NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
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CENTRE FOR RESPIRATORY DISEASES AND MENINGITIS
OUTBREAK RESPONSE, DIVISION OF PUBLIC HEALTH SURVEILLANCE AND RESPONSE

Diphtheria:

NICD Recommendations for

Diagnosis, Management

and

Public Health Response

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Version 2.0 September 2015	Guideline writing committee	Case definitions changed Laboratory diagnostics section updated References and 'quick reference guide' added
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The information contained in this document, be it guidelines, recommendations, diagnostic algorithms or treatment regimens, are offered in this document in the public interest. To the best of the knowledge of the guideline writing team, the information contained in these guidelines is correct. Implementation of any aspect of these guidelines remains the responsibility of the implementing agency in so far as public health liability resides, or the responsibility of the individual clinician in the case of diagnosis or treatment.

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Quick Reference Guide - Diphtheria

Treatment of a diphtheria case (pg. 17-19)

1. Isolate: Prevent transmission of *C. diphtheriae* by practising contact and droplet precautions
2. Provide supportive care: Provide oxygen, monitor with ECG and intubate or perform a tracheostomy if necessary
3. Provide diphtheria antitoxin according to severity of illness and mass of patient
4. Treat with antibiotics

Management of close contacts (pg. 21-23)

1. Identify 'close' and 'at-risk' contacts
2. Collect a nasopharyngeal and oropharyngeal swab from contacts
3. Administer chemoprophylaxis after swab collection
4. Vaccinate contacts appropriately (depending on vaccination status). All contacts require at least one dose
5. Monitor contacts for 10 days for symptoms
6. Collect follow-up swabs (from contacts that were culture or PCR positive for toxigenic *C. diphtheriae* on primary culture) after completion of chemoprophylaxis
7. Repeat chemoprophylaxis if contacts are still *C. diphtheriae* positive

Notification of cases and additional support (pg. 21):

Diphtheria is a Category 1 notifiable medical condition. Immediate reporting should be done telephonically followed by written or electronic notification within 24 hours of diagnosing a case.
Please complete the NMC form (available at http://www.nicd.ac.za/index.php/nmc/notifiable-medical-conditions-list/) and case investigation form (Appendix B, pg. 26-27) and submit to provincial & district CDC coordinators and to the NICD: NMCSurveillanceReport@nicd.ac.za and outbreak@nicd.ac.za

Centre for Respiratory Diseases and Meningitis (NICD):

- Clinical queries: Dr Anne von Gottberg (011-555-0316 annev@nicd.ac.za)
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- After hours: NICD Hotline (082 883 9920)

Diphtheria case definitions (pg. 11):

A suspected case:
A person who presents with an upper respiratory tract illness characterised by sore throat, low-grade fever and an adherent (pseudo-)membrane of the nose, pharynx, tonsils or larynx

A confirmed case:
A person who presents with an upper respiratory tract illness characterised by sore throat, low-grade fever and/or an adherent (pseudo-)membrane of the nose, pharynx, tonsils or larynx
AND
culture of *C. diphtheriae*, *C. pseudotuberculosis* or *C. ulcerans* which is confirmed to be toxin producing by ELEK or *tox* gene positive by PCR

For case definitions of probable cases and asymptomatic carriers see pg. 11

Laboratory identification of *C. diphtheriae* (pg. 12-16):

1. Take an oropharyngeal swab from the affected area (including pseudomembrane if present)
2. Plate swab for single colonies on a) blood agar (incubate at 37°C in CO_2 for 24 hours) and b) on Hoyle's agar (incubate at 37°C in O_2 for 48 hours)
3. *C. diphtheriae* form black colonies on Hoyle's and look similar to staphylococci on blood agar. They are catalase-positive, Gram-positive bacilli
4. Confirm identification using API Coryne or VITEK or MALDI-TOF
5. Submit culture and swab to NICD for confirmation, ELEK and PCR

For laboratory staff:

1. Please routinely screen all oropharyngeal and nasopharyngeal swabs for *C. diphtheriae*
2. Please send any suspect or confirmed isolates of *Corynebacterium* spp. to the NICD for identification/confirmation and for further characterisation (including cutaneous isolates)
3. Please include the original specimen (swab and tissue) for PCR testing
4. Please also send culture-negative swabs to NICD for PCR testing

1. Introduction

Diphtheria is caused by *Corynebacterium diphtheriae* and presents most commonly as a membranous pharyngitis, although other presentations such as cutaneous disease also occur. The organism produces a toxin that causes necrosis of the tissues, leading to respiratory obstruction, and also myocarditis, leading to heart failure and death. The mortality of diphtheria was as high as 50%[1] but declined to about 15% after antitoxin use became widespread. However, after introduction of the vaccine in the 1940-50s[2], diphtheria was practically eradicated and clinical diphtheria become an uncommon disease globally, and in South Africa. However, there is presently global concern that diphtheria is re-emerging. A number of outbreaks of diphtheria have been reported from Eastern Europe[3], Southeast Asia, South America[4], North Africa[5] and the Indian subcontinent. Persons (most especially children) who are not vaccinated or are partially vaccinated are most at risk of diphtheria[1]. Adults are also at risk as immunity due to vaccination wanes over time[1].

2. Microbiology

Diphtheria is caused by infection with toxin-producing (toxigenic) strains of *C. diphtheriae*, *C. ulcerans* or rarely *C. pseudotuberculosis. C. diphtheriae* is a nonsporulating, unencapsulated, nonmotile, pleomorphic, Gram-positive bacillus. When viewed under a light microscope, 'metachromatic granules' can be seen (best seen on methylene blue staining), along with the characteristic "Chinese character" palisading morphology[6]. Formerly, isolates of *C. diphtheriae* were typed using biochemical reactions into four biovars – *gravis, intermedius, mitis* and *belfanti,* but these methods of strain differentiation were superseded by molecular methods (ribotyping) and subsequently by whole genome sequencing.

C. diphtheriae and rare strains of *C. ulcerans* produce a toxin encoded on a lysogenic bacteriophage carrying the *tox* gene that is responsible for the pathogenesis and clinical presentation of diphtheria. Following infection, the phage's circular DNA integrates into the host bacteria's genetic material. Production of the toxin follows. Lysis of the cell releases the toxin and a new bacteriophage. The toxin is a 62,000-dalton polypeptide, that has a benign B sub-unit (which binds and facilitates cell entry), and a highly toxigenic A subunit that inhibits protein synthesis in a variety of tissues including the heart (where it causes myocarditis) and nerves (where it causes demyelination). Toxin production is regulated by the diphtheria toxin repressor protein (DtxR) which is also present in many non-toxigenic isolates. Therefore non-toxigenic isolates serve as a potential reservoir for the

re-emergence of toxigenic isolates if they possess a functional *dtxR* gene and become infected with a tox gene-carrying phage.

3. Epidemiology

3.1. Global epidemiology of diphtheria

Following implementation of widespread immunisation programmes, diphtheria has declined or been eliminated from many developed countries[7]. The disease remains endemic in some developing countries, including the Indian subcontinent, Haiti, Brazil, Nigeria, Indonesia, Philippines, and some Eastern Mediterranean countries. The former Soviet Union experienced a large epidemic of diphtheria during the 1990s, when >157 000 cases and 5,000 deaths were reported[3,8]. Diphtheria usually occurs among susceptible (i.e. non-immune) individuals, and usually reflects inadequate vaccination coverage. Cutaneous diphtheria has been reported predominantly in endemic tropical countries[2]. Recently, there has been increasing case reports of travellers acquiring cutaneous diphtheria associated with both non-toxigenic and toxigenic *C. diphtheriae*. 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

Since the implementation of diphtheria immunisation in South Africa in the 1950s only sporadic cases of disease (mostly involving children aged <15 years) have been identified and reported. Between January 2008 and March 2015, three laboratory-confirmed cases of respiratory diphtheria were reported: two from Western Cape Province (March 2008 and January 2010), and one from Eastern Cape Province (March 2009). The 2015 outbreak of diphtheria in Kwa-Zulu Natal involved 15 diphtheria cases (11 confirmed, 1 probable, 3 possible) of whom four died, with the first case presenting on 15th March 2015, and the last case reported on 13th June 2015. Six asymptomatic carriers of laboratory-confirmed toxigenic *C. diphtheriae* were identified. Cases ranged in age from 4 to 41 years (median 10 years). Children aged <15 years accounted for 73% (11/15) of the cases, with 40% (6/15) occurring in those aged 5 to 9 years. Males accounted for 60% (9/15) of cases. Where vaccination history was verified (n=6), four case-patients were not up to date with their diphtheria immunisations according to age. Outbreak response included the provision of antibiotics to close

contacts, catch-up vaccination campaigns and health promotion activities. Diphtheria antitoxin was obtained through a donation by the Japanese government, and was administered to six case-patients. Subsequently, two additional cases were reported in 2016 from the same region. In 2017, a cluster of three epidemiologically linked cases occurred in the Western Cape and a single case was reported from the Eastern Cape.

4. Pathogenesis, pathology and transmission

Humans are the only known natural host for *C. diphtheriae*. By contrast, *C. ulcerans* and *C. pseudotuberculosis* are zoonotic diseases in humans (acquired from domesticated or wild animals), although human-to-human transmission of these pathogens has been suggested in some cases. *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. After colonisation of the pharynx, *C. diphtheriae* remains in the superficial layers of the respiratory mucosa or skin lesions. The incubation period for respiratory diphtheria is usually 2-5 days, but may range from 1-10 days. Diphtheria toxin causes local tissue necrosis which leads to inflammation, ulceration and oedema of affected tissues, and results in the formation of a classic adherent (pseudo-) membrane. 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.

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 persons may also be asymptomatic nasopharyngeal carriers of toxigenic corynebacteria. Carriage can be eradicated by appropriate antibiotic treatment. Cutaneous diphtheria is likely more transmissible than respiratory diphtheria, and can cause secondary respiratory and cutaneous infections and may be a source of outbreaks. In endemic countries, cutaneous diphtheria lesions probably act as silent reservoirs of disease.

5. Clinical presentation and risk factors for diphtheria

5.1. Respiratory diphtheria

The classic presentation of diphtheria is associated with extensive pseudomembranous pharyngitis, massive swelling of the tonsils, uvula, cervical lymph nodes, submandibular region, and anterior neck ('bull neck')[9,10]. Following an average incubation period of 2-5 days (range 1-10 days), the

onset of disease is usually gradual and initial symptoms include low-grade fever, malaise, cervical lymphadenopathy and sore throat. Respiratory diphtheria may occur in persons with incomplete primary vaccination series, or more rarely, in persons who have been vaccinated. However, disease in persons with prior vaccination is mild, and systemic symptoms do not occur.

5.1.1. Local symptoms and clinical findings

Pharyngeal infection commences with erythema, and progresses to isolated spots of grey and white exudate. Finally the exudate coalesces into a pseudomembrane. The pseudomembrane is usually found 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. Localised tonsillar disease is usually mild, but involvement of posterior pharynx, soft palate and periglottal areas is often associated with more severe generalised 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.

5.1.2. Systemic manifestations

Systemic manifestations 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.

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 but 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.

Renal complications may develop as a direct effect of the toxin on the kidney and may result in renal failure.

5.2. Cutaneous diphtheria

Unlike respiratory diphtheria where the incubation period is known, the incubation period for cutaneous diphtheria is not well defined and may be 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 are extremely variable[6].

C. diphtheriae can colonise existing skin lesions such as those resulting from surgery or trauma, or from underlying skin conditions (pyoderma, eczema, impetigo, dermatitis) and insect bites.

Chronic non-healing ulcers are the typical manifestation of cutaneous diphtheria, 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. 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. Common sites for lesions include lower legs, feet and hands. 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.

5.3. 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.

5.4. Non-toxigenic C. diphtheriae

Non-toxigenic *C. diphtheriae* typically causes 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.

6. *Case definitions and classification*

Case definition	Clinical criteria		Epidemiological criteria		Laboratory criteria
Suspected case	A person who presents with an upper respiratory tract illness characterised by sore throat, low-grade fever and an adherent (pseudo) membrane of the nose, pharynx, tonsils and/or larynx OR Cutaneous diphtheria as described in probable		None		None
Probable case[a]	A person who presents with an upper respiratory tract illness characterised by sore throat, low-grade fever and an adherent (pseudo) membrane of the nose, pharynx, tonsils and/or larynx	OR	Has an epidemiological link to a confirmed case or asymptomatic carrier, or has a skin lesion		Not confirmed
Confirmed case[b]	A person who presents with an upper respiratory tract illness characterised by sore throat, low-grade fever AND/OR an adherent (pseudo) membrane of the nose, pharynx, tonsils and/or larynx		N/A	AND	Positive on culture for toxigenic *C. diphtheriae* (also *C. ulcerans* or *C. pseudotuberculosis*) or PCR positive for *tox* gene
Asymptomatic carrier	No symptoms		With or without epidemiological link to a confirmed case	AND	Positive on culture for toxigenic *C. diphtheriae* (also *C. ulcerans* or *C. pseudotuberculosis*) or PCR positive for *tox* gene
Unclassified	A person presenting with an upper respiratory tract illness or other signs or symptoms compatible with diphtheria		None		Isolation of non-toxigenic *C.diphtheriae*/ C. ulcerans/*C. pseudotuberculosis*
Discarded	A person who presents with an upper respiratory tract illness characterised by sore throat, low-grade fever and an adherent (pseudo) membrane of the nose, pharynx, tonsils and/or larynx		No epidemiological link to confirmed or probable case		Laboratory testing was negative for *C. diphtheriae/C. ulcerans/ C. pseudotuberculosis* OR yielded another organism (e.g. *S. pyogenes*)

[a] It would be unwise to exclude persons with pharyngeal symptoms and no membrane, who have an epidemiological link to a confirmed case, when laboratory testing is not done, or is inconclusive.
When persons with clinical symptoms compatible with diphtheria (including a pharyngeal membrane) have no epidemiological link with a confirmed case, and laboratory testing is not possible, or inadequate, extensive epidemiological investigations should be done, including laboratory investigations of contacts. If asymptomatic carriers are found, the case will be reassigned to the probable category. Given the findings of the outbreak in KZN and the recognition that vaccination coverage amongst 6 and 12 year old children is sub-optimal, this category exists in order to broaden case detection. [b] Confirmed diphtheria is possible even when persons do not have a membrane

7. *Laboratory detection of diphtheria*

7.1. Specimen collection from suspected cases of respiratory or cutaneous diphtheria, and contacts

Suspected case:

Swabs should be collected prior to treatment and taken from the oropharynx and underneath the pseudomembrane (if present), or wound (cutaneous). Pseudomembrane tissue should also be collected if possible. Dacron, Rayon or nylon-flocked swabs should be used and placed in Amies or Stuart's transport media (Fig. 1). Tissue should be placed in sterile saline (not formalin). Specimens must be transported to the laboratory, with ice packs, as soon as possible. Please use the specimen submission form available at the end of this document (Appendix A).

Contacts: Nasopharyngeal and oropharyngeal swabs should be collected prior to chemoprophylaxis. Following completion of chemoprophylaxis, swabs should be collected again from *C. diphtheriae*-positive contacts after 2 weeks of commencing with chemoprophylaxis to ensure eradication of carriage. Refer to Fig. 2 for the correct swabs to use.

Persons may find the collection of pharyngeal and particularly nasopharyngeal swabs uncomfortable. The procedures may induce coughing, spluttering, sneezing and watering eyes. It is important that persons collecting the specimen are appropriately protected. Droplet precautions are necessary, including a surgical mask. Eye protection may be advisable. Persons collecting the swabs should ensure that they are adequately protected through vaccination, and that booster vaccines against diphtheria are up to date.

Figure 1. Amies transport media (with charcoal) used for the transport of throat and nasal swabs

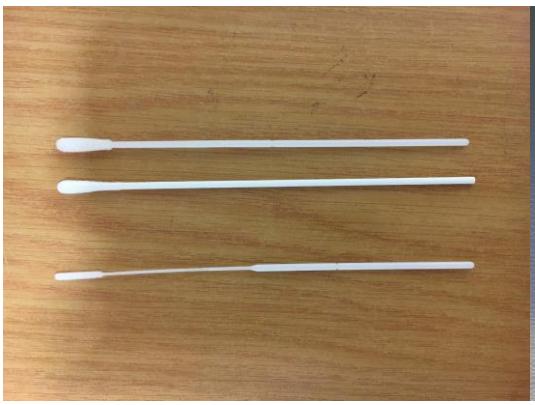

Figure 2A. Top two swabs may be used for throat. Bottom swab (thin/flexible shaft) to be used for nasopharyngeal specimen collection.

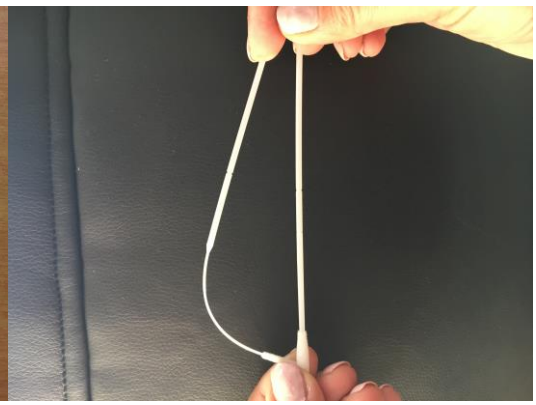

Figure 2B. Note difference in flexibility of shaft. Nasopharyngeal swab = thin/flexible shaft, Throat swab = no flexibility.

7.1.1. Procedure for the collection of oropharyngeal swabs from persons with suspected diphtheria or contacts

1. The pharynx should be clearly visible and well illuminated.
2. Depress the tongue with a tongue depressor and swab the throat without touching the tongue or inside the cheeks.
3. Rub vigorously over any membrane, white spots, or inflamed areas; slight pressure with rotating movement must be applied to the swab.
4. If any membrane is present, lift the edge and swab beneath it to reach the deeply located organisms.
5. Place the swab in Amies transport medium and dispatch immediately to the laboratory for culture.

7.1.2. Procedure for the collection of nasopharyngeal swabs from contacts of persons with suspected or confirmed diphtheria

1. Through one nostril, insert the swab into the nose beyond the anterior nares.
2. Gently introduce the swab along the floor of the nasal cavity, under the middle turbinate, until the pharyngeal wall is reached. Do not use force to overcome any obstruction.
3. Place the swab in Amies transport medium and dispatch immediately to the laboratory for culture and PCR.

7.1.3. Procedure for the collection of pus swabs or tissue/skin lesions

1. Lesions should be cleaned with sterile normal saline and crusted material removed
2. Press the swab firmly into the lesion.

3. 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 in sterile saline and transported immediately to the laboratory for culture. Specimens for culture or PCR must NOT be placed in formalin. Additional tissue specimens may be collected for submission to the histopathology laboratory if desired.

7.2. Processing of specimens for the detection of C. diphtheriae

7.2.1. Staining and microscopic examination of specimens

The 'chinese lettering' that is typical of coryneform bacteria and the metachromatic granules that are specific to *C. diphtheriae* are not sufficiently sensitive nor specific enough to be useful in the diagnosis of diphtheria[6]. Rather, diagnosis relies on the detection of *C. diphtheriae* through culture or PCR detection of the *tox* gene[11].

7.2.2. Procedure for the isolation of *C. diphtheriae* from culture of clinical specimens

1. Roll the swab, or place the tissue on a segment of a blood agar plate and a solid agar plate of selective tellurite-containing media (e.g., Hoyle's agar).
2. Incubate the blood agar and selective media at 37°C in O_2 for 48 hours.
3. Examine plates at 24 and 48 hours for colonies typical of *C. diphtheriae.* On selective media*,* colonies appear greyish black with a garlic-like odour (Fig. 3A and 3B). Other *Corynebacterium* spp. and some staphylococci tolerate tellurite and thus may also grow on selective media and appear greyish black.
4. Perform a Gram's stain of typical colonies. Coryneform bacteria will appear as pleomorphic Gram-positive rods that occur in angular arrangements, (may appear coccobacillary in older cultures).
5. Subculture suspicious colonies onto blood agar in order to carry out identification procedures.

Figure 3A: Typical colonial appearance after 18 hours incubation on Hoyle's medium (~1mm in diameter, black matt colonies, bottom half of agar plate)

Figure 3B: Typical colonial appearance after 18 hours incubation on blood agar

7.2.3. Procedure for the confirmation of suspected *C. diphtheriae* isolates through biochemical testing

Traditional biochemical testing of *C. diphtheriae* will demonstrate a positive catalase reaction, and acid production from glucose and maltose, and not from lactose and sucrose. However, identification is most often through the use of commercial identification kits (e.g., API) or an automated system or Matrix-Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) technology.

7.2.4. Procedure for the confirmation of toxin production in *C. diphtheriae* isolates

An Elek test is carried out to confirm toxin production. Elek testing is available at the Centre for Respiratory Diseases and Meningitis (CRDM), and at Greenpoint NHLS Laboratory. Swabs or tissue can be tested by PCR for the presence of the A and B subunits of the *C. diphtheriae* toxin gene (*tox*). This PCR assay is available at CRDM/NICD. In rare cases, the presence of the *tox* gene does not necessarily indicate that toxin is being produced, and the currently used PCR assay does not distinguish between *C. diphtheriae* and *C. ulcerans*. Therefore, the Elek test must be performed on all isolates suspected of causing clinical diphtheria. Isolates of *C. diphtheriae* (or *Corynebacterium* species) should be submitted for confirmation and toxigenicity testing by the Elek test. Isolates should be submitted as pure cultures heavily inoculated onto Dorset transport medium or other common agar slants or plates and submitted to NICD without delay at ambient temperature (not on ice) (Fig. 4). Submission should not be delayed for incubation of the Dorset or other medium. The organism will grow minimally as it travels at ambient temperature, and further incubation can be done at the NICD if necessary.

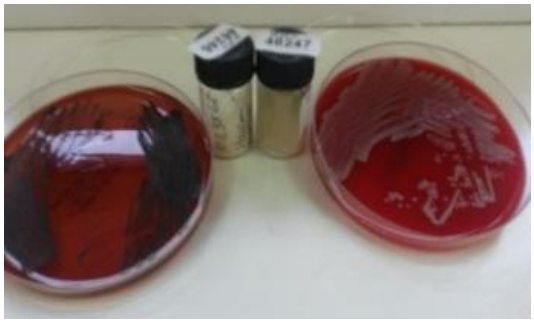

Figure 4: Submit suspected *C. diphtheriae* isolates to NICD on Dorset transport media, or send the blood or Hoyle's agar plate (sealed in e.g. Parafilm M)

7.3. Transport of specimens to NICD

Specimens - Hoyle's plates, Dorset slopes and swabs (including culture negative swabs) should be transported without delay to:

Centre for Respiratory Diseases and Meningitis (CRDM) bacteriology laboratory, National Institute for Communicable Diseases (NICD), 1 Modderfontein Road, Sandringham, Johannesburg, 2131. Please use the specimen submission form attached at the end of these guidelines. For NHLS laboratories, please liase with CRDM NICD regarding transport if unable to use NHLS transport – we can arrange collection and courier. It is important to contact CRDM NICD staff before isolates arrive to ensure that they receive appropriate priority, especially on Fridays and during weekends/public holidays.

Additional information:

If you require additional information, please contact CRDM staff:

- Laboratory Manager: Mrs Linda de Gouveia (011-555-0327 lindad@nicd.ac.za)
- Medical Scientists: Dr Mignon du Plessis (011-555-0387 mignond@nicd.ac.za) or Dr Nicole Wolter (011-555-0352 nicolew@nicd.ac.za)
- Clinical queries: Dr Anne von Gottberg (011-555-0316 annev@nicd.ac.za)
- After hours: NICD Hotline (082 883 9920)

8. Management and treatment of diphtheria

The mainstay of treatment of a suspected diphtheria case is prompt administration of diphtheria antitoxin (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 soon as possible after presentation. The recommended dosage and route of administration depend on the extent and duration of disease. Appropriate antibiotics should also be given, in order to eradicate carriage of the organism, limit transmission, and stop further production of diphtheria toxin.

8.1. Infection prevention and control considerations

Isolate all patients with suspected diphtheria until the diagnosis is confirmed or excluded. Isolate hospitalised 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.

8.2. Supportive care

Refer all probable or confirmed diphtheria cases for specialist assessment by a paediatrician or an Ear, Nose and Throat surgeon. 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.

8.3. 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. DAT is generally not indicated in cases of cutaneous diphtheria without systemic manifestations. However, in cases where the ulcer is very large (>2cm^2) 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.

8.4. Antibiotic treatment

Antibiotic treatment 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 diagnostic specimens should be collected before commencing with antibiotic treatment. However, should antibiotics already have been started, specimens should still be collected. Recommended antibiotics include macrolides (erythromycin, azithromycin or clarithromycin) or benzylpenicillin.

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.

Antibiotic therapy should be administered for 14 days[12]:

Parenteral treatment for patients unable to swallow. Switch to oral as soon as patient is able to swallow:

- Benzylpenicillin, IV, 50 000 units/kg/dose 6 hourly

Oral treatment for patients able to swallow:

- Phenoxymethylpenicillin, oral, 15 mg/kg/dose 6 hourly (maximum: 500 mg per dose)

- IV erythromycin
  For children 40mg/kg/day dose a day (maximum 2g per day), divided dose administered every 6 hours
  For adults, 2g/day, divided dose administered every 6 hours

- Oral erthyromycin
  For children, 40mg/kg/day (maximum 2gm/day), divided dose every 6 hours
  For adults, 2 grams/day divided dose every 6 hours

In individuals with severe penicillin allergy:
Parenteral treatment for patients unable to swallow. Switch to oral as soon as patient is able to swallow:

- Azithromycin, IV, 10 mg/kg daily
  Oral treatment for patients able to swallow
- Azithromycin, oral, 10 mg/kg daily

9. Control and prevention of diphtheria

Adherence to the EPI vaccination schedule including primary vaccinations with diphtheria toxoid-containing vaccine, and booster vaccination at 18 months, and 6 and 12 years is essential for the prevention of diphtheria. All persons who are diagnosed with confirmed or probable diphtheria should receive a booster dose of diphtheria-containing vaccine once they are clinically stable, as infection does not reliably induce protective antibody levels. 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).

Table 3. Currently available vaccines that are appropriate for the prevention of diphtheria*.

Product name	Vaccine description	Appropriate indications
Pentaxim® (DTaP-IPV/Hib)	Diphtheria, tetanus, acellular pertussis, *Haemophilus influenza type b*, inactivated polio	Primary vaccination series, and booster at 18 months licenced for use in children aged 6 weeks to 7 years
Infranix® Hexa (DTaP-IPV/Hib/hep B)	Diphtheria, tetanus, acellular pertussis, *Haemophilus influenza type b*, inactivated polio and hepatitis B	Primary vaccination series, and booster at 18 months licenced for use in children aged 6 weeks to 7 years; can only be given at 6 weeks if Hep B given at birth, else commence schedule at 2 months.
Infanrix® (DTaP)	Diphtheria, tetanus, acellular pertussis	Primary vaccination series, and booster at 18 months, licenced for use in children aged 6 weeks to 7 years
Diftavax® (Td)	Diphtheria (reduced dose), tetanus	Routine booster immunisation. Licenced for use in persons 6 years and older
Adacel Quadra® Boostrix Tetra® (TdaP-IPV).	Tetanus, diphtheria (reduced dose), acellular pertussis, inactivated polio	Active immunisation or booster in persons aged 3 (Adacel Quadra®) or 4 years and older (Boostrix Tetra®)

*Product details and components obtained from South African Medicines Formulary, 2014.

10. Recommended public health response to a case of diphtheria in South Africa

Diphtheria is a Category 1 notifiable medical condition (NMC) in South Africa. All cases (suspected, probable or confirmed) should be notified telephonically by a doctor or nurse within 24 hours. Category 1 conditions require immediate reporting by the most rapid means available upon diagnosis followed by a written or electronic notification to the Department of Health within 24 hours of diagnosis by health care providers, private health laboratories or public health laboratories.

A NMC Case Notification form (available at http://www.nicd.ac.za/index.php/nmc/notifiable-medical-conditions-list/) must be completed and sent to NMCsurveillanceReport@nicd.ac.za or faxed to 0866391638 and also to the local sub district/district as well as District and Provincial communicable disease control (CDC) coordinators urgently (as per routine notifiable medical condition notification procedures). The case should also be reported to infection prevention and control practitioners at healthcare facilities where applicable.

On notification of case-patients the following public health actions should be initiated immediately:

Step 1: Conduct a detailed case investigation

1. Obtain detailed demographic, clinical and risk factor information. A case-investigation form (CIF) is available at the end of this document (Appendix B)
2. Complete the NMC form (available at http://www.nicd.ac.za/index.php/nmc/notifiable-medical-conditions-list/)
3. Submit both forms (CIF and NMC) to the district CDC focal person as well as emailing to NMCSurveillanceReport@nicd.ac.za and outbreak@nicd.ac.za
4. Compile a case and contact line list and apply case definitions (Appendix C)

Step 2: 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; and kissing/sexual contacts of the patient
    - If the index case is a young child, persons 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. 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. 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

Step 3: Swab collection in close contacts and eligible at-risk contacts

- Collect nasopharyngeal and oropharyngeal swabs for culture and PCR – this should be done before chemoprophylaxis is administered.
- Should a contact test positive for toxigenic *C. diphtheriae*, the person will require full treatment and follow-up cultures as per symptomatic cases. Infection control measures should be implemented (isolation with standard, contact and droplet precautions) 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.* Disinfection of toys, pacifiers and other fomites that the patient used or touched should also be done.

Step 4: 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 azithromycin may be used for chemoprophylaxis:

<u>Benzylpenicillin:</u>

Children < 6 years: Single dose: 600 000 units IM

Children > 6 years: Single dose: 1.2 million units IM

Adults: Single dose: 1.2 million units IM

<u>Azithromycin:</u>

Children Oral, 10 mg/kg per day on day one THEN 5 mg/kg per day for four days (total of 5 days)

Adults Oral, 500 mg on day one THEN 250 mg daily for four days (total of 5 days)

All close contacts: if primary culture was positive, follow up with second oropharyngeal and naspharyngeal swab after 2 weeks of initiating chemoprophylaxis and treat again if organism has not been eradicated.

Step 5: Monitor close and eligible at-risk contacts

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.

Step 6: 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.

Step 7: 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 of age 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 according to Table 3 above.

Step 8: Alert other healthcare facilities in the area

Alert healthcare practitioners in the area and inform them to maintain a high index of suspicion for diphtheria amongst persons presenting with pharyngitis, or chronic, non-healing ulcers. Provide fact sheets about the disease aimed at healthcare professionals

Step 9: Conduct health promotion activities and health education

Identify at-risk populations, such as school children, health care workers for health promotion activities. Produce and distribute information, education and communication materials that provide basic information about the disease and the vaccine and vaccine schedule. Encourage good personal hygiene practices (hand hygiene and cough etiquette)

Step 10: Vaccination campaigns in response to outbreaks

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

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APPENDIX A

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

1 Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6000
www.nicd.ac.za

Specimen and isolate submission form

Please submit this form when sending any clinical specimen or isolate to the NICD for testing:

Date of sending (dd/mm/yyyy):_____

At the NICD, for the attention of:_____

Sending clinician / laboratory details:

Sending clinician / laboratory name:_____

Sending laboratory contact person:_____

Sending clinician / laboratory contact details (please tick preferred method of contact):

☐ Tel: _____ ☐ Fax: _____ ☐ E-mail:_____

Specimen / isolate details:

Date of specimen collection (dd/mm/yyyy):

☐ Clinical specimen Specimen type:_____

☐ Isolate Suspected agent:_____

Test requested / reason for sending:_____

Previous laboratory results/ comments (or attach copy of test results):_____

_____

Patient details:

First name:_____ Surname:_____Gender: ☐ Male ☐ Female

Birthdate (dd/mm/yyyy): _____ Age: _____ Age units:_____

Clinical diagnosis:_____

Date of symptom onset (dd/mm/yyyy) : _____ Patient identifier:_____

Additional comments:_____

_____

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Division of the National Health Laboratory Service

APPENDIX B

DIPHTHERIA CASE INVESTIGATION FORM (CIF)

This form should be completed in full for each suspected Diphtheria case/contact

INVESTIGATOR DETAILS

Name		Surname	
Contact number		Date of investigation	

SOURCE(S) OF INFORMATION

Interview	Yes ☐ No ☐		Medical record review	Yes ☐ No ☐		
Person(s) interviewed	Clinician ☐	Parent ☐	Caregiver ☐	Guardian ☐	Patient ☐	Contact ☐

DEMOGRAPHIC DETAILS

Name		Surname		Date of birth	
Age(years)		Gender (M/F)		Contact number	

Race	Black ☐	Coloured ☐	Indian ☐	White ☐	Other ☐	Specify other

Residential address	

Code		District		Province	
Occupation			Is the person a learner?		Yes ☐ No ☐
If learner, name of school				Grade	

CLINICAL DETAILS

Symptomatic? (Y/N)		If symptomatic date of onset of symptoms	

If symptomatic, tick all the listed symptoms below that the person experienced:

Fever ☐	Swollen neck ☐	Fatigue ☐	Shortness of breath ☐	Difficulty swallowing ☐
Malaise ☐	Sore throat ☐	Stridor ☐	Change in voice ☐	Membrane in mouth ☐
Other ☐	If other, specify			

Did the person experience any complications? (Y/N)	

If complications experienced, tick all the listed complications below that the person experienced:

Airway obstruction ☐	Myocarditis ☐	Peripheral neuritis ☐	Kidney failure ☐	Other ☐

If other, specify	
List any comorbidities	

ADMISSION DETAILS

Admitted? (Y/N)		Previous admissions in the last year? (Y/N)		Number of previous admissions	
Date of current admission		Health facility name			
Ward		Placed in isolation? (Y/N)		Outcome	Died ☐ Discharged ☐ UNK/RHT ☐
Admission/facility record number		Outcome date			
Was patient referred? (Y/N)		Name of referring facility			
Date of referral		Date of first presentation			

TREATMENT INFORMATION

Is person on antibiotic therapy? (Y/N)		Name of antibiotic			
Dose (mg)		Date start		Date finish	
Has this person received Diphtheria Anti-Toxin? (Y/N)					

VACCINATION HISTORY

Vaccination history available? (Y/N)		Source of history	RTHC ☐	Medical records ☐	Self-reported ☐

Primary series of vaccinations			*Booster doses*		
	Date received			Date received	
6 weeks ☐	Date received		6 years ☐	Date received	
10 weeks ☐	Date received		12 years ☐	Date received	

EXPOSURE HISTORY

Travel history

Has this person travelled *outside* the borders of South Africa within 10 days prior to onset of illness? (Y/N)		
If yes, specify country (ies) visited		

Date of departure from South Africa		Date of return to South Africa	

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Has this person travelled *within* the borders of South Africa within 10 days prior to onset of illness? (Y/N)
If yes, specify area (s) visited below:

Place visited	Date of arrival	Date of departure

Contact history

Has this person had contact with a suspected or confirmed diphtheria case? (Y/N)
If yes, provide details of the suspected or confirmed case:
Include name, address, contact details

Has this person had contact with any person(s) with similar symptoms or illness? (Y/N)
If yes, provide details of the symptomatic or ill person(s):
Include name, address, contact details

Has this person attended any gatherings within 10 days prior to onset of illness? (Y/N)
If yes, provide details:

Name of event		**Location**		**Date of event**	

LABORATORY INFORMATION

Were specimens collected from this person for laboratory testing? (Y/N)		**Collection date**	

Specimen type	Nasal swab ☐	Throat swab ☐	Skin/wound swab ☐	Other ☐	Specify other

Health facility laboratory specimen number	
Test conducted	***Test result***

DATA CAPTURE INFORMATION

Data capture date		**Data capturer name**		**Line-list record number**	

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Division of the National Health Laboratory Service

APPENDIX C

DIPHTHERIA LINE LIST

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Case Information									
Surname	Name	Age	DOB	City/Town/ Village	District	Province	Date of Symptom Onset	Date of Admission to hospital	Date of Death
							dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy

For all information pertaining to location, please list information on where the contact will be residing for the next week.

Contact Information															
Surname	Name	Sex (M/F)	Age (yrs)	DOB	Relation to Case	Date of Last Contact with Case	Type of Contact (1 or 2)* List all	Street address	City/Town	District	Contact Phone Number	Learner or Employed (Y/N) If yes, school or workplace name?	Swab Taken (Y/N) Date	Antibiotic Prophylaxis Given (Y/N) Date	Vaccine Given (Y/N) Date
						dd/mm/yyyy									
						dd/mm/yyyy									
						dd/mm/yyyy									
						dd/mm/yyyy									
						dd/mm/									

Types of contact:
1: Direct, physical contact with the case (dead or alive)
2: Slept or spent time in the same household or room as the case