DIPHTHERIA

1. **Agent**: Diphtheria is caused by Gram-positive *Corynebacterium diphtheriae* bacteria that produce diphtheria toxin (toxigenic strains). Important sites of infection are the respiratory mucosa (respiratory diphtheria) and the skin (cutaneous diphtheria). Rarely, other mucosa—the eye, ear, or genitals— may be infected. Respiratory diphtheria cases are very uncommon in the United States— six cases were reported during 2000-2018. Diphtheria is endemic in countries throughout Africa, Latin American, Asia, the Middle East, and parts of Europe where toxoid-containing vaccines are not in widespread use. Both respiratory and non-respiratory disease (caused by diphtheria toxin producing *Corynebacteria*) require immediate public health follow-up. Non-toxigenic infections are **much more common than toxigenic** infections. Non-toxigenic infections are typically less severe and are not vaccine-preventable, as vaccines target diphtheria toxin rather than the bacteria.

2. **Identification**:

    a. **Symptoms/Signs**: Respiratory diphtheria usually presents as membranous nasopharyngitis or obstructive laryngotracheitis. Initial symptoms include a sore throat, difficulty swallowing, malaise, and low-grade fever. The hallmark of respiratory diphtheria is the presence of a tough, grayish white pseudomembrane over the tonsils, the pharynx, or larynx. The pseudomembrane is strongly adherent and attempts to dislodge it usually result in bleeding. The membrane may progressively extend into the larynx and trachea and cause airway obstruction, which, if left untreated, can be fatal. Exam may reveal large tender cervical lymph nodes and marked swelling and edema of neck (“bull neck”).

    Absorption of the diphtheria toxin from site of infection can cause systemic complications, including damage to myocardium, nervous system and kidneys.

    Cutaneous diphtheria may present as a scaling rash or ulcer with clearly demarcated edges and membrane, but any chronic skin lesion may harbor *C. diphtheriae* along with other organisms. The systemic complications from cutaneous diphtheria with toxigenic strains appears to be less than from other sites.

    b. **Differential Diagnosis**: Bacterial and viral pharyngitis, Vincent's angina, Ludwig’s angina, infectious mononucleosis, syphilis, and candidiasis.

    c. **Diagnosis**: Diagnosis of diphtheria is confirmed by isolating C. diphtheriae and testing the isolate for toxin production by the Elek test, an in vitro immunoprecipitation (immunodiffusion) assay. Labs should be made aware of concern for *C. diphtheriae* so a tellurite medium is used for culture. Other tests, such as polymerase chain reaction (PCR) and matrix assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF), may identify *C. diphtheriae*. However, when used alone, these tests do not confirm toxin production and are considered supplemental.

3. **Incubation**: 2-5 days (range: 1-10 days).

4. **Reservoir**: Human.

5. **Source**: Discharges from nose, throat, skin, eye and other lesions of infected persons.

6. **Transmission**: Spread person-to-person by respiratory droplets and/or contact with discharges from skin lesions or fomites. Raw milk has served as a vehicle.

7. **Communicability**: In untreated people, organisms can be present in nose, throat, eye, and skin lesion discharges for 2-6 weeks. Chronic carriers may shed organisms for 6 or more months. Effective antibiotic therapy typically terminates shedding within 48 hours.

8. **Specific Treatment**:

    a. **Case**:
    - **Diphtheria Antitoxin (DAT)**: To avoid complications from circulating

diphtheria toxin, DAT can be given after clinical diagnosis. There is no need to wait for bacteriological confirmation. Antitoxin can reduce mortality but is only effective before toxin enters the cell and therefore must be administered early. However, there is a 10% risk of hypersensitivity and/or serum sickness, so sensitivity screening should be performed. This product is available to U.S. physicians under an FDA-approved Investigational New Drug (IND) protocol. Physicians requesting DAT should contact the LA County Vaccine Preventable Disease Control Program (VPDCP) at 213-351-7800 during normal working hours to arrange for its release from the CDC Quarantine Station at Los Angeles International Airport. After working hours, contact the Administrative Officer of the Day through the County Operator at 213-974-1234.

- **Antibiotics:** Appropriate antibiotic therapy should be administered for at least 14 days to kill the organism and prevent further toxin production. Antibiotic choices include:
  - Erythromycin (10 mg/kg/dose up to maximum of 500 mg 4 times a day for 14 days)
  - Procaine Pencillin G (300,000 units IM every 12 hours for patients <10 kg, and 600,000 units IM every 12 hours). After patient is able to tolerate oral intake, can switch to oral penicillin V (250 mgs four times a day) for a total of 14 days.

Repeat nose and throat cultures should be obtained 24 hours after completion of therapy until 2 consecutive cultures taken 24 hours apart are negative.

- **Immunizations:** Because disease doesn't confer immunity, vaccine (Tdap or Dtap) should be administered during convalescence.

REPORTING PROCEDURES

1) Report confirmed or suspected case immediately by telephone (Title 17, Section 2500, *California Code of Regulations)*. Call VPDCP during working hours (213-351-7800). After working hours, contact the Administrative Officer of the Day through County Operator (213-974-1234).

2) **Report Form**: **DIPHTHERIA CASE REPORT (CDPH 8579).**

3) **Definitions**:

   a) **CSTE Diphtheria Case Definitions (2019) Clinical Criteria**
   - **Respiratory:** Upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx OR
   - **Non-respiratory:** Infection of a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa)

   b) **Laboratory Criteria** - Confirmatory laboratory evidence includes:
   - Isolation of *C. diphtheriae* from any site AND
   - Confirmation of toxin-production by Elek test or by another validated test capable of confirming toxin production
   - If antibiotic therapy was started prior to specimen collection with a negative culture, 2 sources can support a presumptive diagnosis
     (1) Positive PCR for diphtheria gene
     (2) Isolation of *C. diphtheriae* from cultures of specimens from close contacts

   c) Supportive laboratory evidence: Histopathologic diagnosis

   d) Epidemiologic linkage requires direct contact with a laboratory-confirmed case of diphtheria

Case:

Confirmed case:

- 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.

Suspected case:

- 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

Contact:

Has had face-to-face contact to a case within 5 days of case's onset of symptoms

Carrier:
Is an asymptomatic primary contact with positive culture for toxigenic *C. diphtheriae*

Chronic carrier:
Has been free from the symptoms of diphtheria for 4 weeks or longer and who harbors virulent diphtheria bacilli. Consider as a case.

NOTE: When *C. diphtheriae* or other diphtheroids are seen on smears from colonies, the lab reports this as positive. However, confirmation requires further biochemical studies, showing toxin production.

4) **Epidemiologic Data to be collected for suspected or confirmed cases:**

a) Date of onset.

b) Clinical history, signs and symptoms, nature and location of membrane

c) History of exposure.

d) Laboratory data.

e) Immunization history of case: dates, dose, and type.

f) Identification of household contacts.

g) Treatment:
- DAT: date, hour, units, route administered, manufacturer
- Antibiotics: date, dosage, interval in between doses, duration
- Other medications; dosage dates.

h) Travel history 2 weeks prior to onset, contact with travelers or immigrants (within incubation period).

INFECTION CONTROL OF CASE, CONTACTS & CARRIERS

Public Health Nursing Protocol:
Home visit is required – a face to face interview is required.

Refer to "Public Health Nursing Home Visit REQUIRED Algorithm" (B-73, Public Health Nursing Home Visit Protocol).

CASE (Confirmed or suspected): Isolate all cases using contact and droplet precautions

- Public Health home visit is required per B73, Public Health Nursing Home Visit Protocol.
- Release after 2 negative nose and throat cultures, taken not less than 24 hours apart and at least 24 hours after antibiotic treatment stopped.
- Isolation may be terminated if bacilli are not virulent (*California Code of Regulations*, Section 2566).
- If case dies, refer to **Part III, MORTICIANS AND CEMETERIES**.

CONTACTS:

Members of the family and intimate contacts (caretakers, relatives, friends who regularly visit home) and medical staff exposed to oral or respiratory secretions of case should be examined, cultured (nose and throat), given vaccine and considered for antimicrobial prophylaxis as described below:

Immunization for contacts:

1) A fully immunized person exposed to a case or carrier should be given a booster dose of a preparation containing diphtheria toxoid (DtaP, Tdap) if they have not received one within 5 years.
2) All under-immunized contacts (defined as having received less than 3 doses of

diphtheria toxoid or whose immunization status is unknown) should be immunized according to the Advisory Committee on Immunization Practice's requirement for their age.

Antibiotic prophylaxis for contacts:

Close contacts, regardless of their immunization status, should receive antimicrobial prophylaxis with oral erythromycin (10 mg/kg/dose 4 times a day for 7 days, maximum dose 500 mgs/dose) or a single IM dose of penicillin G benzathine (600,000 U for persons weighing less than 30 kg and 1.2 million U for persons weighing 30 kg or more).

Quarantine for contacts:

1) A nurse or physician visits all contacts under quarantine daily to observe and detect suspect cases. Symptomatic contacts are isolated until cultures rule out diphtheria. Begin antitoxin at first signs of illness.
    a. Release 7 days after last exposure to case or carrier.

2) Contacts who work in a sensitive occupation and school children should be removed from work or school until adequately prophylaxed as above.

CARRIERS: Routine and Chronic**.**

1) If carrier is a contact to a virulent case, isolate until carrier's virulence is determined. Carriers with positive virulence should be handled as a case.

2) A carrier with negative virulence or whose contact was to an avirulent case may be treated with antibiotic therapy as for all primary contacts and released after 7 days from case's onset.

PREVENTION-EDUCATION

1) Stress importance of routine immunization of all. Immunization for diptheria is required for school entry. California law requires exclusion from school if immunization status does not comply with *California Code of Regulations*, Title 17, regulations.

2) An assessment of immunization levels in the community should be initiated. Special outreach clinics and increased health education should be made available to susceptible populations. Immunize high-risk groups including household or intimate contacts, personnel working with cases or carriers, hospital personnel including nurses and medical students, school contacts.

3) Primary immunization advised for cases and carriers who have received antitoxin.

4) Use pasteurized milk.

5) Disinfect fomites

6) Cover skin breakdown and discharges from lesions.

DIAGNOSTIC PROCEDURES

1. **Culture**: Call Public Health Laboratory, General Bacteriology Section.

   Container: Bacterial Culturette, or if available, Diphtheria Culture Kit.

   Laboratory Form: **Test Requisition and Report Form H-3021**

   Examination Requested: Diagnosis of C. diphtheria

   Material: Nasal, nasopharynx, and throat specimens collected on separate swabs (cotton or synthetic swab), placed into separate Bacterial Culturettes. For symptomatic cases, material should be obtained from beneath the "adherent membrane", on the pharyngeal tonsillar area of the oral cavity. Portions of the membrane may be collected and submitted in sterile saline.

   If specimen cannot be transported to Public Health Laboratory within 8 hours, keep cool in refrigerator (do not freeze) until lab pick-up the next day. Ship with a cold pack. Specimens should be transported and received in the PHL within 24 hours of collection.

2. **Virulence Testing**:

   a. Noncutaneous Case: If *C. diphtheriae* is

found on cultures of nose or throat specimens, isolate should be sent to Public Health Lab. Once identification is verified, the Public Health Lab will send to the Centers for Disease Control and Prevention (CDC) Laboratory for virulence testing.

b. Cutaneous Case: Specimens are very unlikely to be toxigenic; however, testing should be performed to rule out toxin production. Diphtheria in non-respiratory sites became reportable in 2019.

c. Carrier: If carrier is a contact to a virulent case, then carrier's specimen should be sent to Public Health Lab, and then to the CDC Laboratory for virulence testing. Virulence testing is not recommended for specimens obtained from a carrier whose contact was to an avirulent case.

INFECTION CONTROL:

For respiratory diphtheria, droplet precautions in addition to standard precautions are indicated until 2 negative cultures collected separated by 24 hours at least 24 hours after antimicrobial therapy.