%) were in persons 15 years of age and older, and 4 of 5 fatal cases were in unvaccinated children. Cutaneous diphtheria due to nontoxigenic strains is still known to occur, particularly among homeless persons.

3. CASE DEFINITION

A. Clinical description

An upper-respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane of the tonsil(s), pharynx, and/or nose

B. Laboratory criteria for diagnosis

- Isolation of *Corynebacterium diphtheriae* from a clinical specimen

OR

- Histopathologic diagnosis of diphtheria

C. Case classification

Confirmed: a clinically compatible case that is either laboratory confirmed or epidemiologically linked to a laboratory confirmed case

Probable: a clinically compatible case that is not laboratory confirmed and is not epidemiologically linked to a laboratory confirmed case

D. Comment

Respiratory disease caused by non-toxigenic *C. diphtheriae* should be reported as diphtheria.

All diphtheria isolates, regardless of association with disease, must be sent to the Bureau of Laboratories.

Questions regarding the follow-up of a diphtheria case should be directed to the Department of Health, Bureau of Immunization program representative at (850) 245-4342.

4. LABORATORY TESTING

A. Criteria for diagnosis

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

1. Culture and toxigenicity testing: Diphtheria is confirmed by isolation of *Corynebacterium diphtheriae* on culture and toxigenicity testing. Healthcare providers who suspect diphtheria need to 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. .

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 toxin gene at CDC using PCR.

2. 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 likely to be susceptible to diphtheria while levels between 0.01–0.09 IU/ml indicate basic immunity. Testing for levels of immunity is available at commercial laboratories.

B. Services available at Bureau of Laboratories

BPHL can culture clinical specimens for *C. diphtheriae*. BPHL can also perform PCR on *C. diphtheriae* isolates to detect the presence of the toxin-producing gene. 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.

BPHL and CDC do not perform serologic testing for diphtheria. All requests for diphtheria testing to be done at BPHL should be done in consultation with a BOE epidemiologist.

C. Specimen collection

Culture specimens: Using respiratory precautions, health care providers should collect specimens from both the throat and nasopharyngeal area including the area underneath the edge of the pseudomembrane if possible. Collection of a portion of the adherent pseudomembrane in addition to the swabs is ideal. Throat cultures should be obtained with a cotton or Dacron[®] swab and placed in Amies or similar transport media. Collection of additional specimens for submission to CDC for PCR testing is recommended at the time of collection of specimens for culture. Clinical specimens should reach the BPHL 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 at 4° C.

Suspected diphtheria isolates and clinical specimens should be submitted with a completed BPHL clinical laboratory submission form available at:

http://www.doh.state.fl.us/lab/PDF_Files/DOH_Form_DH1847_1009_v12152010.pdf

All *C. diphtheria* isolates are to be forwarded to the CDC Diphtheria Laboratory for reference testing with shipping arranged through BOE and BPHL.

For additional information regarding laboratory testing for diphtheria, see:

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

5. CASE INVESTIGATION

Interview the case-patient 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 BOE and/or BOI:

If diphtheria is highly suspected, do the following:

- Assure that the patient is in strict isolation with droplet precautions.
- Request that specimens are collected to confirm the diagnosis. Facilitate the transportation of specimens to the Bureau of Laboratories.
- Collect serum to be held for serologic testing, as needed.
- Presumptive treatment with antitoxin and antibiotics should be recommended. Consult with CDC regarding the need for treatment with diphtheria antitoxin. Treatment should not be delayed pending laboratory confirmation when the diagnosis of diphtheria is strongly suspected. BOE should be notified if antitoxin is being requested.

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.

The search 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-patient, and determine their immunization status. See below for managing contacts.

D. Environmental evaluation

None

E. Merlin data entry

Create a case in Merlin under disease code **DIPHThERIA-03290**. Enter the data collected into Merlin, being sure to include all required fields on the Basic Data screen, complete the Case Symptoms screen, and attach all relevant labs. Please attach **ALL** labs received via electronic laboratory reporting (ELR).

6. CONTROLLING FURTHER SPREAD

A. Infection control recommendations / Case-patient management

1. Hospitalized patients with 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 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 immediately as treatment with antitoxin should be initiated.

2. Close contacts should have cultures taken from the nose and throat, regardless of their immunization status or the presence of symptoms.
3. After collecting cultures, 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/day for children and 1 g/d for adults), regardless of their immunization status. Contacts who are found to have positive cultures should have cultures repeated 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 or partially immunized contacts should initiate or complete the primary series immediately according to the ACIP recommended schedule as age appropriate.
5. Close contacts should watch for symptoms of diphtheria during the 7–10 days after exposure, particularly if they are unimmunized.
6. Close contacts who handle food or 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.)
7. Confirmed carries should receive an appropriate course of antibiotic therapy and cultures repeated at 2 weeks.

For additional information regarding case-patient 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 the BOE.

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: 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
Primary 4*	15–18 months	6 months

Booster** 4–6 years

* The fourth dose may be administered at 12 months, provided at least 6 months have elapsed from the third dose.

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

In addition to the primary series given in childhood, booster doses of diphtheria toxoid are recommended every 10 years. The first booster dose may be given at 11–12 years. The ACIP recommends that this dose be given as Tdap followed by Td every 10 years. All adults < 65 years of age should receive a one-time dose of Tdap instead of the next scheduled Td for booster immunization against tetanus, diphtheria and pertussis. A single dose of Tdap, instead of the decennial Td booster, may also be given to adults aged 65 years and over especially those having or plan to have close contact with infants <12 months of age.

For additional information regarding use of the DTaP, DT, Tdap, and Td vaccines, adverse reactions and contraindications see the most recent Red Book and Pink Book (Epidemiology and Prevention of Vaccine Preventable Diseases).

B. Prevention recommendations

Immunization is the best way to prevent diphtheria.

9. IMPORTANT LINKS

A. The Pink Book: <http://www.cdc.gov/vaccines/pubs/pinkbook/default.htm#download>

B. The Red Book: <http://aapredbook.aappublications.org/>

C. Bureau of Laboratories: <http://www.doh.state.fl.us/lab/index.html>

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.