Appendix 1: Case Definitions and Disease-Specific Information

Disease: Diphtheria

Effective: May 2022
Diphtheria

☒ Communicable
☒ Virulent

*Health Protection and Promotion Act* (HPPA):

*Ontario Regulation (O. Reg.) 135/18* (Designation of Diseases)

**Provincial Reporting Requirements**

☒ Confirmed case
☒ Probable case

As per Requirement #3 of the “Reporting of Infectious Diseases” section of the *Infectious Diseases Protocol, 2018* (or as current), the minimum data elements to be reported for each case are specified in the following:

- *O. Reg. 569 (Reports)* under the HPPA;
- The iPHIS User Guides published by Public Health Ontario (PHO);
- For certain vaccines, information to be entered into the applicable provincial inventory system (i.e. Panorama or COVaxON); and
- Bulletins and directives issued by PHO.

Although rare, other toxigenic *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*) may cause clinical diphtheria. Isolation of other toxigenic *Corynebacterium* species in addition to clinically compatible illness is reportable.

**Type of Surveillance**

Case-by-case

**Case Definition**

**Confirmed Case**

Clinical illness (see Clinical Evidence section) and at least one of the following:

- Isolation of *Corynebacterium diphtheriae* (*C. diphtheriae*) with confirmation of toxin from an appropriate clinical specimen (e.g., throat, nasal, nasopharyngeal or cutaneous sites, exudate of membrane)
OR
• Isolation of other toxigenic *Corynebacterium* species (*Corynebacterium ulcerans* [*C. ulcerans*] or *Corynebacterium pseudotuberculosis* [*C. pseudotuberculosis*]) from an appropriate clinical specimen (e.g., throat, nasal, nasopharyngeal or cutaneous sites, exudate of membrane)

OR
• Histopathologic diagnosis of diphtheria

OR
• Epidemiological link to a laboratory-confirmed case (contact within two weeks prior to onset of symptoms)

**Probable Case**
• Clinical illness (see Clinical Evidence section) in the absence of laboratory confirmation or in the absence of an epidemiological link to a laboratory-confirmed case.

**Outbreak Case Definition**
Not applicable.

**Clinical Information**

**Clinical Evidence**
Clinical illness is characterized as an upper respiratory tract infection (nasopharyngitis, laryngitis or tonsillitis) with 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 known cause
Clinical Presentation

Diphtheria is an acute bacterial disease primarily involving the upper respiratory tract, cutaneous, or other mucous membranes (e.g., conjunctivae, vagina).\textsuperscript{1} Respiratory diphtheria can be classified based on clinical manifestation. Anterior nasal diphtheria may appear as mild or chronic unilateral mucopurulent to serosanguinous nasal discharge and excoriations.\textsuperscript{1, 2} Onset of symptoms often cannot be distinguished from those of a common cold.\textsuperscript{2}

Pharyngeal and tonsillar diphtheria initially presents with low-grade fever, sore throat, difficulty swallowing, malaise and anorexia.\textsuperscript{2, 3} The characteristic lesion is an asymmetrical adherent greyish white membrane with surrounding inflammation visible on the tonsils and oropharynx within two to three days of illness.\textsuperscript{1, 3} Neck swelling and enlarged cervical lymph nodes may give the appearance of a “bull neck”.\textsuperscript{1} Pharyngeal membranes may extend into the trachea resulting in upper airway obstruction and subsequent acute respiratory distress; asphyxia can occur in young children.\textsuperscript{1, 3} Systemic complications from dissemination of diphtheria toxin can result in myocarditis and central nervous system effects.\textsuperscript{3}

Laryngeal diphtheria can be confined to this site or an extension of pharyngeal diphtheria, characterized by fever, hoarseness, stridor and a barking cough that can progress to airway obstruction, coma and death.\textsuperscript{2}

The case-fatality rate for respiratory diphtheria is 5% to 10%.\textsuperscript{1}

Cutaneous diphtheria is localized to the area of infection and rarely associated with systemic complications.\textsuperscript{3} Disease is often associated with infections acquired in tropical countries and has also been observed among disadvantaged populations such as homeless persons and injection drug users.\textsuperscript{2, 6, 7} Lesions may vary from scaly rash to ulcers with demarcated edges.\textsuperscript{2} Individuals with cutaneous diphtheria do not meet the surveillance case definition (see Case Definition section) but should be managed as carriers.\textsuperscript{8} Asymptomatic carriage with \textit{C. diphtheriae} is well recognized.\textsuperscript{4, 8, 9, 10} Rare case reports have suggested the possibility of asymptomatic carriage of \textit{Corynebacterium ulcerans} (\textit{C. ulcerans}) and of \textit{Corynebacterium pseudotuberculosis} (\textit{C. pseudotuberculosis}).\textsuperscript{9, 11}
Laboratory Evidence

Laboratory Confirmation
The following will constitute a confirmed case of diphtheria:

- Isolation of *C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis* with confirmation of toxin from an appropriate clinical specimen;
- Histopathologic diagnosis of diphtheria.

Approved/Validated Tests

- Standard culture for *C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis*.
- Elek* test for toxin detection.
- Consult with the laboratory prior to testing to discuss specimen collection and testing methodology.

Indications and Limitations

- All positive smears require follow-up testing for confirmation.
- Exclusive use of direct-stained smears to diagnose diphtheria is unreliable and not recommended.
- Nucleic acid amplification testing (NAAT) for diphtheria toxin gene may be performed. Positive NAAT results must be confirmed by a positive modified Elek test.
- Diphtheria serology testing has been discontinued at the Public Health Ontario Laboratories.
- Further strain characterization (i.e. biotype testing) may be indicated for epidemiological, public health and control purposes.

For further information about human diagnostic testing, contact the Public Health Ontario Laboratories or refer to the Public Health Ontario Laboratory Services webpage.

* The Elek test is an immunoprecipitation-based assay named after the bacteriologist S.D. Elek (1949) that is designed to determine if *Corynebacterium* isolates produce Diphtheria Toxin.
Case Management

In addition to the requirements set out in the Requirement #2 of the “Management of Infectious Diseases – Sporadic Cases” and “Investigation and Management of Infectious Diseases Outbreaks” sections of the Infectious Diseases Protocol, 2018 (or as current), the Board shall investigate cases to determine the source of infection. Refer to Provincial Reporting Requirements above for relevant data to be collected during case investigation.

The following disease-specific information may also be collected:

- Hospitalization: facility name, date of admission and discharge;
- Clinical: symptoms and date of symptom onset, antibiotic therapy and starting date, antitoxin treatment given and administration date;
- Laboratory: specimen type, specimen source, organism name, toxigenicity (i.e., presence of tox gene, identification of toxin using Elek test);
- Immunization status: dates of vaccination with diphtheria-toxoid containing vaccines (agent and administration dates); and
- Exposure history (i.e., travel history, close contacts who have travelled to an endemic region or during an outbreak period, consumption of unpasteurized dairy products, and animal contact, including domestic pets).

Although the surveillance case definition requires the presence of toxin by Elek test, a toxin gene polymerase chain reaction (PCR) result should be acted upon for public health management, without waiting for the Elek result.

Treatment

Medical treatment should be provided immediately without waiting for laboratory confirmation. Antitoxin should be administered as soon as possible to be effective.

Diphtheria antitoxin can be accessed through the Office of Chief Medical Officer of Health, Public Health - Ministry of Health (ministry) during business hours by calling 416-327-7392. After-hours and on weekends and holidays please call the ministry’s Health Care Provider Hotline at 1-866-212-2272.
Refer to the most current version of the ministry’s document Diphtheria Guide for Healthcare Professionals.\textsuperscript{18}

Antibiotic treatment should be provided to eliminate the organism and to prevent transmission. It is not a substitute for antitoxin. Cases should be treated with appropriate antibiotics, intramuscular procaine penicillin G or parenteral erythromycin until oral antibiotics can be safely swallowed, in accordance with treatment guidelines provided by the Public Health Agency of Canada or other expert body.\textsuperscript{10}

Active immunization against diphtheria should be undertaken during convalescence from diphtheria as disease does not necessarily confer immunity.\textsuperscript{4, 8, 9, 10}

**Management of asymptomatic carriers of toxigenic *Corynebacterium* species**

Asymptomatic carriers of toxigenic strains should be treated with antibiotics to eliminate the organism. A 10 day course of a macrolide antibiotic or single dose of intramuscular benzathine penicillin G is recommended, similar to what is advised for contacts (see Contact Management section).\textsuperscript{1} Nasal and throat swabs should be taken at least 24 hours after the completion of antibiotics to confirm eradication.

Unvaccinated and incompletely vaccinated carriers (and those of unknown immunization status) should receive an immediate dose of diphtheria-toxoid containing vaccine and complete the primary series. Please refer to immunization recommendations under management of contacts (see Contact Management section) for additional advice on immunization of asymptomatic carriers.

Contact management of asymptomatic carriers of toxigenic *C. diphtheriae* is also advised.
Contact Management

Risk of infection is directly related to duration of contact, the type of contact and intensity of exposure. Close contacts are defined as household members, persons who have had close face-to-face contact to a case such as intimate contact and health care workers exposed to oropharyngeal secretions from the case, following the same principles as contact management for invasive meningococcal disease. Individuals who have provided wound care in the absence of appropriate personal protective equipment would also be considered contacts. Contact identification and management should be completed for both cases and asymptomatic carriers of toxigenic *Corynebacterium* species.

Close contacts of cases of toxigenic *C. ulcerans* should be managed in the same way as contacts of toxigenic *C. diphtheriae* as case investigations have suggested the possibility of person to person transmission. There is no evidence at present suggesting person to person transmission of *Corynebacterium pseudotuberculosis*.

Close contacts with exposure in the 10 days prior to the onset of symptoms should be identified. In the case of asymptomatic carriers, current close contacts should be identified, unless there is a suspected time of acquisition, in which case all close contacts since that time should be identified.

The management of close contacts, especially household contacts, should include:

- Surveillance for ten days from the date of last contact with the case, regardless of immunization status.
- Education on signs and symptoms of diphtheria.
- Advice to seek medical attention immediately should they develop any clinical manifestations of diphtheria.
- Collection of laboratory specimens (nose and throat swabs, plus swabs of any skin lesions) before chemoprophylaxis. Antibiotic chemoprophylaxis is to be given to all close contacts regardless of immunization status, after laboratory specimens have been collected and regardless of culture result.
- Recommended chemoprophylaxis is a single intramuscular dose of benzathine penicillin G (600,000 units for children weighing < 30 kg or 1,200,000 units for children weighing ≥30 kg and for adults) or a 7- to 10-day
course of oral erythromycin (40 mg/kg/day for children and 1 g/day for adults, in four divided doses). For compliance reasons, if surveillance of contacts cannot be maintained, they should receive benzathine penicillin G. If erythromycin cannot be tolerated another macrolide such as azithromycin or clarithromycin should be used.

- For contacts proven to be carriers, two follow-up cultures should be obtained at least 24 hours apart and at least 24 hours after completion of antibiotic therapy. If repeat cultures are positive, an additional 10 day course of erythromycin (or other macrolide) should be given, unless susceptibility tests indicate otherwise.

- Close contacts should receive an immediate dose of a diphtheria toxoid-containing vaccine as appropriate for age unless the contact is known to have received at least 4 doses if the series was started in infancy, or 3 doses if started on or after 7 years of age and received the last dose of diphtheria toxoid-containing vaccine within the last five years.

- Unimmunized or incompletely immunized contacts should receive an immediate dose of diphtheria toxoid-containing vaccine and complete the primary series. Please refer to the Canadian Immunization Guide for further immunization advice.

- Close contacts, as defined above, who are healthcare workers, attend school or whose occupations involve food handling, close contact with children under 7 years of age or known unimmunized persons should be excluded, have their nose and throat swabbed and start chemoprophylaxis, regardless of immunization status. If the culture results are negative, they may return to work or school while completing the course of antibiotics. In cases where the initial culture is positive, they should remain excluded until chemoprophylaxis is complete and follow-up cultures, from the nose and throat (and skin lesions, if appropriate), taken at least 24 hours after the completion of antibiotics, are negative.

Contacts of cases infected with non-toxigenic Corynebacterium species, including non-toxigenic toxin gene bearing (NTTB) species, are considered to be at extremely low risk and are not routinely offered chemoprophylaxis.
Prevention and Control Measures

In the event that publicly funded antitoxin or toxoid containing vaccine doses are needed for case and contact management, the public health unit should contact the ministry immunization program at vaccine.program@ontario.ca as soon as possible.

Personal Prevention Measures

Immunize as per the current Publicly Funded Immunization Schedules for Ontario.\textsuperscript{15}

In Ontario, the Immunization of School Pupils Act (ISPA) is the legislation that governs the immunization of school pupils for the designated diseases that are included in the Act. All students without a valid exemption must have documented receipt of diphtheria toxoid-containing vaccine according to the specified schedule.\textsuperscript{16}

In Ontario, the Child Care and Early Years Act, 2014 (CCEYA) is the legislation that governs licensed child care settings. Pursuant to O. Reg. 137/15 under the CCEYA, children who are not in school and who are attending licensed child care settings must be immunized as recommended by the local medical officer of health prior to being admitted. Under the CCEYA parents can provide a medical reason as to why the child should not be immunized or object to immunization on religious/conscience grounds.\textsuperscript{17}

Diphtheria toxoid-containing vaccines are only available as combination vaccines. Completion of the primary series (three doses recommended at two, four and six months of age) induces more than 97\% protective antibody levels against diphtheria.\textsuperscript{3} The primary series is followed by three booster doses during childhood (at 18 months of age, between four to six years of age, and between 14 and 16 years of age). Adults should receive booster doses with a diphtheria toxoid-containing vaccine every ten years.\textsuperscript{3}

Infection Prevention and Control Strategies

In addition to routine practices, hospitalized confirmed or suspect cases, and carriers of toxigenic Corynebacterium species, should be cared for using the following precautions:
• Pharyngeal diphtheria: droplet precautions until two cultures from both the nose and throat collected at least 24 hours apart and at least 24 hours after completing antibiotic treatment are negative.\textsuperscript{1, 4, 8, 9, 10} Where culture is impractical, precautions may end after 14 days of appropriate antibiotic therapy.\textsuperscript{1}

• Cutaneous diphtheria: contact precautions until two cultures of skin lesions collected at least 24 hours apart and at least 24 hours after completing antibiotic treatment are negative.\textsuperscript{1, 4, 8, 9, 10}

• Non-hospitalized carriers of toxigenic \textit{Corynebacterium} species:\textsuperscript{1, 4, 10}
  
  o Exclusion from the workplace or school until two negative cultures (nasal and throat swabs) are obtained at least 24 hours after completion of antibiotics (see Treatment section).
  
  o Minimize contact with other persons in the household and practice routine and droplet precautions.

Refer to \textbf{Public Health Ontario's website} to search for the most up-to-date information on Infection Prevention and Control.

\textbf{Disease Characteristics}

\textbf{Aetiologic Agent} - Diphtheria is caused by \textit{C. diphtheriae}, an aerobic gram-positive bacillus with four biotypes: gravis, mitis, belfanti and intermedius.\textsuperscript{1, 2} Strains may be toxigenic or nontoxigenic. Only the toxigenic strains produce exotoxin and can cause serious diseases.\textsuperscript{1, 3} The nontoxigenic strains typically produce a milder clinical illness, but have been associated with infective endocarditis.\textsuperscript{1}

Whether a strain is toxigenic is assessed by the presence of the \textit{tox} gene and confirmation of toxin using the Elek test. Non-toxigenic \textit{C. diphtheriae} usually lack the entire \textit{tox} gene; however, some non-toxigenic strains carry variants of the \textit{tox} gene although they cannot produce toxin. These strains are designated as NTTB \textit{C. diphtheriae}.\textsuperscript{4} Although NTTB species are relatively rare, they have been found among Canadian laboratory isolates.\textsuperscript{5}
Modes of Transmission - Transmission of *C. diphtheriae* is most often person-to-person spread from the respiratory tract. Both cases and carriers can be a source of infection. Rarely, transmission may occur from skin lesions or articles soiled with discharges from lesions of infected persons (fomites) and can cause respiratory diphtheria in the contact. *C. ulcerans* has been associated with consumption of raw dairy products and animal contact, including domestic pets. *C. pseudotuberculosis* has been associated with contact with cattle, sheep and goats.

Incubation Period - Usually two to five days; range from one to 10 days.

Period of Communicability - Variable; until virulent bacilli have disappeared from discharges and lesions, usually two weeks or less and seldom more than four weeks for respiratory diphtheria. Chronic carriers may shed organisms for six months or more. Effective antibiotic therapy promptly terminates shedding.

Reservoir - Humans are the sole reservoir of *C. diphtheriae*. Animal reservoirs exist for other *Corynebacteria* (see above).

Host Susceptibility and Resistance - Lifelong immunity is generally, but not always, acquired following disease or inapparent infection. Infants born to immune mothers have passive protective immunity that typically lasts less than six months. Immunization with diphtheria toxoid produces prolonged but not lifelong immunity and hence the need for booster doses throughout life.

Please refer to [PHO’s Reportable Disease Trends in Ontario reporting tool](https://www.pho.on.ca/) and other reports for the most up-to-date information on infectious disease trends in Ontario. For additional national and international epidemiological information, please refer to the Public Health Agency of Canada and the World Health Organization.
References


Case Definition Sources


Document History

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