Alberta Public Health Disease Management Guidelines

Diphtheria

Alberta

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Health and Wellness Promotion Branch

Public Health and Compliance Branch

Alberta Health

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Case Definition

Confirmed Case

- An upper respiratory tract illness with an adherent pseudo-membrane of the nose, pharynx, tonsils, or larynx and any of the following:
  - isolation of toxin-producing *C. 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) in the absence of a more likely etiology with isolation of toxin-producing *C. diphtheriae* from that site.

Probable Case

- In the absence of a more likely diagnosis, an upper respiratory tract illness with each of the following:
  - an adherent pseudo-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.

Reporting Requirements

Physicians, Health Practitioners and Others

Physicians, health practitioners and others shall notify the Medical Officer of Health (MOH) (or designate) of the zone, of all confirmed and probable cases in the prescribed form by fastest means possible (FMP).

Laboratories

All laboratories shall report all positive laboratory results:

- by FMP to the MOH (or designate) of the zone, and
- by mail, fax or electronic transfer within 48 hours (two business days) to the Chief Medical Officer of Health (CMOH) (or designate).

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- The MOH (or designate) where the case currently resides shall notify the CMOH (or designate) by FMP of all confirmed and probable cases.
- The MOH (or designate) where the case currently resides shall forward the initial Notifiable Disease Report (NDR) of all confirmed and probable cases to the CMOH (or designate) within one week of notification and the final NDR (amendment) within two weeks of notification.
- For out-of-province and out-of-country reports, the following information should be forwarded to the CMOH (or designate) by phone, fax or electronic transfer within 48 hours (two business days):
  - name,
  - date of birth,
  - out-of-province health care number,
  - out-of-province address and phone number,
  - positive laboratory report, and
  - other relevant clinical / epidemiological information.

Epidemiology

Etiology

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae. C. diphtheriae* is a non-sporulating, gram positive, irregularly staining, non-motile, pleomorphic bacillus with four biotypes (gravis, mitis, intermedius, and belfanti). All four biotypes can cause toxigenic or non-toxigenic disease.[1,2] On the rare occasion, other *Corynebacterium* species such as *C. ulcerans* or *C. pseudotuberculosis* may produce the diphtheria toxin.[3]

Clinical Presentation

Diphtheria is an acute bacterial disease whose main sites of infection are the respiratory mucosa, which results in respiratory diphtheria. Symptomatic skin infections with toxin producing strains can also result in cutaneous diphtheria.[3] Occasionally, invasive infections such as bacteremia, endocarditis and arthritis can occur when the bacterium disseminates from the main site of infection.[1] Refer to Table 1 and 2 for more information on clinical manifestations.

Table 1: Respiratory Diphtheria

Types	Disease Description
Nasal[1,4,5]	• Infection of the anterior nares that is similar to a common cold. • Mucopurulent nasal discharge is often present along with a white membrane on the nasal septum. • Overall, presents as a mild infection due to poor absorption of toxin. • Antitoxin and antibiotic therapy quickly resolves infection.
Pharyngeal/ Tonsillar[1,3–5]	• Most common with infection of the pharynx and tonsil with insidious onset. • Early symptoms: sore throat, low-grade fever, anorexia and malaise. • A white and glossy pseudo-membrane appears two to three days later in the pharyngeal/tonsillar area; progresses to a dirty gray color with patches of black or green necrosis; if dislodged, results in bleeding. • 'Bull neck' appearance may be seen in severe cases due to the swelling of the anterior neck and submandibular area. • For some patients recovery may occur after infection without treatment. • Others may develop severe illness due to amount of toxin absorbed; symptoms include rapid pulse, pallor, stupor, and coma; may die within six to 10 days.
Laryngeal[1,4,6]	• May manifest as extension of pharyngeal infection or may be primary infection. • Symptoms: hoarseness, fever, respiratory stridor, cyanosis, barking cough, increased restlessness and anxiety. • Membrane can lead to coma, airway obstruction and death.

Table 2: Cutaneous Diphtheria[1,3,4,7]

Disease Description
• Lesions begin as vesicles that progress to clearly demarcated ulcers that appear similar to impetigo. Classic diphtheria lesions are usually covered with a slightly raised, dirty gray membrane.[1,5] • Mainly manifest as chronic non-healing ulcers along with other pathogens (group A streptococci and *Staphylococcus aureus*). • Can be caused by toxigenic or non-toxigenic strains of *C. diphtheria.* • More common in warmer climates and areas with overcrowding and poor hygiene. • Infection is usually mild and invasive/systemic disease is rare. • May act as a reservoir for transmission that can result in respiratory or cutaneous infections in other susceptible.

Absorption of diphtheria toxin causes systemic complications. Toxin is disseminated via blood stream from site of infection and causes damage to distant tissues and organs.[4,7] The most common complications are myocarditis, neural toxicity and renal failure.[1,4]

Respiratory diphtheria had a case fatality rate of 50% before treatment was available.[8] After immunization and treatment became more widely available, the case-fatality rate significantly declined and remains at about 5–10%. However adults over 40 years of age and young children under five years of age are known to have higher death rates of up to 20–40%.[3,4,6]

Non-toxigenic strains can cause asymptomatic carriage or mild illness such as sore throat without a membrane; however, cases of invasive disease have been reported.[2,3] Asymptomatic or mild infections can occur in partially and completely immunized individuals and populations. This results in undiagnosed and underreported cases.[7–9]

Diagnosis

Diagnosis is usually based on history, clinical presentation and laboratory testing. The successful isolation of *C. diphtheriae* depends on rapid inoculation of the specimen on special culture media that has to be prepared in the laboratory **prior** to receiving the specimen. Consequently, clinicians are advised to call the Microbiologist on call (MOC) at Alberta Public Health Laboratories (ProvLab) **prior** to specimen collection for specific instructions on how to collect and submit specimens. *C. diphtheriae* positive specimens are further assayed for the presence of diphtheria toxin. This requires an additional 48 to 72 hours. Refer to the ProvLab Guide to Services for more information on specimen collection recommendations.[10]

Isolation of *C. diphtheriae* by culture from throat specimens (including swab of membrane if present) for respiratory diphtheria and skin lesion swabs for cutaneous diphtheria, confirms diagnosis. Specimens should be collected **BEFORE** starting treatment.

With routine diphtheria immunization in Canada, the majority of cases are now mild infections. As classic respiratory diphtheria is increasingly rare in Canada, it becomes increasingly difficult for physicians to recognize and diagnose diphtheria on clinical grounds alone. However, where history and clinical presentation suggest respiratory diphtheria, it is essential to begin therapy as soon as possible to avoid complications.[2,5]

Treatment

Type	Description of Treatment
Respiratory	**Diphtheria Antitoxin** • Diphtheria antitoxin (DAT) is considered the mainstay of treatment as it neutralizes circulating toxin and prevents progression of disease. • Treatment should begin as soon as possible based on clinical symptoms and not wait for laboratory confirmation. Collect specimens prior to starting treatment, if possible. • A person's eligibility for DAT will be determined through discussion between the treating physician, MOH and CMOH. Refer to Appendix 1: Diphtheria antitoxin (DAT) procurement. – If, after the discussion, it is the decision of the treating physician to give DAT it will be released by the CMOH. The final decision to administer DAT lies with the treating physician. • For more information on use of DAT, refer to AIP and the product information sheet that comes with the product. **Antibiotics** • Antibiotic therapy with penicillin, erythromycin or another macrolide such as azithromycin or clarithromycin is required to eradicate the organism, to stop toxin production and prevent further transmission. Antimicrobial susceptibility testing may be required. • Cases should be treated for 14 days and have **two** cultures from the nose and throat collected at least 24 hours apart and at least 24 hours after completion of antibiotics. • If cultures are positive, antibiotics are required for another 10 days with repeat follow-up cultures (as described in bullet above) after completion of antibiotics. • **NOTE:** If cultures are positive after 10-day course of antibiotics, consult with an infectious disease specialist on further antibiotic treatment recommendations. • For more information, refer Appendix 2: Recommended Antibiotics for Treatment and Prophylaxis.
Cutaneous	**Antibiotics** • DAT is not recommend for cutaneous diphtheria.(2,5) • Thorough cleansing of lesion with soap and water.(2) • Antibiotic treatment with penicillin, erythromycin or other macrolide such as azithromycin or clarithromycin for 14 days is recommended.(5,6,11) Antimicrobial susceptibility testing may be required • Obtain **two** cultures from nose, throat and skin lesions at least 24 hours apart and at least 24 hours after cessation of antibiotic therapy. • If cultures are positive, an additional 10-day course of antibiotics should be given with repeat follow-up cultures (as described in bullet above) after completion of antibiotics.(2) • **NOTE**: If cultures are positive after 10-day course of antibiotics, consult with an infectious disease specialist on further antibiotic treatment recommendations.

Transmission

The most common mode of spread are via respiratory droplets or direct contact with either respiratory secretions or exudate from infected skin lesions.(3,5)

Incubation Period

Typically two to five days with a range of one to 10 days for respiratory diphtheria. The incubation period for cutaneous diphtheria maybe longer as it is not well defined.(7)

Period of Communicability

The period of communicability is variable, however, individuals with diphtheria are usually infectious as long as there is virulent bacteria present in respiratory secretions which is usually two weeks or less and seldom more than four weeks without treatment.[12,13] After completion of 48 hours of appropriate antibiotic therapy, persons are no longer communicable.[14] Asymptomatic chronic carriers colonized with *C. diphtheriae* in the nasopharynx or the skin may shed for six months or longer without effective antibiotic therapy.[14]

Host Susceptibility

Travelers to diphtheria endemic areas who are not immunized or are partially immunized are at a higher risk of infection.[2,14] Adequate immunization is extremely protective against disease caused by toxin-producing strains of *C. diphtheriae* but does not inhibit carriage, regardless of toxin-producing status.[3] Immunization against diphtheria protects the individual against the effects of diphtheria toxin but not from acquiring bacteria that cause diphtheria infection.[14] However, immunized individuals who become infected may be asymptomatic or have milder symptoms.[2,9]

Natural infection does not confer lifelong immunity therefore eligible individuals who have recovered from diphtheria infection should be offered diphtheria vaccine as per the AIP.

Incidence

Diphtheria is a nationally notifiable disease in Canada. The highest ever-recorded number of diphtheria cases in Canada was in 1921 when approximately 9,000 cases were reported. Introduction of infant and childhood immunization programs have reduced the number of reported diphtheria cases. On average, 0–5 isolates of toxigenic strains are reported each year in Canada.[14]

Toxigenic respiratory diphtheria cases are very rare in Alberta; the last case occurred prior to 1995.[15] Cutaneous diphtheria cases are more common, however only a small number (0–2 cases/year) are determined to be toxigenic.[16]

Diphtheria is endemic in the Middle East, the South Pacific, Asia, Dominican Republic, Haiti and Eastern Europe and endemicity is mainly due to low vaccination coverage in these areas.[8,17]

Public Health Management

Key Investigation

- Rapid clinical and public health responses are required to control diphtheria. The two primary goals of investigation are:
  - prompt diagnosis and management of case(s), and
  - rapid identification and effective management of close contacts in order to prevent secondary cases.
- Notify ProvLab MOC as soon as diagnosis is suspected to ensure appropriate clinical specimen(s) are collected in appropriate media prior to commencing treatment.
- Confirm diagnosis as per case definition.
- Obtain history of illness including date of onset of signs and symptoms.
- Determine diphtheria-specific immunization history:
  - number of doses,
  - date administered,
  - where the person was immunized (e.g., out of country), and
  - if not immunized, determine reason why.
- Determine possible source of infection:
  - Identify recent contact with a known diphtheria case/carrier or person with diphtheria-like illness or articles soiled with the discharges from lesions of infected individuals.
  - Identify travel history within last two weeks to a region that is endemic or experiencing a diphtheria outbreak.
  - Determine recent immigration (within last six months) from an area with known endemic disease.
  - Assess if members in the household have similar symptoms.
- Determine possible transmission settings (e.g., childcare settings, homeless shelters, overcrowded housing).
- Identify **close contacts** and assess immunization history. The risk of transmission is directly related to the closeness, duration of contact, and intensity of the exposure.
- Identify close contacts who(se):
  - have contact with children,
  - occupations involve the care of the sick and dependent,
  - occupations involve the handling of food; and
  - attend school.

Close Contact Definition

Individuals who were in contact with the case in the previous ten days AND are[5,11]

- living in the same household or share sleeping arrangements,
- sexual contacts,
- childcare and nursery school contacts,
- other individuals who had direct contamination of the nose or mouth with oral and/or nasal secretions of the case (e.g., kissing, shared cigarettes, shared drinking bottles or utensils),
- healthcare staff exposed to oropharyngeal secretions of the infected person without appropriate infection prevention and control precautions, and/or
- regular visitors in the home (e.g., grandparents, housekeeper, tutor).

Management of a Case

Case	Precautions
Respiratory	**Hospitalized case:** • Isolation, routine and droplet precautions apply until two cultures from both nose and throat taken at least 24 hours apart, and at least 24 hours after cessation of antimicrobial therapy, are negative.
	Non-hospitalized case[(A)]: • Contact precautions apply until two cultures from both nose and throat, taken at least 24 hours apart and at least 24 hours after cessation antimicrobial therapy, are negative. • Individuals with non-severe disease can be treated and followed by a community physician with support from public health professionals. Consultation with an infectious disease specialist may be required, to determine appropriate course of treatment and follow-up.
Cutaneous	**Hospitalized case:** • Routine and contact precautions apply until two cultures from both nose, throat and skin lesions, taken at least 24 hours apart and at least 24 hours after cessation of antimicrobial therapy, are negative.
	Non-hospitalized case[(A)]: • Individuals are most commonly treated and followed by a community physician with support from public health professionals. Consultation with an infectious disease specialist may be required to determine appropriate course of treatment and follow-up. • Recommend minimal contact with others until two cultures from both nose, throat and skin lesions, taken at least 24 hours apart and at least 24 hours after cessation of antimicrobial therapy, are negative. • Articles in contact with infected individual and articles soiled by discharges of the case should be washed as per normal practices.

[(A)] Examples of non-hospitalized: community/home, settings, long-term care, assisted living settings, shelter.

- Provide information about disease transmission and measures to minimize transmission.
- Instruct cases to pay strict attention to personal hygiene by:
  - covering mouth and nose with tissue when coughing,
  - placing all contaminated tissues directly into garbage,
  - washing hands with soap and water every time there is contact with respiratory secretions or infected wounds, and
  - keeping all infected wounds covered.

Case Exclusion

- The MOH **shall exclude** cases from workplace, school or childcare settings until 14 days of antibiotic therapy is completed and **two** cultures from nose, throat and/or lesions collected at least 24 hours apart and at least 24 hours after cessation of antimicrobial therapy are negative (if skin lesion/wound has healed, swab skin where lesion/wound located).

NOTE: Since infection with diphtheria does not always confer immunity, assess immunization status of persons recovering from diphtheria disease and offer immunization if necessary to complete a primary series of diphtheria containing vaccine as per AIP (as indicated by age and immunization history), unless serological testing indicates protective levels of antitoxin.

Management of Contacts

- Provide information about diphtheria disease including signs and symptoms.
- Determine the type of exposure, the setting, and the time since last exposure from the case.
- All close contacts should have a single swab for culture taken from each of the nose, the throat and skin lesions (where present).
- Collect swabs **PRIOR** to initiating antibiotic prophylaxis. See post-exposure prophylaxis section for more details.
- Refer symptomatic contacts for assessment as appropriate.
- Any asymptomatic contact identified as having a positive swab for toxigenic diphtheria should be treated as a carrier (see **Management of Carriers** section below).
- Advise asymptomatic contacts to monitor closely for symptoms for at least 10 days after their last exposure with the infected person and to notify public health if they develop symptoms.
- Determine diphtheria-specific immunization history (i.e., type of vaccine, number of doses and date of administration).
- Contacts not up-to-date for diphtheria immunization should be offered age-appropriate diphtheria containing vaccine according to the current AIP.

Contact Exclusion

- The MOH **shall exclude** contacts from the following pending first set of negative specimen results:
  - contact with children,
  - occupations involving the care of the sick and dependent,
  - occupations involving the handling of food, and
  - school.

  NOTE: For more information refer to Appendix 3: Management of Contacts and Carrier Algorithm.

Post-Exposure Prophylaxis (PEP) of Contacts

- PEP should be offered to all **close contacts** regardless of their immunization status and **AFTER** swabs from the nose, throat and skin lesions (where present) have been taken.
- Contacts are given PEP to treat incubating disease and eliminate carriage and thereby reduce risk of transmission to other susceptible contacts.[5]
- Recommended antibiotics for PEP are penicillin, erythromycin or another macrolide such as azithromycin or clarithromycin. For more information, refer to Annex 2: Recommended Antibiotics for Treatment and Prophylaxis
- There is no acceptable clinical evidence for prophylactic use of DAT for contacts.
- Eligible contacts should receive diphtheria-containing vaccine as per the *AIP* to ensure they are up-to-date for diphtheria immunization.

Management of Carriers

- A carrier is defined as a person who harbors and may transmit *C. diphtheriae* but who has no symptoms. Carriers can include those with otitis media or nasal infections and asymptomatic pharyngeal infection due to toxigenic *C. diphtheriae*.
- Carriers are **NOT** reportable to Alberta Health.
- The MOH **shall exclude** carriers from the following until completion of antibiotic therapy and **two** cultures from nose, throat and/or lesions are collected at least 24 hours apart and at least 24 hours after cessation of antimicrobial therapy are negative:
  - contact with children,
  - occupations involving the care of the sick and dependent,
  - occupations involving the handling of food, and
  - school.

  NOTE: For more information, refer to Appendix 3: Management of Contacts and Carriers Algorithm.

- If repeat cultures are positive, recommend an additional 10 day course of antibiotics[2] and continue with exclusion.
- **NOTE:** If cultures are positive after 10-day course of antibiotics, consult with an infectious disease specialist on further antibiotic treatment recommendations.
- Carriers should be instructed to pay strict attention to personal hygiene by:
  - covering mouth and nose with tissue when coughing,
  - placing all contaminated tissues directly into garbage,
  - washing hands with soap and water every time there is contact with respiratory secretions or infected wounds,
  - cleaning wounds and skin lesions vigorously with soap and water, and
  - keeping all infected wounds covered.

Treatment of Carriers

- Carriers should be given antibiotic treatment regardless of immunization status.
- Recommended antibiotics: penicillin, erythromycin or other macrolide. For more information refer to Appendix 2: Recommended Antibiotics for Treatment and Prophylaxis
- DAT has no proven role in the treatment of diphtheria carriers.
- If not fully immunized, all carriers should be offered age-appropriate diphtheria containing vaccine according to the current AIP with measures taken to ensure completion of series.

Preventive Measures

- Educate the public on the risks of diphtheria infection and the importance of immunization.
- Refer to the AIP for current diphtheria vaccine recommendations.
- Persons traveling to countries where diphtheria is endemic should ensure they are immunized.

Appendix 1: DAT Procurement

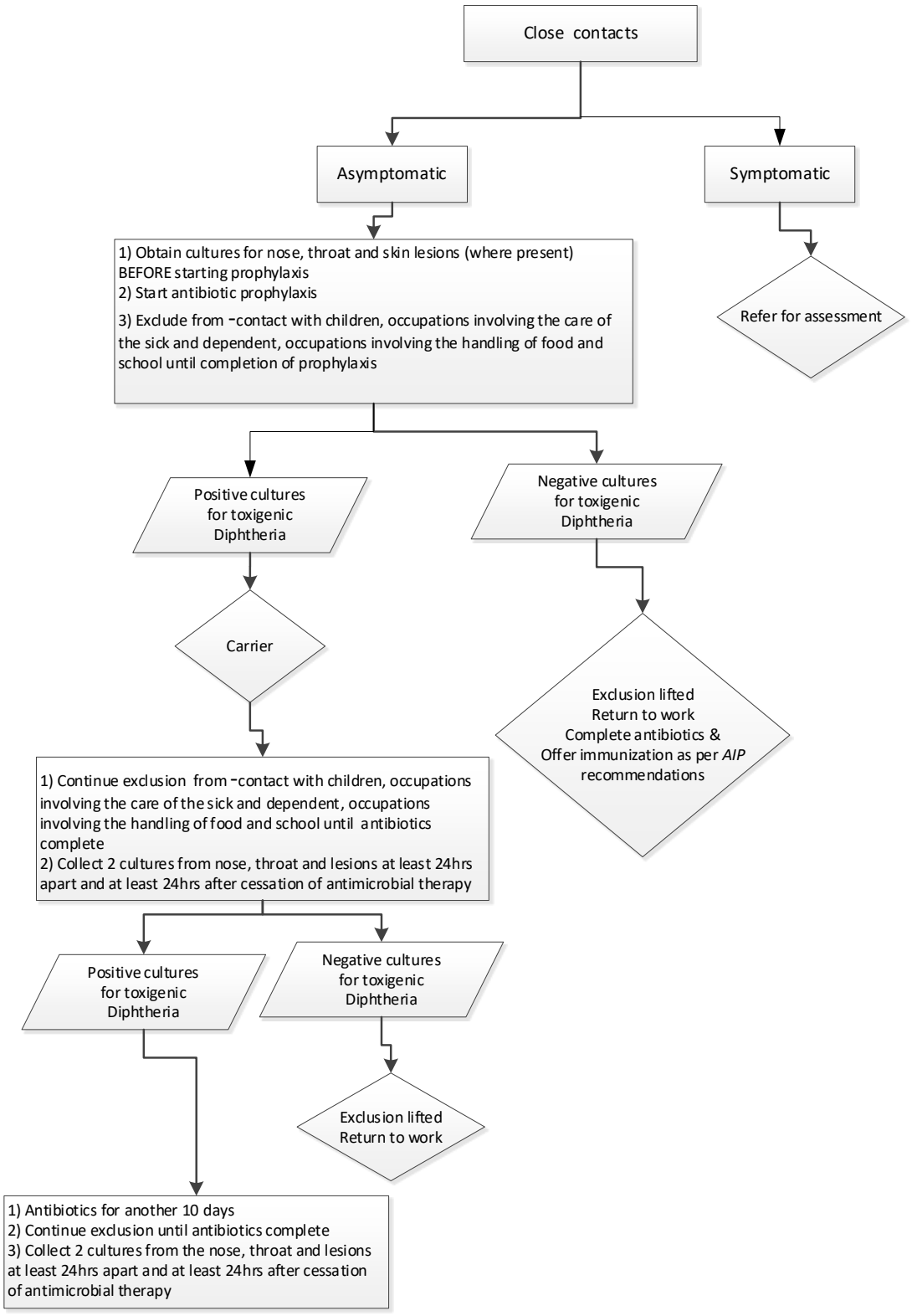
- Currently there is no licensed product made in Canada. DAT is made available from Health Canada's Special Access Program (SAP).
- The MOH (or designate) must complete an SAP "Form C" (patient follow-up form) and send it back to the CMOH: this form will accompany all shipments of DAT.
- The CMOH will communicate with the Immunization Team at Alberta Health during work hours or directly with the Provincial Vaccine Depot (VPD) on call after hours to facilitate access and shipment under strict cold-chain management from the Provincial Vaccine Depot (PVD) to the facility pharmacy by the most rapid mode of transport available.
- The CMOH will contact Health Canada's SAP for urgent delivery of more vials if required.
- **Please return if the product is not used.** If the DAT is not used, the product can be shipped (maintaining cold-chain) back to the PVD.

Appendix 2: Recommended Antibiotics for Treatment and Prophylaxis

	Antibiotic
Case[1]	**Procaine Penicillin G** 300,000 units IM every 12 hours for patients ≤10 kg 600,000 units IM every 12 hours for patients >10 kg until the patient can take oral medicine, followed by: **Penicillin V** 125mg-250 mg orally four times daily for a total treatment course of 14 days. ***OR*** **Erythromycin** 125mg-500mg orally four times a day for 14 days **Other Macrolide** *If the first two options are not available or cannot be tolerated, another macrolide such as* ***azithromycin*** *or* ***clarithromycin*** *should be used. Antimicrobial susceptibility testing may be required*
Contact/Carrier[2]	**Penicillin G benzathine** <30kg: 600,000 units IM one time ≥30kg: 1.2 million units IM one time ***OR*** **Erythromycin** Adults: 40-50mg/kg orally per day for 7-10 days (max 1g/day) **Erythromycin for pediatric population is not available in Canada as of spring 2017* ***OR*** **Other Macrolide** *If the first two options are not available or cannot be tolerated, another macrolide such as* ***azithromycin*** *or* ***clarithromycin*** *should be used. Antimicrobial susceptibility testing may be required*

NOTE: *In general, Alberta Health does not provide publically funded medications for treatment of diphtheria cases, contacts and carriers. However in order to protect the public and reduce further transmission, consideration may be given on a case-by-case basis to cover the cost of antibiotic treatment and prophylaxis.*

Appendix 3: Management of Diphtheria Contacts and Carriers



Appendix 4: Revision History

Revision Date	Document Section	Description of Revision
September 2021	General	• Updated Template • Diagnosis and Treatment section moved to Epidemiology • Updated web links

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