Diphtheria

Investigative Guidelines

March 2021

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 *respiratory* diphtheria cases (including suspect cases) immediately. Laboratories are required to report all isolation of *Corynebacterium diphtheriae* immediately, day or night.

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 section (ACDP) immediately, day or night. Call 971-673-1111 to reach the state epidemiologist on call.
2. Begin investigation of all reported cases within 24 hours, chiefly to determine whether they truly have diphtheria. (Most will not.) Submit all case data electronically within 7 days of initial report.
3. 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.

1.4 State Public Heath Reporting Responsibilities

ACDP on-call epidemiologist should notify CDC Emergency Operations, immediately, day or night.

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

Corynebacterium 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, which causes the classical manifestations of diphtheria. Toxin is produced by bacteria infected by a bacteriophage containing the *tox* gene.

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

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; respiratory obstruction can ensue. Laryngeal diphtheria can present as a slowly progressive croup that 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 may be manifested by a scaling rash or by ulcers with clearly demarcated edges and membrane, but any chronic skin lesion may harbor *C. diphtheriae* along with other organisms. Generally, the organisms isolated from cases in the United States were nontoxigenic. The severity of the skin disease with toxigenic strains appears to be less than from other sites.

2.3 Reservoirs

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

Typically, 2–5 (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 Suspect Case Definition (not reportable to OHA)

In the absence of an epidemiologic linkage to either confirmed or presumptive case, any of the following:

- adherent membrane of the nose, pharynx, tonsils, or larynx; or
- isolation of *Corynebacterium diphtheriae* from the nose or throat

Note: 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*). All isolates of *C. diphtheriae*, *C. ulcerans*, and *C. pseudotuberculosis* should also be forwarded to CDC. Since 1980, cutaneous diphtheria has not been nationally notifiable.

3.4 Services Available at the Oregon State Public Health Laboratory

The OSPHL provides culture of clinical specimens and confirmation of isolates for *Corynebacterium diphtheriae.* Specimens must follow the instructions provided on the OSPHL Lab Test Menu at www.healthoregon.org/labtests. Complete the OSPHL General Microbiology Test Request Form and submit with the specimen. Oregon clinical microbiology laboratories usually have the form or it can be requested from the OSPHL.

The OSPHL forwards isolates to CDC to determine biotype, to be tested for the diphtheria toxin gene by PCR, and toxigenicity testing using the Elek test. Submissions to CDC should first be sent to the OSPHL unless otherwise approved by ACDP.

If specimens will be sent directly to the CDC or designated laboratory, pre-approval by the CDC may be needed and the CDC specimen submission instructions followed. These are available at: www.cdc.gov/diphtheria/laboratory.html. Local providers and laboratories must collaborate with the OSPHL to complete the paperwork for direct submission.

Please also complete the form titled OSPHL Specimen Information for Testing at the CDC, available at: www.bitly.com/OR-CDC-Testing. Submit this form via fax to the OSPHL General Microbiology section. The OSPHL will return to you the CDC 50.54 form to accompany the specimen.

As soon as diphtheria is suspected, and even if antibiotic therapy has been started (but antibiotics reduce the likelihood of finding it), see that the following are collected using respiratory precautions. This list is intended as a quick reference. Please follow links provided above for complete instructions.

- 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*.) This specimen type can only be tested by the CDC.

  All submissions should be shipped for overnight delivery.

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*,certain fusiform bacteria, Epstein-Barr virus, and cytomegalovirus. Encourage the patient's physician to order appropriate tests to rule out infection by these organisms.

Testing for serum antibody levels is available at commercial laboratories. Testing of serum collected prior to the administration of antitoxin can help assess 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.

Before they get prophylactic antibiotics, 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.

4. ROUTINE CASE INVESTIGATION

Diphtheria is vanishingly rare in the United States; only one case was reported during 2004–2014. Initial public health action consists of helping the clinician to obtain and ship appropriate specimens to rule out the diagnosis, and of collecting clinical, vaccination, and potential exposure information to assess the likelihood that diphtheria could be present.

4.1 Identify the Source of Infection

Ask the patient about potential sources of infection, especially travel to or exposures to persons from countries where diphtheria remains prevalent, in the 10 days prior to onset.

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

Antitoxin

The mainstay of treatment of a case of suspected diphtheria is prompt administration of diphtheria anti-toxin. Treatment with horse-derived diphtheria antitoxin, available only via Investigational New Drug protocol (www.cdc.gov/diphtheria/downloads/protocol.pdf) after consultation with ACDP and CDC, is paramount in cases of true diphtheria (see page 9-10). That said, clinical suspicion of diphtheria must be tempered by the knowledge that true diphtheria is now vanishingly rare in the United States—only 55 cases reported nationwide from 1980 to 2010. For this reason, we recommend a relatively high threshold for treatment with diphtheria antitoxin (see algorithm), but in the end will defer to the patient's physician. Contact the OHA on-call epidemiologist (971-673-1111), who can then contact CDC's Emergency Operations Center (770-488-7100) to obtain diphtheria antitoxin. The recommended dosage and route of administration depend on the extent and duration of disease. Detailed recommendations can be obtained from the package insert. Before administration, patients should be tested for sensitivity to horse serum and, if necessary, desensitized.

Antibiotics

Persons with suspected diphtheria should also receive antibiotics to eradicate carriage of *C. diphtheriae*, to limit transmission, and to halt further toxin production. The drug of choice for diphtheria is erythromycin. There are no clinical data regarding efficacy of other macrolides in the treatment of diphtheria, but *C. diphtheriae* is susceptible *in vivo* to azithromycin and to clarithromycin; these drugs are reasonable alternatives for patients who cannot tolerate erythromycin or when it is unavailable. The recommended antibiotic treatment for diphtheria is erythromycin orally or by injection (40 mg/kg/day; maximum, 2 g/day) for 14 days, or procaine penicillin G daily, intramuscularly (300,000 units every 12 hours for those weighing 10 kg or less, and 600,000 units every 12 hours for those weighing more than 10 kg) for 14 days. Oral penicillin V 250 mg

4 times daily is given instead of injections to persons who can swallow. The recommended regimen for azithromycin is infants aged <6 months: 10 mg/kg per day for 5 days; infants and children aged >6 months: 10 mg/kg (maximum 500 mg/dose) on day 1, followed by 5 mg/kg per day (maximum 250 mg/dose) on days 2 –5 and adults: 500 mg on day 1, followed by 250 mg per day on days 2 – 5. The disease is usually not contagious 48 hours after antibiotics are instituted. Elimination of the organism should be documented by two consecutive negative cultures after therapy is completed.

Strict isolation should be imposed until at least two cultures, obtained ≥24 hours after discontinuation of antibiotics, are negative. Both nasal and pharyngeal swabs should be obtained for culture.

5.2 Contact Management

Identify close contacts, especially household members and other persons directly exposed to oral secretions of the patient. Close contacts include household members and other persons who have spent *at least* 4 hours (cumulatively, within one week of index patient's onset) in close, face-to-face association with the case; **or** anyone directly exposed to the patient's nasopharyngeal secretions (e.g., via kissing, mouth-to-mouth resuscitation, intubation, or nasotracheal suctioning). Vaccination against diphtheria (with Td, Tdap, or DTaP, as appropriate; see Table below) should be recommended for all contacts who are not up to date.

Obtain from each close contact, regardless of their immunization status, both throat and nasal swabs for culture. After specimen collection, each contact should receive antibiotic prophylaxis. Azithromycin, benzathine penicillin or erythromycin are recommended. A single dose of intramuscular benzathine penicillin G (600,000 units for persons <6 years of age, and 1.2 million units for persons ≥6 years of age) or a 7- to 10-day course of oral erythromycin (40mg/kg/d for children and 1 g/d for adults) has been recommended. The recommended regimen for azithromycin is: infants aged <6 months: 10 mg/kg per day for 5 days; infants and children aged ≥6 months: 10 mg/kg (maximum 500 mg/dose) on day 1, followed by 5 mg/kg per day (maximum 250 mg/dose) on days 2 –5 and adults: 500 mg on day 1, followed by 250 mg per day on days 2 –5.

Close contacts should be monitored closely for symptoms of diphtheria for 7 days.

Recommended diphtheria toxoid vaccination for contacts, by previous vaccination history		
	≥3 doses	
<3 doses or unknown	Last dose >5 years previously	Last dose <5 years previously
Immediate dose; complete primary series according to schedule	Immediate booster dose	Children in need of their 4th primary dose or booster dose should be vaccinated; otherwise vaccination not required

Treat any confirmed carrier with an adequate course of antibiotic, and repeat cultures at a minimum of 2 weeks after completion of antimicrobial therapy 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

Immunization with the combination 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 contraindications. The primary DTaP series consists of three doses, 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 pre-school 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 ≥5 years earlier.

For added protection against pertussis, adults ≥19 years of age 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.

UPDATE LOG

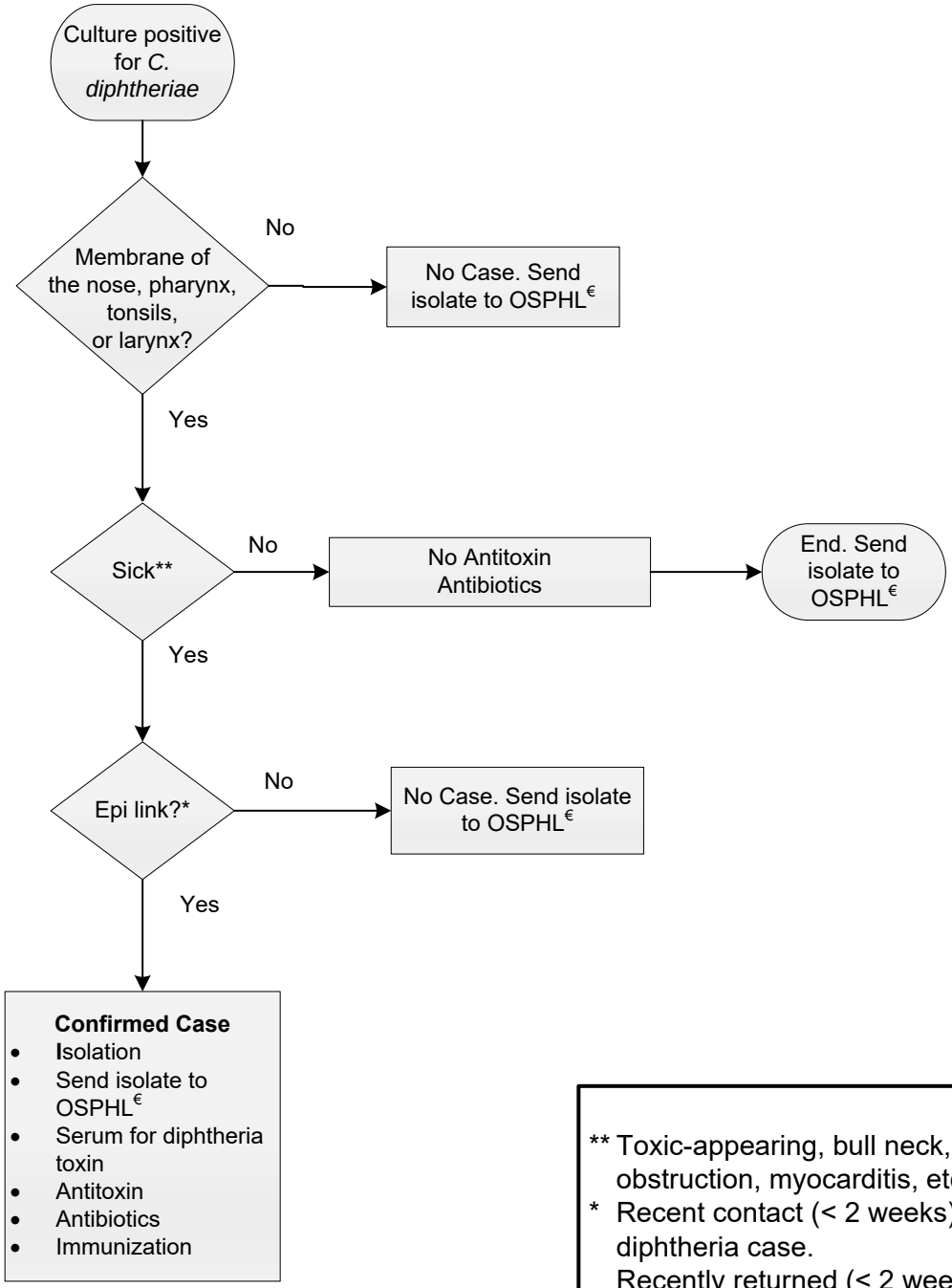
March 2021. Reporting period updated for LHDs. It's now immediately reportable. (Juventila Liko) https://secure.sos.state.or.us/oard/viewSingleRule.action;JSESSIONID_OARD=0Fu2JSSGgBnydkcVHysg6pRnTJNubDoX42LIYX9TFLuFSYf2G1P-!-1212097070?ruleVrsnRsn=268992

March 2017: Suspect case definition added. Case and contact management clarified. Reference for diphtheria antitoxin added. (Juventila Liko)

December 2015: Updated into new template. (Leslie Byster)

January 2012: Created (Paul Cieslak and Juventila Liko)

ACDP Recommendations
How to Manage a Suspect Case of Diphtheria†

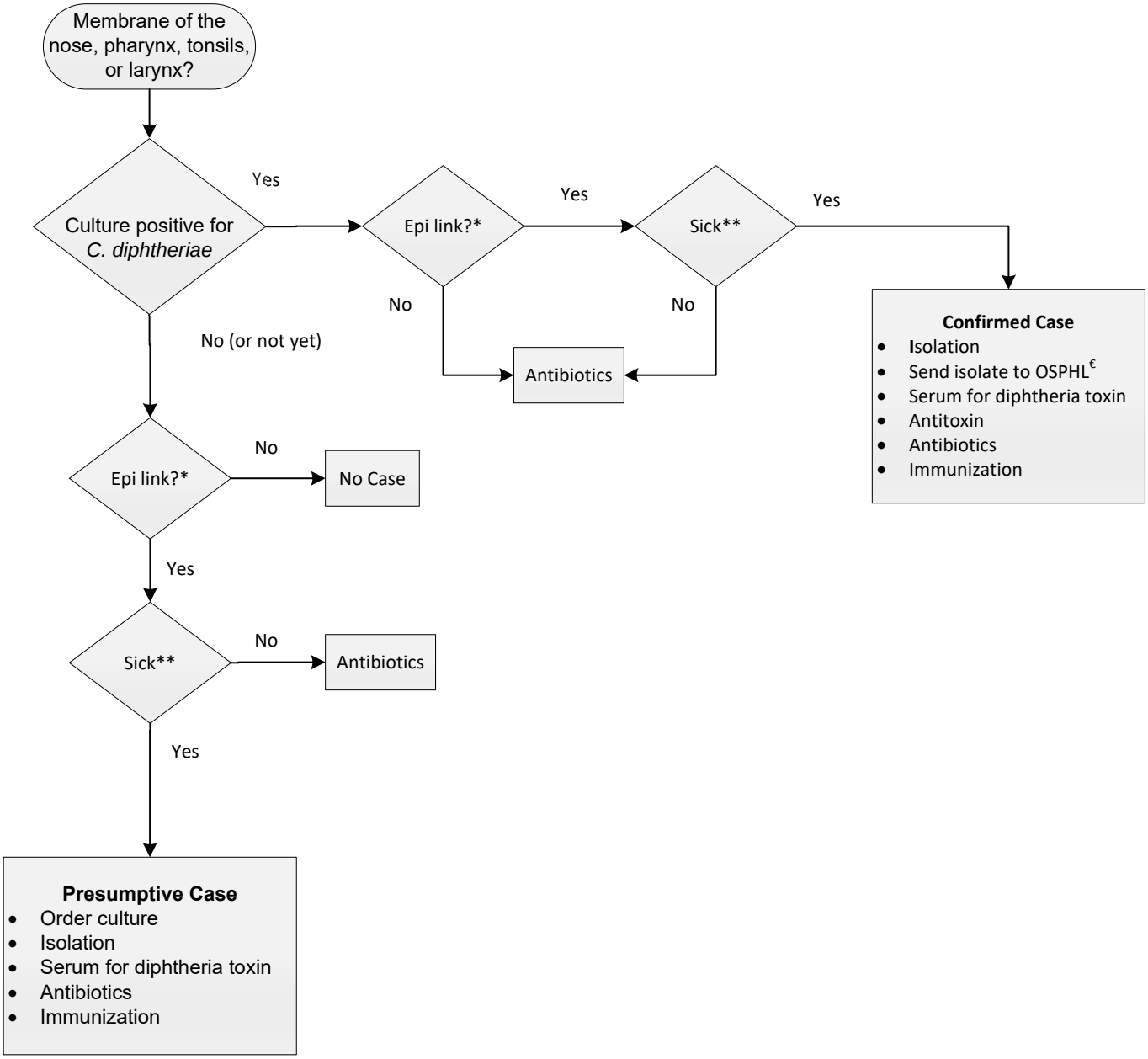


** Toxic-appearing, bull neck, airway obstruction, myocarditis, etc.

* Recent contact (< 2 weeks) with a diphtheria case.
Recently returned (< 2 weeks) from travel to area with endemic diphtheria.
Recent contact (< 2 weeks) with visitor from areas with endemic diphtheria.

€ For referral to CDC for toxin testing

† But ultimately, defer to clinician judgment



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