Diphtheria is an acute disease caused by toxin-producing strains of the bacterium *Corynebacterium diphtheriae*¹. Diphtheria is rarely reported in the United States². Prior to universal childhood immunization, diphtheria was a major cause of illness and death among children, and half of people who acquired diphtheria died³. Diphtheria is still considered to be endemic in some low to middle income countries with low vaccine coverage³. Complications include myocarditis, neuritis, paralysis, pneumonia and respiratory failure, and death¹.

**A. Agent**

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae*⁴. *C. diphtheriae* is an aerobic, gram-positive bacillus. Toxin production (toxigenicity) occurs only when the bacillus is itself infected (lysogenized) by specific viruses (corynebacteriophages) carrying the genetic information for the toxin (*tox* gene). Diphtheria toxin causes the local and systemic manifestations of diphtheria. *C. diphtheriae* has four biotypes: gravis, intermedius, mitis, and belfanti. All biotypes can become toxigenic and cause severe disease. All isolates of *C. diphtheriae* should be tested for toxigenicity⁴.

**B. Clinical Description:**

Clinical features of diphtheria depend on the mucous membrane affected and whether the strain is toxigenic or nontoxigenic¹. Sites of infection include mucosal membranes and the skin². The pharynx and tonsils are the most common mucosal sites of infection¹. The following five classifications of diphtheria infection are described:

I. Anterior Nasal Diphtheria – Similar to the common cold, fairly mild symptoms¹

II. Pharyngeal/Tonsillar Diphtheria – Most common, symptoms include a bluish-white membrane covering tonsils to most of soft palate, low grade fever, malaise, sore throat, membrane can result in respiratory obstruction, may result in death¹

III. Laryngeal Diphtheria – symptoms include fever, hoarseness, barking cough, and development of membrane, may result in death¹

IV. Cutaneous Diphtheria – In the US, most often associated with the homeless population, symptoms include rash or ulcers, infection can occur in any chronic skin lesion¹

Other rare sites of infection include the external auditory canal and mucous membranes of vulvovaginal and conjunctival areas ³.

**C. Reservoirs:**

Humans are the only known reservoir².

**D. Mode of Transmission:**

Diphtheria can be spread person to person by direct or droplet contact, and can also be spread by articles soiled with discharge from skin lesions or raw milk².
**E. Incubation Period:**
The incubation period usually is 2 to 5 days (range, 1–10 days)\(^4\).

**F. Period of Communicability:**
Period of communicability is variable, but is typically two weeks or less although can be up to four weeks for respiratory diphtheria\(^2\). Carriers may shed *C. diphtheriae* for six months or longer\(^2\). Diphtheria is not contagious 48 hours after the start of appropriate antibiotics\(^1\).

**G. Susceptibility and Resistance:**
Infants of immune mothers are thought to be immune up to six months of life\(^2\). In most cases, lifelong immunity is acquired after infection\(^2\). There are currently four vaccines that are used to prevent diphtheria, all are combination vaccines: DTaP, Tdap, DT, and Td\(^1\). The vaccine, when given properly and on the correct schedule, confers a protective level of more than 95%\(^1\).

*For Children:*
5 doses of DTaP are recommended for ages 2 months, 4 months, 6 months, 15-18 months and 4-6 years \(^1\)
1 dose of Tdap is recommended at 11-12 years\(^1\)

*For Adults:*
Tdap or Td booster is recommended every 10 years\(^1\)

Diphtheria toxoid efficacy:
- 95% in adults with 3 doses and infants with 4 doses\(^1\)

**H. Treatment**
Diphtheria is treated with diphtheria antitoxin in conjunction with appropriate antibiotic therapy with erythromycin or penicillin\(^4\). Both should be administered immediately following specimen collection\(^4\). Antitoxin is available through the CDC, through their Emergency Operations Center and can be requested in collaboration with the state health department\(^1\). Before antitoxin is given, tests for sensitivity to horse serum should be performed\(^4\). Erythromycin should be given either orally or parenterally for 14 days, or penicillin G procaine given intramuscularly for 14 days\(^4\). Immunization against diphtheria should be done during convalescence from diphtheria\(^4\). For cutaneous diphtheria, the lesion should be thoroughly cleaned with soap and water and appropriate antimicrobial treatment should be given for 10 days\(^4\).

**I. Clinical Case Definition\(^5\):**
Diphtheria is caused by toxin-producing Corynebacterium diphtheriae (*C. diphtheriae*). This disease primarily manifests as respiratory infections that may result in death, but it may also present as mild infections in non-respiratory sites, such as the skin. While respiratory diphtheria is now extremely rare, non-respiratory infections caused by toxin-producing bacteria have
recently been detected. Nonrespiratory disease caused by toxin-producing C. diphtheriae may act as a source of transmission and can lead to new respiratory and non-respiratory diphtheria disease; both respiratory and non-respiratory disease caused by toxin-producing bacteria require public health follow-up. This diphtheria surveillance case definition better reflects the epidemiology of diphtheria in the U.S., in order to focus efforts on identifying disease caused by toxin-producing bacteria and appropriately guide public health interventions.

**Clinical Criteria for Diagnosis**
- Upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx OR
- Infection of a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa)

**J. Laboratory Criteria for Diagnosis**

**Confirmatory Laboratory Evidence**
- 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

**Supportive Laboratory Evidence**
- Histopathologic diagnosis

**Epidemiologic Linkage**
- Epidemiologic linkage requires direct contact with a laboratory-confirmed case of diphtheria.

### Case Classification

<table>
<thead>
<tr>
<th>Confirmed</th>
<th>Suspect</th>
</tr>
</thead>
<tbody>
<tr>
<td>An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx and any of the following</td>
<td>In the absence of a more likely diagnosis, an upper respiratory tract illness with each of the following:</td>
</tr>
<tr>
<td>isolation of toxin-producing Corynebacterium diphtheriae from the nose or throat OR</td>
<td>an adherent membrane of the nose, pharynx, tonsils, or larynx AND</td>
</tr>
<tr>
<td>epidemiologic linkage to a laboratory-confirmed case of diphtheria.</td>
<td>absence of laboratory confirmation AND</td>
</tr>
</tbody>
</table>

**K. Classification of Import Status:**

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Laboratory Testing:
The test that is used to confirm diphtheria infection is culture and toxigenicity testing. Both throat and nasopharyngeal swabs should be collected from patients suspected of having diphtheria and their close contacts. It is recommended that the swab be collected from the area beneath the membrane if possible, or a part of the membrane can be removed for testing. The swab should be placed in semi-solid transport media (Stuart media or Amies gel). Isolates should be received by Arizona State Public Health Laboratory (ASPHL) within 24 hours of collection. ASPHL must be notified 24 hours in advance of specimen submission. If approved, isolates will be forwarded to CDC for toxin testing.

Assessing Laboratory Results:
Cultures are checked each day for growth of C. diphtheriae. Suspicious colonies are checked microscopically and identification of suspected isolates is made using biochemical tests. Cultures that are negative are held for 48 hours before being reported as negative. Any cultures that have positive growth of C. diphtheriae are sent to the Centers for Disease Control and Prevention for virulence production. Treatment should be initiated if a clinical diagnosis of diphtheria is suspected, regardless of availability of laboratory results. Isolation of C. diphtheriae is confirmatory for diphtheria infection.

Outbreak Definition:
A single case should be considered a potential outbreak.

Time Frame:
Providers must submit a report by telephone or through an electronic reporting system to the local health department within 24 hours after a case or suspect case is diagnosed, treated, or detected or an occurrence is detected. The local health agency must notify Arizona Department of Health Services (ADHS) within 24 hours after receiving a report. They must also submit an epidemiologic investigation report within 30 calendar days after receiving a report.

Forms
N/A

Investigation Steps:
- Confirm Diagnosis
- Confirm diagnosis with appropriate medical provider and case definition.
- Collect demographic data:
  - Birth date, county, sex, race/ethnicity, address, phone number(s).
- If case was hospitalized:
  - Obtain medical records including admission notes, progress notes, lab report, and discharge summary.

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• Isolates should be forwarded to ASPHL for confirmation and further testing. Respiratory disease caused by non-toxigenic *C. diphtheriae* should be reported as diphtheria. All diphtheria isolates, whether associated with disease or not should be forwarded to ASPHL.

1) **Conduct Case Investigation**
   a) Note date investigation was started. Collect information on the following:
      i) Date of illness onset, clinical and vaccine status data, hospitalizations (dates and duration of stay), site of infection (e.g. nose, throat, larynx), signs and symptoms (e.g. fever, sore throat, neck edema, high-pitched breathing), and complications (e.g. myocarditis, neuritis).
      ii) Outcome (survived or date of death), with postmortem examination results and death certificate diagnoses; treatment, including date of administration and number of units of antitoxin, antibiotics given and dosages, duration of therapy.
      iii) Laboratory: culture, biotype and toxigenicity test, PCR, molecular typing.
      iv) Vaccine information: dates and types of diphtheria vaccination, number of doses, manufacturer name, and vaccine lot number; if not vaccinated, reason for not getting vaccinated.
   b) **Determination of risk factors and transmission settings (focus within the incubation period prior to symptom onset for):**
      i) Local or international travel history during 6-week period before illness.
      ii) Onset or date of presentation to provider, include dates and location.
      iii) Contact with immigrants or returning travelers from endemic-disease areas: include dates and locations.
      iv) Source of milk supply. Contact with domestic pets, horses, or dairy farm animals.
      v) Immunization histories (both case and contacts): immunization dates and type.
   c) **Name, address, telephone, and occupation of case and contacts**
   d) **Name of school and grade of case and contacts (if applicable)**
   e) **Investigation of epi-links among cases (cluster, household, co-workers, etc.)**

2) **Conduct Contact Investigation**
   a) Focus on those in contact with case prior to (for identification of asymptomatic carriers and unreported cases) and after onset of symptoms to prevent spread.
      i) Consider the following types of contacts: household members and others with a history of direct habitual close contact including sexual contacts, healthcare staff exposed to nasopharyngeal secretions, people sharing utensils, or kitchen facilities and people caring for children.
   b) **Follow-up symptomatic contacts as suspect cases.**
      i) A contact meeting the clinical definition is considered a probable case (without laboratory results) OR
      ii) A confirmed case (with laboratory results or with epidemiological linkage to a lab confirmed case).
   c) **Focus within the incubation period prior to symptom onset for:**
      i) Local or international travel history during 6-week period before illness onset date of presentation to provider; Include dates and locations
      ii) Source of milk supply; Contact with domestic pets, horses, or dairy farm animals.
      iii) Immunization histories (both cases and contacts): immunization dates and type.

*Infection can occur in immunized and partially immunized persons, although disease is often less severe in these populations than among unimmunized persons.*
3) **Initiate Control and Prevention Measures**

Per [A.A.C R9-6-325](#), a diagnosing health care provider or an administrator of a health care institution, either personally or through a representative, shall:

a. Isolate and institute droplet precautions for a pharyngeal diphtheria case or a suspect case until:
   - Two successive sets of cultures negative for *C. diphtheriae* are obtained from nose and throat specimens collected from the case or suspect case at least 24 hours apart and at least 24 hours after cessation of treatment; OR
   - Fourteen calendar days after initiation of treatment
b. Isolate and institute contact precautions for a cutaneous diphtheria case or suspect case until:
   - Two successive sets of cultures are negative for *C. diphtheriae* are obtained from skin specimens collected from the case or suspect case at least 24 hours apart and at least 24 hours after cessation of treatment; OR
   - Fourteen calendar days after initiation of treatment.

4) **Isolation, Work and Child Care Restrictions**

a) Cases shall be excluded from food handling until two successive negative cultures from the nose and throat or skin are obtained from specimens collected at least 24 hours or more apart and 24 hours or more after cessation of treatment.

b) If the specimen is positive for *C. diphtheriae* the contact shall be considered a case and the case control measures apply.

Per [A.A.C R9-6-325](#), a local health agency shall:

a. Exclude each diphtheria contact from working as a food handler, caring for patients in a health care institution, or caring for children in or attending a school or child care establishment until a set of cultures negative for *C. diphtheriae* is obtained from the contact’s nose and throat specimen.

b. In consultation with ADHS, quarantine a contact of diphtheria, if indicated, until 2 successive sets of cultures negative for *C. diphtheriae* are obtained from nose and throat specimens collected from the contact at least 24 hours apart.

c. Offer each previously immunized diphtheria contact a vaccine containing diphtheria toxoid, and

d. Offer each unimmunized diphtheria contact the primary vaccine series and treatment.

5) **Case Management**

a) Because the condition of patients with diphtheria can deteriorate rapidly, a single dose of equine antitoxin should be administered on the basis of clinical diagnosis, even before culture results are available.

   i) Diphtheria antitoxin is currently available only through the CDC, epidemiologic and clinical information are needed prior to its release.

   ii) Patients should be tested for sensitivity to horse serum and, if necessary, desensitized before administration of the antitoxin.

b) Erythromycin or penicillin G procaine should be administered daily for 14 days to eradicate the organisms and prevent spread.

   i) Antimicrobial therapy is not a substitute for antitoxin treatment but is administered to eradicate the organism, prevent further production of toxin, and decrease the chance of further transmission.
6) **Contact Management, including Susceptible Contacts**
   a) Contacts shall be given antimicrobial prophylaxis irrespective of their immunization status:
      i) Oral erythromycin for 7 days.
      ii) Penicillin G Benzathine.
   b) Maintain a listing of all contacts and information on their signs and symptoms, immunization histories, cultures and results, prophylaxis recommendations and compliance (antibiotics and booster doses), and the disposition of the contact after 7 days of active surveillance.
      i) Symptomatic contacts are treated as suspect cases.
      ii) Asymptomatic contacts that are culture-positive are carriers, not cases.
      iii) Previously immunized contacts should receive a booster dose of diphtheria toxoid if >5 years have elapsed since their last dose.
      iv) Non-immunized contacts (those with <3 doses of unknown histories) should begin and/or continue with a primary series according to published recommendations for routine immunizations.
   c) Contacts of cutaneous diphtheria should be treated as described above; however, if the strain is shown to be non-toxigenic, investigation of contacts may be discontinued.
   d) Contacts should have cultures taken from the nose and throat and be under active surveillance for 7 days after last contact with an infectious case.
   e) Management of culture-positive secondary cases (symptomatic contacts):
      i) Treat and manage as described in Case Management section, including strict isolation for two weeks OR
      ii) Until 2 successive sets of nose and throat swabs, collected >24 hours apart, are culture negative for *C. diptheriae*.
   f) Management of carriers (asymptomatic contacts with a positive culture):
      i) Ensure that antimicrobial treatment is received.
      ii) Instruct carriers to isolate themselves from situations where they could come into close contact with inadequately vaccinated persons until after successful treatment has been received.
      iii) To ensure eradication of the organism: >24 hours after the completion of antimicrobial prophylaxis, repeat cultures with two consecutive sets of nose and throat swabs, collected >24 hours apart with the second set collected at a minimum two weeks after the antibiotic treatment.
      iv) If any culture is positive, an additional 10-day course or oral erythromycin should be administered and the cultures repeated.
   g) Close contacts of carriers should proceed with the preventive measures described for the close contacts of cases, but:
      i) Close contacts of persons with clinical diphtheria must be assigned the highest priority for preventive measures.
      ii) Contact of carriers should be given secondary priority.

The risk of developing diphtheria is sevenfold higher after household exposure to a clinical diphtheria case than after household exposure to a carrier.

7) **Notifications**

Per [A.A.C R9-6-325](#), a local healthy agency shall:
   a. Upon receiving a report of a diphtheria case or suspect case, notify ADHS within 24 hours after receiving the report and provide to ADHS the information contained in the report
   b. Conduct an epidemiologic investigation of each reported diphtheria case or suspect case; and
   c. For each diphtheria case, submit to ADHS information required under R9-6-206

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R. Outbreak Guidelines:
Refer to the general outbreak guidelines section for general information on conducting an outbreak investigation.

References


7. Arizona Administrative Code, Department of Health Services, Communicable Diseases and Infestations, Title 9, Chapter 6, Available from: http://apps.azsos.gov/public_services/title_09/9-06.pdf

CDC Diphtheria:
http://www.cdc.gov/diphtheria/index.html

CDC Immunization Schedules
Available at: http://www.cdc.gov/vaccines/schedules/hcp/index.html

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