Diphtheria

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To identify diphtheria cases.
2. To prevent the spread of diphtheria.
3. To identify groups of unimmunized children and adults.

1.2 Laboratory and Physician Reporting Requirements

Physicians are required to report all cases (including suspect cases) immediately. Laboratories are required to report all isolation of Corynebacterium diphtheriae immediately.

1.3 Local Health Department Reporting and Follow-Up Responsibilities

1. Report all confirmed and presumptive acute cases (see definitions below) to the Acute and Communicable Disease Prevention (ACDP) within 24 hours.
2. Begin follow-up within 24 hours. Submit all case data electronically within 7 days of initial report.
3. Assess diphtheria immunization status of the population at risk.
4. Initiate special control measures within 24 hours of initial report:
   • Identify contacts of the case during the period of communicability.
   • As appropriate, alert physicians, hospital rooms, and other sites visited by the case during the period of communicability.

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

* C. diphtheriae * is an aerobic gram-positive bacillus. * C. diphtheriae * has four biotypes—gravis, intermedius, belfanti and mitis. All four biotypes are capable of producing an identical exotoxin. Toxic production results when the bacteria are infected by a bacteriophage containing the diphtheria gene tox.

2.2 Description of Illness

Diphtheria is an acute bacterial infection caused by toxigenic strains of * Corynebacterium diphtheriae *. The toxin causes local tissue destruction and membrane formation. It primarily affects the tonsils, pharynx, nose and larynx. Other mucous membranes, skin, and rarely the vagina or conjunctivae can also be involved.

The onset in insidious with early symptoms of malaise, sore throat, anorexia and low-grade fever. The characteristic lesion of laryngeal diphtheria in the throat is an adherent greyish-white membrane that first occurs on the tonsils, but may spread up onto the palate and involve the pharynx and result in respiratory obstruction. Laryngeal diphtheria can present as a slowly progressive croup which can result in death if the airway obstruction is not relieved.

Patients with severe pharyngeal disease may develop neck swelling, giving a characteristic “bull neck” appearance. Non-toxigenic strains of * C. diphtheriae * rarely cause local lesions, but may cause infective endocarditis.

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 (1%–2% of infections with toxigenic strains).
Diphtheria

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

2.3 Reservoir
Humans are the usual reservoirs, and carriers are usually asymptomatic.

2.4 Sources and Routes of Transmission
Transmission is most often person-to-person spread from the respiratory tract. Rarely, transmission may occur from skin lesions or articles soiled with discharges from lesions of infected persons (fomites).

2.5 Incubation Period
The incubation period of diphtheria is 2–5 days (range, 1–10 days).

2.6 Period of Communicability
Transmission may occur as long as virulent bacilli are present in discharges and lesions. The time is variable, but organisms usually persist 2 weeks or less, and seldom more than 4 weeks, without antibiotics. Chronic carriers may shed organisms for 6 months or more. Effective antibiotic therapy promptly terminates shedding.

3. CASE DEFINITIONS, DIAGNOSIS, AND LABORATORY SERVICES

3.1 Confirmed Acute Case Definition
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.

3.2 Presumptive Case Definition
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
- epidemiologic linkage to a laboratory-confirmed case of diphtheria

3.3 Services Available at the Public Health Lab
OSPfHL can culture clinical specimens for *Corynebacterium diphtheriae* and forward isolates to CDC to be tested for the diphtheria toxin gene by PCR. Submissions to CDC should go through OSPfHL unless diphtheria antitoxin has been ordered — in which case they should be sent directly to CDC (see below; also www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/downloads/dipcollection.pdf.

As soon as diphtheria is suspected, and even if antibiotic therapy has been started, see that the following are collected using respiratory precautions:
- Swabs from the throat and the nose or nasopharynx. Polyester swabs submitted from multiple sites are preferable. Either cotton or polyester swabs are acceptable for culture, but cotton swabs cannot be used for PCR testing.
- If possible, an additional swab from beneath the pharyngeal pseudomembrane.
- If possible, a portion of the adherent pseudomembrane, placed in a screw-top container with a small amount of sterile saline. (This greatly increases the likelihood of culturing C. diphtheriae.)

Swabs should be placed into one of the following transport media:
- Amies
- Stuart
- Silica gel sachets

All submissions should be shipped for overnight delivery. Swabs and isolates should be shipped at ambient temperature. Tissue samples should be shipped refrigerated (on ice or ice packs).
Ship to CDC or OSPHL as follows:

- If diphtheria antitoxin has been ordered, ship directly to CDC. Each specimen or isolate submitted should be accompanied by a completed DASH form (available at www.cdc.gov/ncidod/dvbid/misc/CDC50_34.pdf.) For additional information regarding collection, storage and shipping of specimens, see www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/downloads/dipcollection.pdf.

- If diphtheria antitoxin has not been ordered, ship to OSPHL. Each specimen or isolate submitted should be accompanied by a completed OSPHL microbiology requisition forms; Oregon clinical microbiology laboratories have them.

Note: Diphtheria is now exceedingly rare in the U.S., and other pathogens can cause a pharyngeal or tonsilar pseudomembrane; these include some streptococci, *Arcanobacterium haemolyticum*, *Candida albicans*, some fusiform bacteria, Epstein-Barr virus, and cytomegalovirus. Encourage the patient’s physician to order appropriate tests to rule out infection by these organisms.

Serum collected prior to the administration of antitoxin can assist with assessing the probability of the diagnosis. 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, making diphtheria unlikely. Diphtheria antibody levels of 0.01–0.09 IU/ml indicate limited immunity. Testing for serum antibody levels is available at commercial laboratories.

Note: Collection of clinical specimens from close contacts of a suspect diphtheria case (potential carriers) can aid in the presumptive diagnosis of suspect diphtheria cases who may have received antibiotic therapy prior to specimen collection.

For additional information regarding laboratory testing for diphtheria, see: www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/downloads/dipcollection.pdf

### 4. ROUTINE CASE INVESTIGATION

Diphtheria is an uncommon and a rare disease in the United States. Immediate action on all highly suspect cases (including cutaneous) is warranted until they are shown not to be caused by toxigenic *C. diphtheriae*. 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. Since 1980, cutaneous diphtheria has not been a nationally reportable disease.

#### 4.1. Identify the Source of Infection

Ask the patient about potential sources of infection in the 10 days prior to onset. The source of infection for persons with diphtheria may be asymptomatic carriers (persons infected with *C. diphtheriae* bacteria in the nose and/or throat but who do not have disease symptoms). Carriers often augment the spread of the bacteria to other persons.

#### 4.2. Identify Potentially Exposed Persons

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

#### 4.3. Environmental Evaluation

None.

### 5. CONTROLLING FURTHER SPREAD

#### 5.1. Case Management

The mainstay of treatment of a case of suspected diphtheria is prompt administration of diphtheria antitoxin. This should be given without waiting for laboratory confirmation of a diagnosis. The recommended dosage and route of administration depend on the extent and duration of disease. Diphtheria antitoxin is currently available for treatment of clinical cases of respiratory diphtheria in the United States only through CDC under an FDA-approved Investigational New Drug protocol. The healthcare provider should contact CDC Emergency Operations Center (770-488-7100) to obtain diphtheria antitoxin. Strict
Diphtheria isolation should be imposed until at least two cultures are negative 24 hours after antibiotics were discontinued.

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. Treatment with erythromycin or penicillin is administered as a 14-day course.

Because diphtheria disease does not always confer immunity, an age-appropriate vaccine containing diphtheria toxoid should be administered during convalescence.

5.2. Contact Management

Identify close contacts, especially household members and other persons directly exposed to oral secretions of the patient. Culture all close contacts, regardless of their immunization status. Ideally, culture should be from both throat and nasal swabs. After culture, all contacts should receive antibiotic prophylaxis. Inadequately immunized contacts should receive DTaP/DT/Td/Tdap boosters. If fewer than three doses of diphtheria toxoid have been given, or vaccination history is unknown, an immediate dose of diphtheria toxoid should be given and the primary series completed according to the current schedule. If more than 5 years have elapsed since administration of diphtheria toxoid-containing vaccine, a booster dose should be given. If the most recent dose was within 5 years, no booster is required. Unimmunized contacts should start a course of DTaP/DT/Td vaccine and be monitored closely for symptoms of diphtheria for 7 days.

Treat any confirmed carrier with an adequate course of antibiotic, and repeat cultures at a minimum of 2 weeks to ensure 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 erythromycin and should submit samples for follow-up cultures. Treat any contact with antitoxin at the first sign of illness.

5.3. Prevention

Primary diphtheria immunization with the combination vaccine DTaP (diphtheria-tetanus toxoids-acellular pertussis vaccine) is recommended for all persons at least 6 weeks old but less than 7 years of age without a history of contraindications. The primary vaccination with DTaP consists of a three-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 15–18 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 aged 4–6 years 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.

Adolescents 11–18 years of age should receive a single booster dose of Tdap instead of Td for immunization against tetanus, diphtheria, and pertussis if they have completed the recommended childhood DTP/DTaP vaccination series. Thereafter, routine booster doses of Td vaccine should be given at 10-year intervals. Adolescents and adults who have never been vaccinated against diphtheria should receive a primary series of three doses of Td/Tdap. The first two 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 should be one of the doses in the 3-dose primary series, preferably the first one. Td is preferred to TT for adults as part of wound management if the last dose of Td was received five or more years earlier.

For added protection against pertussis, adults 19 years and older should receive a single dose of Tdap to replace a single routine booster dose of Td, if they received their last dose of Td 10 or more years earlier and have not previously received a dose of Tdap.