NICD Recommendations for the Management and Public Health Response to Diphtheria

Compiled by the Division of Public Health Surveillance and Response, National Institute for Communicable Diseases (NICD) of the National Health Laboratory Service (NHLS)

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1. Introduction and background to the recommendations

Diphtheria is an uncommon disease in South Africa. However, there is concern that there may be re-emergence of this disease as seen in other regions of the world over the past decade – most notably Eastern Europe, Southeast Asia, South America and the Indian subcontinent. Persons (most especially children) who are not vaccinated or are partially vaccinated are most at risk of diphtheria. Adults are also at risk as immunity due to vaccination wanes over time. Diphtheria is most common in areas where people live in crowded conditions with poor sanitation.

An outbreak of laboratory-confirmed toxigenic *C. diphtheriae* has been confirmed in KwaZulu-Natal Province, affecting incompletely immunized children of primary-school-going age in eThekwini and Ugu Districts. The first case in eThekwini District was identified on 14 March 2015, followed by two possibly epidemiologically-linked cases on 30 March 2015; all three cases presented with features of classical respiratory diphtheria, and one case-patient died. On 24 April 2015, two siblings with probable diphtheria were identified in Port Shepstone (Ugu District), and are still under investigation.

The recommendations in this guidance document have been derived from guidance documents produced by the World Health Organization (WHO), United Kingdom (Public Health England), and United States of America (Centers for Disease Control and Prevention, American Academy of Pediatrics). This material is intended for use by healthcare professionals. All healthcare professionals should exercise their own professional judgement in confirming and interpreting the recommendations presented in this document.

2. The disease

Diphtheria is a contagious and potentially life-threatening bacterial disease. It is caused by infection with toxin-producing (toxigenic) strains of *Corynebacterium diphtheriae*, *C. ulcerans* or rarely *C. pseudotuberculosis*.

It occurs primarily in two forms: the most common form is disease affecting the upper respiratory tract mucosa (‘respiratory’ diphtheria), and the skin (cutaneous diphtheria). Oral mucosal lesions may also occur; rarely, extra-respiratory mucosal sites may be affected (including the eye, ear or genitals).

Pathogenesis

*C. diphtheriae* is not typically invasive, and usually remains in the superficial layers of the respiratory mucosa or skin lesions; this may provoke a mild inflammatory response in the local tissues. It is not the presence of the organism but the action of diphtheria toxin produced by toxigenic strains of the organism which results in clinically significant disease. Diphtheria toxin causes local tissue necrosis which leads to inflammation, ulceration and oedema of affected tissues, and may result in the formation of a classic pseudomembrane; this accounts for the clinical signs and symptoms at the site of infection. Additionally, diphtheria toxin can be absorbed into the bloodstream, causing a variety of systemic effects including myocarditis and demyelinating peripheral neuritis. Rarely, *C. diphtheriae* may disseminate from the respiratory tract or skin to cause distant systemic infections, including bacteraemia, endocarditis and septic arthritis.
Transmission

C. diphtheriae, C. ulcerans and C. pseudotuberculosis are spread via large respiratory droplets or direct contact with infected skin lesions or respiratory secretions, or rarely by fomites. A single case of sexually transmitted toxigenic C. diphtheriae presenting as urethritis has been reported.

Humans are the only known natural host for C. diphtheriae. However, a recent report of the isolation of non-toxigenic C. diphtheriae from a cat suggests that humans might not be the only reservoir. By contrast, C. ulcerans and C. pseudotuberculosis are zoonotic diseases in humans (from domesticated or wild animals), although human-to-human transmission of these pathogens has been suggested in some cases.

Incubation period

The incubation period for respiratory diphtheria is usually 2-5 days, but may range from 1-10 days. The incubation period for cutaneous diphtheria is not well-defined and may be much longer than the range for respiratory disease.

Communicability and carriage

- Respiratory diphtheria
  Persons with respiratory diphtheria are contagious during disease, but may also be contagious during the incubation period (when they are asymptomatic), and sometimes also during convalescence (when carriage may last many weeks). Healthy people may also be asymptomatic nasopharyngeal carriers of toxigenic corynebacteria, but the duration of carriage in such persons is unknown (may be many weeks or even months). Carriage can be eradicated by appropriate antibiotic treatment.

- Cutaneous diphtheria
  Cutaneous diphtheria is likely more transmissible than respiratory diphtheria, and can cause secondary respiratory and cutaneous infections and may even be a source of outbreaks. In endemic countries, cutaneous diphtheria lesions probably act as silent reservoirs of infection.

Prevention

Diphtheria can be prevented by active immunisation with formalin detoxified diphtheria toxin (toxoid). Diphtheria toxoid immunisation effectiveness was evaluated in case-control studies during a prolonged widespread epidemic in countries of the former Soviet Union in the 1990s; three or more doses induced 95.5% (92.1 – 97.4%) protective efficacy among children <15 years. Protection increased to 98.4% (96.5-99.3%) after 5 or more doses. In South Africa, the Expanded Program of Immunisation (EPI) schedule now includes 6 doses of diphtheria vaccine. The primary series of vaccines are given in three doses at 6, 10, and 14 weeks of age using diphtheria toxoid given as DTaP-IPV/Hib (Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine and Haemophilus influenzae type b combined) or DTaP-IPV//Hib/HepB. The fourth dose (first booster) is given at 18 months using DTaP-IPV/Hib or DTaP-IPV/Hib/HepB. As from 01 February 2008, two additional booster doses have been introduced by the SA-EPI program. Diftavax® (Td) vaccine (containing tetanus and a reduced strength of diphtheria toxoid) is now administered at 6 and 12 years of age, respectively. Td vaccine has replaced DT vaccine, which was previously administered at 5 years of age. Td is licenced for use as a booster in persons ≥6 years of age.

Antitoxin (antibody) levels decline following vaccination, with the result that a high proportion (20-80%) of adults are susceptible to diphtheria. During the 1990s epidemic in countries of the former Soviet Union, 38-82% of cases occurred in adults, most of whom had received the primary series and a booster dose of diphtheria toxoid at 14-16 years of age. The World Health Organization (WHO) recommends that people living in low-endemic or non-endemic areas (South Africa can be
considered low/non-endemic) should receive booster doses approximately 10 years after completing the primary series (i.e. the 12 years of age booster in the South African EPI schedule) and subsequently every 10 years throughout life.

Diphtheria (all forms) can occur in fully vaccinated persons, though this is less common and such persons tend to present with mild disease and they rarely develop systemic toxic manifestations.

3. Epidemiology

3.1 Global epidemiology of diphtheria

Respiratory diphtheria
Historically, respiratory diphtheria occurred worldwide and was one of the leading causes of childhood deaths due to an infectious agent in the early 1900s. Following widespread immunisation programmes, diphtheria has declined or been eliminated from many developed countries. The disease remains endemic in some developing countries, including the Indian subcontinent, Haiti, Brazil, Nigeria, Indonesia, Philippines, and some Eastern Mediterranean countries. Occasional sporadic cases and clusters of diphtheria continue to be reported from low-endemic and non-endemic countries; reservoirs for disease and transmission dynamics in these settings remain obscure. There is an ever-present risk that diphtheria can re-emerge in countries where diphtheria has been eliminated or occurs rarely, and potentially cause widespread outbreaks if there is decreased immunity in the population at risk. The former Soviet Union states experienced a large epidemic of diphtheria during the 1990s, when >157 000 cases and 5 000 deaths were reported; reduced primary childhood immunisation coverage rates coupled with a large pool of susceptible non-immune adults set the stage for the largest diphtheria outbreak reported in the post-immunisation era. Diphtheria usually occurs among susceptible (i.e. non-immune) individuals, and usually reflects inadequate vaccination coverage. In the pre-immunisation era, diphtheria primarily affected children <15 years (i.e. children who had not been previously exposed to diphtheria and had not yet developed infection-induced immunity) whereas in the post-immunisation era outbreaks have also involved susceptible adults (i.e. adults who were unimmunised, or incompletely immunised – including those who received primary childhood vaccination series but no subsequent diphtheria booster doses).

The main risk factor of diphtheria is being unvaccinated or incompletely vaccinated. Diphtheria can occur in fully vaccinated persons, though this is uncommon and disease is usually mild in such cases. In temperate zones disease usually occurs during colder months with marked increases in number of cases during winter and spring seasons. Persons with asymptomatic carriage of *C. diphtheriae* act as important reservoirs for endemic and epidemic diphtheria. Fortunately, in areas of high vaccination coverage, carriage rates are markedly reduced; however, reservoirs for infection in such settings may persist and the risk of diphtheria is not entirely eliminated. Importation of toxigenic *C. diphtheriae* in symptomatic or asymptomatic travellers is also an important risk for introducing disease into susceptible populations.

Cutaneous diphtheria
Historically, cutaneous diphtheria was reported predominantly in endemic tropical countries. There are increasing case reports of travellers acquiring cutaneous diphtheria (associated with both non-toxigenic and toxigenic *C. diphtheriae*). Many of these persons were healthy travellers with no underlying disease. The travel destinations associated with exposure to *C. diphtheriae* include the Indian subcontinent, the Middle East, Africa (including Nigeria, Kenya, Angola, and more recently Mozambique), South Pacific (Indonesia, Philippines, Papua New Guinea), South East Asia (Thailand,
Cambodia, Vietnam), South America (Brazil, Dominican Republic), Haiti, and certain eastern European countries (in particular Latvia and Russia).

3.2 Epidemiology of diphtheria in South Africa

The true prevalence of disease in South Africa is unknown. However, the incidence of clinical diphtheria has been reduced by widespread childhood immunisation such that only sporadic cases of disease (mostly involving children <15 years) have been identified and reported in the last decade. Between January 2008 and March 2015, three laboratory-confirmed cases of respiratory diphtheria had been reported: two from Western Cape Province (March 2008 and January 2010), and one from Eastern Cape Province (March 2009). A case of diphtheria was identified in KwaZulu-Natal Province during March 2015, followed by further cases with at least one likely epidemiological linkage, constituting the first diphtheria outbreak reported by the province in decades.

4. Clinical features of diphtheria

a. Respiratory diphtheria

Following an average incubation period of 2 to 5 days (range 1-10 days), the onset of disease is usually gradual. There are two manifestations of disease: local (which depends on the site/s of infection, and severity of disease related to the local effects of diphtheria toxin) and systemic (due to the effects of absorbed and disseminated diphtheria toxin).

Local manifestations

i. Nasal diphtheria

A serosanguinous or seropurulent nasal discharge is typical, and is usually associated with a whitish membrane on the nasal mucosa (particularly on the septum). The disease is generally mild, and systemic signs and symptoms are rare.

ii. Typical respiratory diphtheria

The faucial area (posterior structures of the mouth and proximal pharynx) is the most common site for non-cutaneous clinical diphtheria; disease most often localised to the tonsillopharyngeal area. The presentation and course of respiratory diphtheria is variable, ranging from mild (e.g. mild pharyngitis without a pseudomembrane) to severe (e.g. toxic diphtheria). The onset is gradual (over a few days) and initial symptoms include low-grade fever, malaise, cervical lymphadenopathy and sore throat. On examination, pharyngeal erythema is noted, which may progress to isolated spots of grey and white exudate. In at least one third of cases, local diphtheria toxin production induces the formation of a pseudomembrane; in previously vaccinated individuals, the pseudomembrane is usually absent. The pseudomembrane usually begins forming on the tonsils, and may extend to involve the tonsillar pillars, uvula, soft palate, oropharynx, nasopharynx or even tracheobronchial mucosa. The membrane is initially glossy and white, but evolves to a dirty grey-white colour; necrotic green or black patches on the membrane may also be seen. The membrane is fibrinous and firmly adherent, and typically bleeds when scraped or dislodged. The extent of the pseudomembrane generally correlates with the severity of disease: localized tonsillar disease is usually mild, but involvement of posterior pharynx, soft palate and periglottal areas is often associated with more severe generalized symptoms (malaise and weakness), more severe local symptoms (including extremely painful throat, difficulty swallowing, and
drooling), and cervical swelling due to cervical lymphadenopathy and oedema of the anterior cervical tissues. Marked cervical lymphadenopathy and swelling result in the classical ‘bull-neck’ appearance of severe respiratory diphtheria, and results in respiratory stridor. Hoarseness and barking cough usually indicate laryngeal involvement, and tracheobronchial involvement is usually associated with dyspnoea and respiratory compromise. The classic presentation of toxic diphtheria is associated with extensive pseudomembranous pharyngitis, massive swelling of the tonsils, uvula, cervical lymph nodes, submandibular region, and anterior neck (‘bull neck’).

iii. **Laryngeal diphtheria**
Pharyngeal infection may extend to involve the larynx, or occasionally the infection may begin in the larynx itself. Symptoms include hoarseness and a brassy cough, and in severe cases dyspnoea and respiratory stridor. Laryngeal diphtheria presents as gradually worsening hoarseness and stridor, usually as an extension of pharyngeal involvement in children.

iv. **Tracheobronchial diphtheria**
Oedema and membrane formation in the trachea and bronchi result in respiratory compromise. In children, this is characterized by dyspnea, use of accessory respiratory muscles and inspiratory recession of intercostal, supraclavicular and substernal tissues. Urgent intubation and mechanical removal of membrane is indicated in such cases.

**Systemic manifestations**

These occur following absorption and dissemination of the diphtheria toxin through the blood stream to other organs, most importantly the heart, nervous system and kidneys. The risk of developing cardiac and/or neurological toxicity is proportional to the severity of local infection; in one large outbreak 30% of patients hospitalised with severe forms of respiratory diphtheria developed systemic manifestations, with cardiac complications being the most common. The severity of systemic manifestations is proportional to the extent and severity of local disease, especially with regards cardiac complications.

i. **Cardiac complications:**
Myocarditis is the most common cardiac complication (and the most common systemic complication overall), and subtle evidence of myocarditis (as evidenced by ECG changes including ST-T wave changes, QTc prolongation, or first-degree heart block) can be detected in as many as two-thirds of patients. Up to 25% of patients develop clinical cardiac dysfunction, with the severity proportional to that of the local disease. Cardiac toxicity can be acute (manifesting during illness), or delayed (manifesting 7-14 days after the onset of respiratory symptoms during recovery). Acute cardiac toxicity presents as cardiac failure and circulatory collapse, whilst delayed toxicity presents as progressive dyspnoea, weakness, diminished heart sounds, cardiac dilatation and gallop rhythm.

Subtle ECG changes (particularly ST-T wave changes and first degree heart block) can progress to severe forms of heart block, AV dissociation and other arrhythmias which carry a poor prognosis. Because patients without clinical evidence of myocarditis may have significant ECG changes, it is important to monitor ECG patterns regularly in all patients with diphtheria. Serum AST levels may also be useful in monitoring myocarditis.
Neurological complications occur in about 5% of cases overall; whilst rare in patients with mild disease, up to 75% of patients with severe diphtheria develop some manifestation of neurological involvement. Local neuropathies (i.e. paralysis of the soft palate and posterior pharynx) are most common in the first few days of disease, and manifest as regurgitation of swallowed fluids through the nose. Cranial neuropathies (most commonly oculomotor and ciliary, but also facial or laryngeal cranial nerves) may also occur later in the course of disease. Demyelinating peripheral neuritis is a delayed complication, usually developing weeks to months after acute disease and ranges from mild weakness with diminished tendon reflexes, to total paralysis. Predominantly a motor deficit, it usually begins as proximal weakness in the upper and lower limbs, extending distally. Neurologic toxicity usually resolves completely, but may be slow with prolonged convalescence.

Encephalitis and cerebral infarction have also been described, but are extremely rare complications.

Renal complications
Direct toxin effects on the kidneys may result in renal failure in severe cases.

b. Cutaneous diphtheria
Unlike respiratory diphtheria where the incubation period is known, the incubation period for cutaneous diphtheria is not well-defined and may be much longer than the range for respiratory disease. Persons with cutaneous diphtheria may subsequently develop respiratory diphtheria and serious complications. Cutaneous diphtheria can occur in persons who have been fully vaccinated, as is the case with respiratory diphtheria. Disease in such persons is usually milder, and they rarely develop systemic toxic manifestations.

The types and appearance of cutaneous diphtheria is extremely variable. C. diphtheriae can colonise any skin lesion of other origin, including surgical wounds, traumatic wounds, underlying skin conditions (pyoderma, eczema, impetigo, dermatitis) and insect bites. Chronic non-healing ulcers are the typical manifestation, usually with a time course of weeks to months. An ulcerative lesion (historically termed ecthyma diphtheriticum) is often the presenting lesion; it begins as a vesicle or pustule filled with straw-coloured fluid which breaks down quickly. The lesion then progresses to form a punched-out ulcer (or multiple ulcers) of variable size, often with elevated margins. Common sites for lesions include lower legs, feet and hands. Lesions are initially painful and may be covered with an adherent eschar (essentially a dark pseudomembrane) during the first 2 weeks. The lesion then becomes painless and the pseudomembrane falls away leaving a haemorrhagic base, sometimes associated with a serous/serosanguinous exudate. The surrounding tissue is oedematous and may be pink, purple or dark in colour; there may be blisters and even bullae in some cases. In mild forms of the disease, a scaling rash may be the only manifestation.

Bacterial co-infection of cutaneous diphtheria lesions is common, most notably with *Staphylococcus aureus* and *Streptococcus pyogenes*. This may mask or delay the diagnosis of cutaneous diphtheria.
c. Other presentations of diphtheria

- Localised infection with C. diphtheriae is occasionally seen in unusual sites, including the ear, conjunctivae or vagina.
- Invasive disease due to toxigenic C. diphtheriae does occur, but is uncommon; bacteraemia, endocarditis and septic arthritis have been described.

d. Non-toxigenic C. diphtheriae

Non-toxigenic C. diphtheriae typically cause chronic skin ulceration; less common manifestations include upper respiratory tract infections, or rarely, invasive diseases (including endocarditis, mycotic aneurysms, osteomyelitis and septic arthritis). Classically, persons with underlying medical conditions (including alcoholism and IV drug users) appear to be at higher risk of developing sporadic invasive disease from non-toxigenic C. diphtheriae. However, in the last two decades clusters and outbreaks of invasive disease caused by unique epidemic strains of non-toxigenic C. diphtheriae disease have been described in marginalised social groups (homeless persons in the US, urban poor in Canada, Australian aboriginal populations) with high morbidity and mortality.

5. Identifying a suspected case of diphtheria and differential diagnosis of diphtheria

It is important that clinicians are aware of the range of clinical presentations and appropriate diagnostic investigations in order to detect cases timeously and limit mortality. Respiratory diphtheria should be included in the differential diagnosis when certain signs and symptoms are present:

- Symptoms and signs of respiratory tract disease (mildly painful pharyngitis, naso-pharyngitis, tonsillitis, laryngitis, tracheitis or any combination of these) with absent or low-grade fever plus an adherent pseudomembrane, which bleeds if scraped or dislodged
- Symptoms and signs of respiratory tract disease as above with one or more of the following symptoms or clinical features: dyspnoea, difficulty swallowing and drooling, stridor, bull-neck, circulatory collapse, acute renal insufficiency, myocarditis.

Other infections that may cause a membranous pharyngitis include group A β-haemolytic streptococci, S. aureus, Arcanobacter hemolyticum, Candida albicans, Borrelia vincenti (Vincent’s angina), Haemophilus influenzae (acute epiglottitis), viruses (including EBV, HSV and adenovirus), and toxoplasmosis.

6. Laboratory diagnosis

Confirmation of the diagnosis of diphtheria depends upon isolation of a toxin-producing strain of C. diphtheriae, C. ulcerans or C. pseudotuberculosis from a clinical specimen. Non-toxigenic C. diphtheriae may be isolated from nasal and pharyngeal swabs, blood cultures and/or other sites but these strains do not cause clinical diphtheria and do not require the same public health response.

a. Collection of clinical specimens for isolation of C. diphtheriae, C. ulcerans or C. pseudotuberculosis

- Clinical specimens should be taken before antibiotics are given if possible. However, should antibiotics already have been given, specimens should still be collected.
- Specimens should be taken from the nasopharynx, the throat, and from the membrane, if present. Table 1 gives guidance on clinical specimen collection.
- Multiple site sampling should be done as this may increase the organism recovery rate.
• If possible, a specimen should be taken from under the membrane (where bacteria are concentrated). Removal of sections of membrane for culture and histology is also valuable.
• The specimens should be sent to the laboratory immediately, as rapid inoculation of special culture media is important.
• The laboratory must be informed that diphtheria is suspected, so that specimens can be inoculated on special culture media that facilitates the isolation of *Corynebacterium* spp. Routine culture procedures are not optimised for *Corynebacterium* spp. detection and as a result these organisms may ordinarily be missed, particularly if they are not abundant or overgrown by other nasopharyngeal flora.

Table 1. Guidance on collection of clinical specimens for the isolation of *C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis*

1. **Throat specimens**
   - The pharynx should be clearly visible and well illuminated
   - Depress the tongue with a tongue-depressor and swab the throat without touching the tongue or inside the cheeks
   - Rub vigorously over any membrane, white spots, or inflamed areas; slight pressure with rotating movement must be applied to the swab.
   - If any membrane is present, lift the edge and swab beneath it to reach the deeply located organisms.
   - Transport the swab immediately to the laboratory for culture.

2. **Nasopharyngeal specimens**
   - Through one nostril, insert the swab into the nose beyond the anterior nares.
   - Gently introduce the swab along the floor of the nasal cavity, under the middle turbinate, until the pharyngeal wall is reached.
   - Force must not be used to overcome any obstruction.
   - Transport the swab immediately to the laboratory for culture.

3. **Skin lesions**
   - Lesions should be cleaned with sterile saline and crusted material removed.
   - Press the swab firmly into the lesion.
   - Transport the swab immediately to the laboratory for culture.

4. **Tissue specimens**
   - If sections of membrane are removed, they should be placed in a universal specimen container and transported immediately to the laboratory for culture. Specimens for culture must NOT be placed in formalin.
   - Additional tissue specimens may be collected for submission to the histopathology laboratory if desired.
b. Laboratory diagnosis

Laboratory diagnosis is by culture of an isolate of *C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis* in a clinical laboratory. Such isolates must undergo further testing to determine whether they are toxigenic (i.e. toxin-producing). The gold standard test for determining toxin expression is the Elek test; this is a specialised test that usually takes a few days. If available, PCR testing for the presence of the *tox* gene may be useful since it allows a rapid assessment of whether the isolate is likely to be toxigenic, which may assist in guiding the immediate public health response. However, all PCR-positive isolates must undergo Elek testing for toxin expression, since there are isolates of *C. diphtheriae* and *C. ulcerans* that harbour the *tox* gene (and therefore test positive on PCR) but do not express the toxin (and test negative on Elek testing) – these are termed non-toxigenic toxin gene bearing (NTTB) isolates. NTTB corynebacteria are not known to cause epidemic outbreaks of diphtheria, and their significance is uncertain; there is a hypothetical risk that these isolates may express toxin if they become exposed to toxigenic isolates in the natural environment. At present, the National Health Laboratory Service Green Point Complex in Cape Town is the only clinical laboratory in South Africa which is able to perform Elek toxigenicity testing. PCR testing for *tox* gene is currently not available in South Africa.

7. Case definition and classification

7.1 Case definitions

◊ **Clinical Case Definition for respiratory diphtheria:** a person who presents with an upper-respiratory tract illness characterized by sore throat, low-grade fever and an adherent membrane of the nose, pharynx, tonsils, or larynx

◊ *Other presentations of diphtheria:*
  o A patient with mild respiratory symptoms but no membrane
  o A patient with a skin lesion, and *C. diphtheriae/C. ulcerans/C. pseudotuberculosis* has been isolated from a nasopharyngeal swab or skin lesion swab
  o Rare presentations: endocardial, laryngeal, conjunctival, otic, genital

◊ **Laboratory diagnostic criteria/confirmation:** Isolation of a toxin-producing *C. diphtheriae/C. ulcerans/C. pseudotuberculosis* from a clinical specimen

7.2 Case classification

i. **Suspected case:**
  o A person who meets the clinical case definition for respiratory diphtheria and has no laboratory confirmation and no epidemiologic link to a laboratory-confirmed case
ii. Probable case:
   o A person who meets the clinical case definition for respiratory diphtheria plus one of the following
     ▪ Isolation of C. diphtheriae/C. ulcerans/C. pseudotuberculosis but toxigenicity status has not yet been confirmed
     ▪ Has an epidemiologic link with a laboratory-confirmed case
   OR
   o A person presenting with mild respiratory symptoms with no membrane or other presentations of diphtheria*, but has an epidemiologic link to a laboratory-confirmed case
iii. Confirmed case:
   o A person who meets the clinical case definition for respiratory diphtheria and is laboratory confirmed
   OR
   o A person presenting with mild respiratory symptoms with no membrane or other presentations of diphtheria* and is laboratory confirmed
iv. Asymptomatic carrier
   o A person with no symptoms but has laboratory confirmation of a toxigenic strain
v. Discarded
   o A suspected or probable case in whom other compatible organisms are isolated or if C. diphtheriae/C. ulcerans/ C. pseudotuberculosis is isolated but is confirmed to be a non-toxigenic strain

8. Management of cases of confirmed or probable diphtheria
   The mainstay of treatment of a suspected diphtheria case is prompt administration of diphtheria antitoxin treatment (DAT); this should be given without waiting for laboratory confirmation of a presumptive diagnosis of diphtheria. DAT only neutralises toxin before its entry into cells so it is critical that DAT be administered as a matter of urgency. The recommended dosage and route of administration depend on the extent and duration of disease. Antibiotics should also be given, in order to eradicate carriage of the organism, limit transmission, and stop further production of diphtheria toxin.

a. Infection prevention and control considerations
   • Isolate all patients with suspected diphtheria until the diagnosis is confirmed or excluded
   • Isolate patients with standard, contact (use of gloves and plastic aprons etc.) and droplet precautions (wearing a surgical face mask) until two cultures from the throat and nose (and skin lesions in cutaneous diphtheria) taken at least 24 hours apart after completion of antibiotic therapy are negative for toxigenic C. diphtheriae, C. ulcerans or C. pseudotuberculosis. In the absence of such follow-up cultures, patients should be isolated until they have completed 14 days of antibiotic therapy.
   • Where patients are not hospitalised, restrict contact with others until completion of antibiotic therapy

b. Supportive care
   Refer all probable or confirmed diphtheria cases for specialist assessment.
Patients with respiratory diphtheria require careful monitoring (ideally in a high or intensive care setting) for potentially life-threatening complications from local disease (e.g. airway obstruction or respiratory compromise due to tracheobronchial disease) or systemic manifestations (especially cardiac complications). Because patients without clinical evidence of myocarditis may have significant ECG changes, it is important to monitor ECG patterns regularly in all patients with diphtheria. Serum AST levels may also be used to monitor myocarditis.

c. Diphtheria antitoxin treatment (DAT)
   - DAT neutralises circulating unbound diphtheria toxin and prevents progression of disease. Since the antitoxin does not neutralize toxin that is already bound to tissues, delaying its administration is associated with an increased mortality.
   - DAT should only be administered in a hospital setting.
   - DAT should be given to all probable classic respiratory diphtheria cases without waiting for laboratory confirmation; a decision to administer DAT is based on clinical diagnosis, and should not await laboratory confirmation.
   - DAT is generally not indicated in cases of cutaneous diphtheria without systemic manifestations. However, in cases where the ulcer is very large (>2cm²) and membranous, the risk of systemic absorption of toxin and subsequent systemic complications is increased and DAT may be considered.
   - The dosing of DAT is product-specific and is detailed in the package insert.

d. Antibiotic treatment
   - Antibiotic treatment it is not a substitute for DAT treatment.
   - Although antibiotics have not been demonstrated to affect healing of local infection, they are given to eradicate the organism from the nasopharynx and prevent further transmission to others.
   - All specimens should be collected before antibiotic treatment is started. However, should antibiotics already have been started, specimens should still be collected.
   - Recommended antibiotics include macrolides (erythromycin, azithromycin or clarithromycin) or benzylpenicillin – refer to Table 2 for dosing guidance. Parenteral benzylpenicillin (or erythromycin if available) should be used until the patient is able to swallow, when oral treatment with either a macrolide or benzylpenicillin can be commenced. Antibiotic therapy must be given for a total of 14 days.
   - Elimination of the organism must be confirmed after antibiotic treatment is completed: two sets of nasopharyngeal and throat swabs must be collected for culture, taken at least 24 hours apart and more than 24 hours after completing antibiotics. If the toxigenic strain persists, an additional 10 days of antibiotic treatment is indicated.
Table 2: Antibiotic treatment for diphtheria

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<th>1. Parenteral treatment for patients unable to swallow</th>
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<tr>
<td></td>
<td>Penicillin G</td>
<td>Erythromycin</td>
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<tr>
<td>Children</td>
<td>50 000 units/kg/dose IV 12 hourly</td>
<td>15-25 mg/kg/dose 6 hourly IV (maximum 1g per dose)</td>
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<tr>
<td>Adults</td>
<td>50 000 units/kg/dose (max 1.2 million units per dose) IV 12 hourly</td>
<td>15-20 mg/kg/day (maximum 4g per dose) in 4 divided doses given 6 hourly</td>
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<tr>
<th>2. Oral treatment for patients able to swallow</th>
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<tr>
<td>Penicillin V</td>
<td>Macrolides</td>
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<tr>
<td>Children</td>
<td>Penicillin V</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>15 mg/kg/dose (maximum 500 mg per dose) po 6 hourly</td>
<td>15-25 mg/kg/dose (maximum 1g per dose) po 6 hourly</td>
<td>10 mg/kg po daily</td>
</tr>
<tr>
<td>Adults</td>
<td>500 mg po 6 hourly</td>
<td>500 mg – 1g po 6 hourly (maximum 4g/day)</td>
</tr>
</tbody>
</table>

e. Immunisation
- Infection does not reliably induce protective antibody levels, so all confirmed or probable cases should receive a booster dose once they are clinically stable. The booster dose should be given as a diphtheria-toxoid containing vaccine appropriate to age and immunisation history (i.e. DTaP-IPV/Hib or DTaP-IPV/Hib/HBV or Td or Tdap-IPV).
- Offer an accelerated diphtheria vaccination series to children, adolescents or adults who are unimmunised or incompletely immunised (contact a vaccine-preventable disease expert to discuss this)
- Children who have completed their primary diphtheria vaccination series plus routine booster/s, and adolescents and adults who have been previously immunised can be offered a diphtheria-containing vaccine booster dose (Td or Tdap-IPV).

9. Recommended public health response to an outbreak of diphtheria in South Africa
Diphtheria is a notifiable medical condition in South Africa. All suspected/probable/confirmed cases should be reported to infection prevention and control practitioners at healthcare facilities where applicable, as well as District and Provincial communicable disease control coordinators urgently (as per routine notifiable medical condition notification procedures). On notification of such case-patients the following public health actions should be initiated immediately:

a. Conduct a detailed case investigation
   - Obtain detailed demographic, clinical and risk factor information etc.
   - Compile a case line list
   - Compile a case contact line list
b. Identify contacts
   - Close contacts include:
     - Those having close contact with the patient in a household-type setting. This includes those living and/or sleeping in the same household; those such as scholars/students etc. who sleep in the same dormitory/flat or have shared kitchen facilities etc.; and kissing/sexual contacts of the patient
     - If the index case is a young child, childminders/nannies who care for the child
     - Healthcare workers who have given mouth-to-mouth resuscitation to the patient or have dressed the wounds of a cutaneous case without appropriate infection control procedures
   - At-risk contacts – for this group risk of disease will depend on the duration of contact and their immunization status. Examples of such contacts would include:
     - Friends, relatives, and caregivers who regularly visit the home
     - School/pre-school class contacts
     - Those who share the same room at work
     - Other healthcare workers who have had contact with the case

At-risk contacts need to be assessed on a case by case basis by health authorities to determine likely level of risk and need for prophylaxis.

c. Conduct laboratory investigation of close contacts and eligible at-risk contacts
   - Collect nasal and pharyngeal swabs for culture—this should ideally be done before chemoprophylaxis if possible.
   - Should a contact test positive for toxigenic C. diphtheriae, the person will require full treatment and follow-up cultures as per symptomatic cases (precaution should be taken until two cultures (taken at least 24 hours apart) from both nose and throat >24 hours after completing antibiotic therapy are negative for C. diphtheriae). The person will also need to be isolated with standard, contact and droplet precautions; in addition disinfect the immediate environment

d. Administer chemoprophylaxis to close contacts and at-risk contacts
   - Offer post-exposure chemoprophylaxis to all close contacts and eligible at-risk contacts to eliminate asymptomatic carriage and to treat incubating disease. Either benzylpenicillin or erythromycin may be used for chemoprophylaxis, as per Table 3.

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Table 3. Chemoprophylaxis for close contacts and eligible at-risk contacts of diphtheria cases

<table>
<thead>
<tr>
<th>Age group</th>
<th>Benzylpenicillin</th>
<th>Erythromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>&lt;6 years: Single dose of 600 000 units I.M.</td>
<td>&lt;2 years: 125 mg every 6 hours po for seven days</td>
</tr>
<tr>
<td></td>
<td>&gt;6 years: Single dose of 1.2 million units I.M.</td>
<td>2-8 years: 250 mg every 6 hours po for seven days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;8 years: 500 mg every 6 hours po for seven days</td>
</tr>
<tr>
<td>Adults</td>
<td>Single dose of 1.2 million units I.M.</td>
<td>500 mg every 6 hours po for seven days</td>
</tr>
</tbody>
</table>
e. Monitor close and eligible at-risk contacts and

Monitor close contacts and eligible at-risk contacts for signs/symptoms of diphtheria for at least 10 days after last contact with the index case. Educate them about the disease and advise them to seek medical care if they develop symptoms.

f. Exclude close and eligible at-risk contacts in high-risk occupations

Those whose work involves handling food (especially those involved in milk production for *C. ulcerans*), those who work with unvaccinated children, or health and social care workers should be excluded from work until laboratory tests confirm that they are not carriers.

g. Vaccinate close and eligible at-risk contacts

- Diphtheria vaccine is not indicated for routine post-exposure prophylaxis. However, it is an opportunity to check diphtheria vaccination status in contacts, and all unimmunised/incompletely immunised contacts ≤12 years should complete their primary vaccination and booster doses as per the EPI schedule
- Adolescents and adults may also be offered a booster dose of diphtheria-containing vaccine.
  
  Note that:
  - DTaP (Infanrix®) is licenced for use in children aged 6 weeks to 7 years,
  - Td (Diflavax®) is licenced for use in persons 6 years and older
  - Tdap-IPV products are licenced for use in persons from 3 years of age (Adacel Quadra®) and from 4 years of age (Boostrix Tetra®).

h. Alert other healthcare facilities in the area

- Alert healthcare practitioners in the area and inform them to maintain a high index of suspicion
- Provide fact sheets about the disease aimed at healthcare professionals

i. Conduct health promotion activities and health education

- Produce and distribute Information, Education and Communication materials that provide basic information about the disease and, importantly, about the vaccine and vaccine schedule
- Encourage good personal hygiene practices (hand hygiene and cough etiquette)

j. Vaccination campaigns in response to outbreaks

- In the event of an outbreak, selective campaigns targeting at-risk groups (including healthcare workers) may be considered.