

Diphtheria



Public Health Branch

This protocol applies to the management of toxin-producing strains of *Corynebacterium diphtheriae*, *ulcerans* or *pseudotuberculosis* only. In recent years, no toxigenic strains of *C. ulcerans* or *C. pseudotuberculosis* have been isolated in Manitoba.

1. Case Definition

1.1 Confirmed Case:

Clinical illness* OR systemic manifestations compatible with diphtheria in a person with an upper respiratory tract infection or infection at another site (e.g., wound, cutaneous) AND laboratory confirmation of infection including at least one of the following:

- Isolation of *Corynebacterium diphtheriae*, *ulcerans* or *pseudotuberculosis* with confirmation of toxin from an appropriate clinical specimen, including the exudative membrane;
- Histopathologic diagnosis of diphtheria;

OR

Clinical illness* OR systemic manifestations compatible with diphtheria in a person with an upper respiratory tract infection or infection at another site (e.g., wound, cutaneous) AND an

* An upper respiratory tract infection (nasopharyngitis, laryngitis or tonsillitis) with or without an adherent nasal, tonsillar, pharyngeal and/or laryngeal membrane, plus at least one of the following:

- Gradually increasing stridor;
- Cardiac (myocarditis) and/or neurologic involvement (motor and/or sensory palsies) one to six weeks after onset;
- Death, with no reasonable alternative explanation (1).

epidemiologic link (contact within two weeks prior to onset of symptoms) to a laboratory-confirmed case (1).

1.2 Probable Case:

Clinical illness* in the absence of laboratory confirmation or epidemiologic link to a laboratory-confirmed case.

1.3 Carrier of Toxigenic Strain:

A person who harbours and may disseminate a toxigenic strain but who manifests no upper respiratory tract (pharyngitis or laryngitis) or systemic symptoms (2). Carriers include those with otitis media, nasal or cutaneous infections, asymptomatic pharyngeal infections or colonization due to toxigenic strains (2).

2. Reporting Requirements

Laboratory:

- All positive laboratory results for toxin-producing *Corynebacterium* species (*diphtheriae*, *ulcerans*, *pseudotuberculosis*) are reportable to the Public Health Surveillance Unit by secure fax (204-948-3044). A phone report must be made to a Medical Officer of Health at 204-788-8666 on the **same day** the result is obtained, **in addition** to the standard surveillance reporting by fax.
- Manitoba clinical laboratories are required to submit residual specimens or isolate sub-cultures from individuals who tested positive for toxigenic *Corynebacterium diphtheriae*, *ulcerans* or *pseudotuberculosis* to Cadham Provincial Laboratory (CPL) (204-945-6123) within 48 hours of report. Submitting laboratories must notify CPL of the shipment **PRIOR** to submission.

Health Care Professional:

- **Same day** reporting is required for probable (clinical) cases of diphtheria to the Public Health Surveillance Unit by telephone (204-788-6736) during regular hours (8:30 a.m. to 4:30 p.m.) **AND** by secure fax (204-948-3044) on the **same day** that they are identified. The *Clinical Notification of Reportable Diseases and Conditions* form (<http://www.gov.mb.ca/health/publichealth/cdc/protocol/form13.pdf>) should be used. After hours telephone reporting is to the Medical Officer of Health on call at (204-788-8666).
- Cooperation in Public Health investigation is appreciated when required.
- Adverse events following immunization should be reported by health care professional by completing and returning the form available at: http://www.gov.mb.ca/health/publichealth/cdc/docs/aefi_form.pdf.

Regional Public Health or First Nations Inuit Health Branch (FNIHB):

- Individuals with positive laboratory results for toxigenic *C. diphtheriae*, *ulcerans* or *pseudotuberculosis* may be cases or carriers and are referred to Regional Public Health or FNIHB for follow-up. The *Communicable Disease Control Investigation Form* (www.gov.mb.ca/health/publichealth/cdc/protocol/form2.pdf) should be completed for **all cases** and returned to the Public Health Surveillance Unit by secure fax (204-948-3044).
- Refer to section 8.1.3 for the investigation and management of both cases and carriers.

3. Clinical Presentation/Natural History

Respiratory Diphtheria:

Diphtheria presents as an upper respiratory tract illness (laryngitis, nasopharyngitis, or tonsillitis) with low-grade fever, enlarged anterior cervical lymph nodes, and a grayish adherent membrane of the nose, tonsils, pharynx, and/or larynx (2). Although not always present (particularly in people who have been immunized) (3), the membrane is typically gray, thick, fibrinous and firmly adherent (4). Symptoms include a mild fever, sore throat, difficulty swallowing, malaise and loss of appetite (5). Illness can progress to acute respiratory distress, upper airway obstruction and asphyxia in young children (5). Extensive neck swelling with cervical lymphadenitis (bull neck) is a sign of severe disease (6). The case fatality rate for respiratory diphtheria is about 5 – 10% (5, 7). Mechanical airway obstruction and myocarditis account for most diphtheria-related deaths (4). Diphtheria can occur in children and adults with incomplete immunization history (8). While vaccination is the only effective method of preventing the toxin-mediated disease, vaccinated individuals can still be infected by the bacteria and may become asymptomatic carriers of toxin-producing strains which they can transmit to others (9). As most infections in highly vaccinated populations are asymptomatic or result in a mild clinical course (without the classical pseudomembrane of the pharynx) they may remain undiagnosed and hence underreported (3, 10).

Dissemination of diphtheria toxin can cause systemic complications including myocarditis and central nervous system effects (5). Pharyngeal/tonsillar infection is the most common manifestation leading to systemic infection (11).

Cutaneous Diphtheria:

Cutaneous diphtheria may occur and is characterized by shallow skin ulcers, which can occur anywhere on the body and are usually chronic (12). To be considered a case of cutaneous diphtheria, systemic manifestations must also be present as described in the case definition. The lesions of cutaneous diphtheria are variable and may be indistinguishable from impetigo (7) and other chronic dermatologic conditions (e.g., eczema, psoriasis) (13). The ulcers are often associated with infected mosquito bites and are frequently coinfecting with pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes* which may lead to delayed diagnosis of diphtheria (12). Toxic manifestations are uncommon among immunized persons with cutaneous infection (5, 12).

4. Etiology

Diphtheria is caused by toxin-producing strains of the bacterium *Corynebacterium diphtheriae* (6). The toxin inhibits cellular protein synthesis and is responsible for local tissue destruction and pseudomembrane formation (14). The toxin produced at the site of the membrane is absorbed into the bloodstream and then distributed to the tissues of the body (14). There are four biotypes of *C. diphtheriae* (*mitis*, *intermedius*, *gravis* and *belfanti*); all of which may be toxigenic or nontoxigenic (6). No consistent differences are found in severity of disease caused by different biotypes (15). Rarely, other *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*) may produce diphtheria toxin (16). In western Europe and the United Kingdom, toxigenic *Corynebacterium ulcerans* has increasingly been identified as the etiologic agent (17, 18) and it has also been reported in the United States (19, 20).

5. Epidemiology

5.1 Reservoir and Source:

Humans are the sole reservoir for *C. diphtheriae* (6). *C. ulcerans* is a commensal in animals and has been isolated from a wide host of domestic and wild animals, which may serve as a reservoir for human infection (19, 21). *Corynebacterium pseudotuberculosis* is a significant pathogen in animals, particularly sheep (22).

5.2 Transmission:

Diphtheria is transmitted by person-to-person spread by respiratory droplets and close physical contact (5, 15, 18). Rarely, transmission may occur by contact with articles soiled with excretions of infected persons (5). Immunized individuals can still be infected by *C. diphtheriae* and can become asymptomatic carriers of toxin-producing strains (9).

Cutaneous carriage of *C. diphtheriae* is an important source of person-to-person transmission of the pathogen, particularly in communities where vaccination coverage is low (9).

Transmission from cutaneous diphtheria lesions can cause both respiratory and cutaneous disease in susceptible contacts (9). Cutaneous lesions appear to be important in transmission in warm climates or under conditions of poor hygiene (15).

Handling of infected dairy animals and consumption of contaminated milk have been associated with respiratory diphtheria-like disease caused by *C. ulcerans* and *C. pseudotuberculosis* (6, 18, 19). Transmission of *C. ulcerans* from a cat (23), dogs (24, 25) and a pig (26) resulting in human diphtheria have been documented. No direct evidence has been found of person-to-person spread of *C. ulcerans* or *C. pseudotuberculosis* (17).

5.3 Occurrence:

General: In temperate climates, diphtheria occurs year round but most often during the colder months, probably because of close contact of children indoors (15). In the tropics, seasonal trends are less distinct; inapparent, cutaneous, and wound diphtheria are much more common (7). Cutaneous diphtheria is endemic in tropical areas (12) and common among the urban homeless (6).

Diphtheria is endemic in the independent states of the former Soviet Union, Africa, Latin America, Asia, the Middle East, and parts of Europe where childhood immunization coverage with diphtheria toxoid-containing vaccines is suboptimal (6). From 1980 to 2000, reported cases of diphtheria globally decreased from 97,774 to 9,594 (15). Globally, in 2014, 7,321 cases of diphtheria were reported to the World Health Organization (27). Respiratory diphtheria – like illnesses caused by toxigenic strains of *C. ulcerans* are increasingly reported from developed countries (19). In 2012, 27 confirmed cases of diphtheria were reported by the European Union, 11 of which were caused by *C. ulcerans* (28). Most of the cases were in adults ≥ 65 years of age (28). The overrepresentation of reported cases in the elderly suggests either waning immunity in the absence of booster doses or a lack of high vaccination coverage in the past (28).

Canada: From 1992 to 2013, between zero and four cases of diphtheria were reported per year nationally (29). The last death due to diphtheria in Canada was reported in 2010 (11).

Manitoba: Seven cases of diphtheria (two were respiratory) were reported to Manitoba Health, Seniors and Active Living between 2003 and 2015 inclusive. No diphtheria related deaths were evident in these cases. Cases ranged in age from two to 86 years of age. The most recently reported case was in 2011, in a two year old immunized female.

5.4 Incubation Period:

The incubation period is usually two to seven days but occasionally is longer (6).

5.5 Risk Groups:

Unimmunized or inadequately immunized travellers to areas with endemic diphtheria (e.g., the Indian sub-continent, Africa, South East Asia) (18) are at higher risk of acquiring disease (5). Pre-school and school age children are most often affected by respiratory diphtheria (15). Diphtheria is rare in infants younger than six months of age, presumably because of the presence of maternal antibody, and rare among adults, especially those living in urban areas, as a result of acquired immunity (15). Travel does not appear to be a major risk factor for acquiring diphtheria caused by *C. ulcerans* (18). However, handling infected dairy animals and consuming contaminated milk have been associated with respiratory diphtheria-like disease caused by *C. ulcerans* and *C. pseudotuberculosis* (6, 18, 19).

5.6 Period of Communicability:

In untreated persons, the bacterium is present in discharges from the nose and throat and from the eye and skin lesions for two to six weeks after infection (6). Patients treated with an appropriate antimicrobial agent usually are communicable for less than four days (6). Asymptomatic carriers may shed organisms for six months or longer (5, 11).

6. Diagnosis

Respiratory diphtheria should be considered in the differential diagnosis of membranous pharyngitis that includes streptococcal pharyngitis, Vincent angina, infectious mononucleosis, oral syphilis, oral candidiasis, and adenoviruses (7). Presumptive diagnosis is based on observation of a whitish/grayish membrane, especially if extending to the uvula and soft palate, in

association with tonsillitis, pharyngitis or cervical lymphadenopathy, or a serosanguinous nasal discharge. The laboratory should be notified as soon as the diagnosis of diphtheria is suspected since the successful isolation of *C. diphtheriae* depends on the rapid inoculation of special culture media. If symptoms are suggestive of diphtheria, please indicate on the requisition “suspect *C. diphtheriae*”. Acceptable specimens include throat, nasopharyngeal or ear swabs or a swab from a skin lesion in transport medium. If possible, swabs should also be taken from beneath the membrane, or a piece of the membrane should be removed and submitted. Swabs should be taken before antibiotic therapy is initiated. If diphtheria is strongly suspected, specific treatment with antitoxin and antibiotics should be initiated while studies are pending, and should be continued even in the face of a negative laboratory report (refer to section 8.1). Toxigenicity tests are performed on all *C. diphtheriae*, *ulcerans*, *pseudotuberculosis* isolated. Demonstration of toxin production from the organism confirms the diagnosis of diphtheria.

Serology is used for immune status testing only, not for diagnosis.

7. Key Investigations for Public Health Response

- Immunization histories of all cases, carriers and contacts.
- Travel history of cases (i.e., travel to diphtheria-endemic area or an area experiencing an outbreak). High risk areas for diphtheria include but may not be limited to Indian subcontinent, South East Asia, Africa, South America, former Soviet States and Eastern Europe (3).
- Travel history of contacts (i.e., travel to diphtheria-endemic area or to an area

experiencing an outbreak) within several months of the case patient’s illness) as the contact may be the source of infection in the case (3, 4).

- If *C. ulcerans* or *C. pseudotuberculosis* is identified:
 - Investigation of animal exposures (e.g., household pets, farm animals, petting zoos) (19, 30).
 - Recent consumption of any type of unpasteurized milk or dairy products (3).
- Determine if there is a high risk for the case/carrier to transmit infection through his/her work, i.e., foodhandling/processing, work with children less than seven years of age, or health care workers with hands-on patient contact.

8. Control

8.1 Management of Cases:

8.1.1 Respiratory Diphtheria:

- If respiratory diphtheria is strongly suspected, consult Infectious Diseases On Call (204-787-2071) immediately. Diphtheria antitoxin (DAT) (only antitoxin of equine origin is available) should be given immediately after bacteriologic specimens are taken, without waiting for results. If antibiotics have already been started, specimens for culture should still be taken.
- After completion of tests to rule out hypersensitivity, a single dose of DAT is given. Refer to the manufacturer’s product monograph for method of testing for sensitivity to equine serum. The current *Red Book: Report of the Committee on Infectious Diseases* or other clinical text may also be consulted for guidance on sensitivity testing or the US Centers for Disease Control and Prevention

Guidelines

<http://www.cdc.gov/diphtheria/downloads/protocol.pdf> .

The administration of equine antitoxin under the protection of a desensitization procedure must be continuous because protection from desensitization is lost once administration is interrupted. Therefore, all efforts should be made to obtain sufficient antitoxin before treatment is started.

- The dose of antitoxin depends on the site and size of the diphtheria membrane, duration of illness, and degree of toxic effects; presence of soft, diffuse cervical lymphadenitis suggests moderate to severe toxin absorption (6). Refer also to the product monograph included with DAT. The recommended treatment dosage ranges are:
 - Pharyngeal or laryngeal disease of 2 days duration: 20,000 to 40,000 units
 - Nasopharyngeal disease: 40,000 to 60,000 units
 - Extensive disease of 3 or more days duration or any patient with diffuse swelling of the neck: 80,000 to 120,000 units (6).

Intramuscular administration usually suffices; in severe infections, both IV and IM administration may be indicated. The procedure for IV administration is detailed in the product monograph that is included with DAT.

- Diphtheria antitoxin may be ordered by an Infectious Diseases specialist or by the local Medical Officer of Health <http://www.gov.mb.ca/health/publichealth/contactlist.html> through the provincial vaccine warehouse at 204-948-1333 or Toll-free 1-855-683-3306 during regular business hours or at 204-805-4096 after

hours. After regular hours, the Medical Officer of Health on call may be contacted at 204-788-8666. Patient follow-up may be required as per Health Canada regulations for Special Access products <http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogués/index-eng.php>.

- Diphtheria antitoxin will neutralize circulating (unbound) toxin and prevent progression of disease but it will not neutralize toxin that is already affixed to tissues (14). Antimicrobial therapy is also required to eradicate the organism, stop toxin production, and prevent transmission to others (6). Acceptable regimens include erythromycin administered orally or parenterally for 14 days, penicillin G administered intramuscularly or intravenously for 14 days or penicillin G procaine administered intramuscularly for 14 days (6).
- Refer to section 8.1.5 for follow-up testing.
- Recovery from diphtheria disease does not necessarily confer immunity (5). Therefore, patients who have recovered from diphtheria should receive a complete primary course of diphtheria toxoid-containing vaccine (2) and a booster dose every 10 years as per the *Canadian Immunization Guide*. Refer to the current *Canadian Immunization Guide* for age appropriate dosing schedule. Serologic testing is not recommended before or after receiving diphtheria toxoid-containing vaccine (5).

8.1.2 Cutaneous Diphtheria:

- If the case definition for cutaneous diphtheria is met or it is strongly suspected (refer to section 1.1), consult Infectious Diseases On Call (204-787-2071) immediately.

- In most cases of cutaneous diphtheria, large-scale toxin absorption is unlikely and therefore the risk of giving antitoxin is usually considered to be substantially greater than any benefit (3). Some experts recommend 20,000 to 40,000 U of antitoxin, because toxic sequelae have been reported (6).
- Thorough cleansing of the lesion with soap and water and administration of an appropriate antimicrobial agent (refer to treatment for respiratory diphtheria above and section 8.1.5 for follow-up testing) is recommended (6).
- Immunization as per recommendations for respiratory diphtheria under section 8.1.1 above.

8.1.3 Carriers of Toxigenic Strains:

- Carriers, though not considered diphtheria cases should also be identified and managed because they may transmit the organism to others (4).
- Carriers should be given oral erythromycin or penicillin G for 10 to 14 days or a single intramuscular dose of penicillin G benzathine (600,000 U for children weighing less than 30 kg and 1.2 million U for children weighing 30 kg or more and adults) (6).
- Unimmunized carriers and those of unknown immunization status should receive an immediate dose of toxoid-containing vaccine appropriate for age and should complete the full primary course (2). Previously immunized carriers who have not received a booster dose within 10 years, should receive a booster dose of a toxoid-containing vaccine appropriate for age (2). Refer to the current *Canadian Immunization Guide* for age appropriate dosing schedule.

8.1.4 Infection Prevention and Control Measures:

- In hospitalized patients, droplet precautions are indicated for pharyngeal infection and contact precautions for cutaneous infection. Refer to the current Manitoba Health, Seniors and Active Living document *Routine Practices and Additional Precautions: Preventing the Transmission of Infection in Health Care* available at: <http://www.gov.mb.ca/health/publichealth/cdc/docs/ipc/rpap.pdf> .
- Cases/carriers who are not hospitalized should be advised to restrict contact with others until completion of an appropriate course of antibiotics (3).
- Cases/carriers should be instructed to pay strict attention to personal hygiene by:
 - Covering nose and mouth with tissue when coughing;
 - Disposing of all contaminated tissues directly into garbage containers;
 - Washing hands with soap and water or cleaning hands with alcohol based hand rub after contact with respiratory secretions or infected wounds;
 - Cleaning wounds and skin lesions vigorously with soap and water;
 - Keeping all infected wounds covered (2).
- **Exclusion:** Non-hospitalized cases should be excluded from the workplace or school until two negative cultures are obtained after completion of antibiotics (2). Exclusion of carriers may be considered under certain circumstances if risk of transmission to others is considered high. Refer to section 8.1.5 for testing procedure.

8.1.5 Follow-up Testing of Cases and Carriers:

Two consecutive cultures from each site specified below should be taken. The cultures should be taken not less than 24 hours apart, and not less than 24 hours after cessation of antimicrobial therapy to ensure elimination of the organism (6). If any culture is positive, additional therapy for 10 days should be provided, followed by two repeat follow-up cultures as described below (6).

- **Cases** should have cultures of both nose and throat. Skin lesions also require culturing in cases of cutaneous diphtheria.
- **Respiratory carriers** should have cultures of both nose and throat.
- **Cutaneous carriers** should have cultures taken from the site(s) of colonization (i.e., lesion).

8.2 Management of Contacts:

Contacts of cases include household members and other people with a history of direct, habitual close contact (including kissing or sexual contacts), health care personnel exposed to nasopharyngeal secretions, people sharing utensils or kitchen facilities, and people caring for infected children (6). Individuals who have had transient close contact should also be included as contacts if they have been directly exposed to large particle droplets or secretions (3). Health care workers who have taken appropriate additional (isolation) precautions need not be considered contacts.

Note: Contacts of carriers where toxigenic strains of *C. diphtheriae* have been isolated from the nasopharynx, oropharynx, respiratory secretions or middle ear aspirate should be managed the same as contacts of cases as defined above and described below. Contact tracing of carriers where a toxigenic strain of *C. diphtheriae* has been isolated from a wound that does not appear to be a case of cutaneous diphtheria and the patient does not meet the case definition for cutaneous

diphtheria should be considered on a case-by-case basis according to risk.

Regional Public Health/First Nations Inuit Health Branch will identify contacts and coordinate surveillance, immunization, cultures and prophylaxis as necessary.

- Contacts of cases should be prioritized over the contacts of carriers for follow-up.
- All contacts or their parent/guardian should be advised to monitor for symptoms of diphtheria for seven days from the date of last contact with the case/carrier and to contact their health care provider immediately for assessment if a sore throat and/or fever occur (6).
- Contacts should have specimens taken for culturing before any antibiotic prophylaxis is initiated (2).
- Antimicrobial prophylaxis with oral erythromycin (40-50 mg/kg per day for 10 days, maximum 2 g/day) or a single intramuscular injection of penicillin G benzathine (600,000 U for children weighing less than 30 kg and 1.2 million U for children weighing 30 kg or more and adults) should be initiated (6).
- Diphtheria antitoxin (equine) is not recommended for prophylaxis of immunized or unimmunized close contacts of diphtheria cases, due to the substantial risk of allergic reaction to equine serum (5). Also, evidence is lacking on any additional benefit of antitoxin for contacts who have received antimicrobial prophylaxis (5).
- Contacts of cases should receive a dose of diphtheria toxoid-containing vaccine as appropriate for age unless the contact has been fully immunized for age and the last dose of diphtheria toxoid-containing vaccine was given within 10 years (5). The diphtheria toxoid-containing vaccine

series should be completed for previously unimmunized or incompletely immunized contacts (5). Refer to the current *Canadian Immunization Guide* for age appropriate dosing schedule.

- **Exclusion:** Exclusion from work until throat cultures are shown to be negative should be considered for high risk asymptomatic contacts (e.g., health care workers, food handlers, especially those handling milk, those working with unimmunized persons) if they are not compliant with the antimicrobial prophylaxis and immunization recommendations detailed above.
- Contacts with positive cultures should be managed as carriers (refer to section 8.1.3). Follow-up cultures of pharyngeal specimens should be performed (refer to section 8.1.5 above) for contacts proven to be carriers, after completion of therapy (6).

8.3 Management of Outbreaks:

An outbreak is defined as the occurrence of case(s) in a particular area and period of time in excess of the expected number of cases.

- Asymptomatic carriers, rather than persons with overt disease, are usually the major source of transmission during community outbreaks (15).
- Refer to sections 8.1 and 8.2 above for case and contact management.

8.4 Preventive Measures:

- Immunization (only available in combination vaccine) of all children with diphtheria toxoid-containing vaccine is recommended at two, four and six months of age (11). This is followed by a booster dose at 18 months of age, four to six years, at 14-16 years of age and then every 10 years after (11). Diphtheria antitoxin might be less efficient for preventing

diphtheria due to *C. ulcerans* than that due to *C. diphtheriae* (25).

- Individuals travelling to countries where diphtheria epidemics are occurring should ensure that their vaccination status is up to date (11).
- Consider all immigrants who lack evidence of immunization against diphtheria as unprotected and provide immunization with diphtheria-toxoid-containing vaccines as recommended in the current *Canadian Immunization Guide*.
- Clinicians are encouraged to swab any chronic non-healing skin lesions for toxigenic *Corynebacterium species* in patients who have traveled to a diphtheria-endemic area (12).

9. References

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