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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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Disclaimer:

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 suspected diphtheria case (Section 8, pg. 18-19)

1. Isolate: Prevent transmission of *C. diphtheriae* by practising contact and droplet precautions as soon as diphtheria is suspected
2. Provide supportive care: Provide oxygen, monitor with ECG and intubate or perform a tracheostomy if necessary (using appropriate PPE)
3. Provide diphtheria antitoxin according to severity of illness and weight of patient (if indicated & prior to lab confirmation)
4. Treat with appropriate antibiotics
5. Notify the case to the NMC
6. Alert the laboratory and send specimens to confirm diagnosis

Management of close contacts (pg. 20)

1. Identify 'close' and 'at-risk' contacts
2. Collect a nasopharyngeal/mid-turbinate nasal and oropharyngeal swab
3. Administer chemoprophylaxis after swab collection
4. Vaccinate contacts appropriately
5. Monitor contacts for 10 days (from last date of contact) 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 (Section 10, pg. 22-24):

Diphtheria is a Category 1 notifiable medical condition. Immediate reporting, even in the absence of laboratory confirmation, should be done telephonically followed by written or electronic notification within 24 hours of diagnosing a case.

Please complete the NMC form ([NOTIFICATION FORMS - NICD](#)) or App and case investigation form ([Diphtheria - NICD](#)) 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):

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Diphtheria case definitions (Section 6, 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/OR

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* (Section 7, pg. 12-17):

1. Collect an oropharyngeal swab from the affected area, ideally from below the membrane (include pseudomembrane tissue if present)
2. Plate swab for single colonies on a) blood agar (incubate at 37°C in CO₂ for 48 hours) and b) on Hoyle's agar (incubate at 37°C in O₂ for 48 hours)
3. *C. diphtheriae* form black colonies on Hoyle's and look similar to staphylococci on blood agar. They are catalase-positive, small Gram-positive bacilli
4. Confirm identification using API Coryne or VITEK or MALDI-TOF
5. Submit culture and swab/specimen to NICD for confirmation, ELEK testing, PCR, whole genome sequencing

For laboratory staff:

1. Please send any suspect or confirmed isolates of *Corynebacterium* spp. to the NICD for identification/confirmation and for further characterisation (including pus/cutaneous or blood isolates)
2. Please include the original specimen (swab, blood, tissue) (if available) for PCR testing
3. Please also send culture-negative specimens to NICD for PCR testing

1. Introduction

Diphtheria is caused by *Corynebacterium diphtheriae* (or rarely *C. ulcerans* or *C. pseudotuberculosis*) and presents most commonly as a membranous pharyngitis. The most common manifestation of diphtheria is classic respiratory diphtheria, whereby disease is toxin-mediated and characterised by the formation of a pseudomembrane in the upper airways. The mortality of diphtheria was as high as 50% but declined to about 15% after antitoxin use became widespread [1]. Death may occur as a result of acute respiratory obstruction, acute systemic toxicity, myocarditis, renal failure and neurologic complications. *C. diphtheriae* can also infect the skin (known as cutaneous diphtheria). More rarely, it may affect mucous membranes at other sites such as genitalia and conjunctiva [2]. Following introduction of the vaccine in the 1940-50s, diphtheria was practically eradicated and clinical diphtheria became an uncommon disease globally and in South Africa. There is presently global concern that diphtheria is re-emerging. A number of outbreaks of diphtheria have been reported from Eastern Europe, Southeast Asia, South America and West Africa [3–6]. Persons (most especially children) who are not vaccinated or are partially vaccinated are most at risk of diphtheria, however adults may also be at risk due to waning immunity over time, especially in the absence of booster doses during childhood [1].

2. Microbiology

Respiratory diphtheria is caused by infection with toxin-producing (toxigenic) strains of *C. diphtheriae*, or rarely *C. ulcerans* or *C. pseudotuberculosis*. *C. diphtheriae* is a nonsporulating, unencapsulated, nonmotile, pleomorphic, small 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 [7]. 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 multilocus sequence typing and whole genome sequencing.

C. diphtheriae produces an exotoxin, encoded on a lysogenic toxin gene-carrying bacteriophage, 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 B sub-unit (which binds and facilitates cell entry), and a highly toxic 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 toxin repressor protein (DtxR) which is also present in many non-toxigenic isolates. Therefore, non-

toxigenic strains serve as a potential reservoir for the re-emergence of toxigenic strains if they possess a functional *dtxR* gene and become infected with a *tox* gene-carrying phage.

3. Epidemiology

Implementation of the DTP (diphtheria-tetanus-pertussis) vaccine and extensive vaccine coverage led to significant declines in the global incidence of diphtheria. However, since the early 1990s, there has been a global resurgence in *C. diphtheriae* disease, due to disruptions in healthcare systems and vaccination programs [6,8–10] and due to increased reports of non-toxigenic *C. diphtheriae* infections [11–13].

In South Africa, early studies in the 1940s and 1950s reported rates of respiratory diphtheria significantly higher than those in developed countries at the time, ranging from 20-35 per 100,000 population, equating to approximately 3000 case notifications annually [14]. From 1980 to 2014, 412 diphtheria cases were reported by South Africa through the WHO/UNICEF Joint Reporting Process with the majority (>80%) notified prior to 1990 [15]. A laboratory-confirmed respiratory diphtheria case reported in South Africa occurred in a young adult in February 2010 in Western Cape Province (<https://www.nicd.ac.za/archives/>). From March to June 2015, a cluster of 15 respiratory diphtheria cases (in children and adults) was reported from KwaZulu-Natal (KZN) Province in South Africa with a case-fatality ratio of 27% [16]. In 2014, prior to the outbreak, KZN reported coverage for the primary series diphtheria vaccinations in the province at 96%, and 83% for the 18-month booster vaccination. Tetanus-diphtheria (Td) booster coverage rates for 6- and 12-year-old children were 54% and 20%, respectively. A novel, toxin-positive clone, sequence type (ST) 378, was the cause of this outbreak [17]. The 2015 outbreak prompted immediate health promotion activity in the country, including notifications to all healthcare practitioners and laboratories to consider and exclude *C. diphtheriae* in the differential diagnosis for a sore throat, and to submit any isolates including those isolated from blood (infective endocarditis) and cutaneous diphtheria cases to the national reference laboratory (NICD) for further characterization (toxin confirmation and strain typing). An additional 44 *C. diphtheriae* infections have been reported from 2015 to date (26 May 2023) representing toxin-positive and –negative respiratory diphtheria (n=16), toxin-negative endocarditis (n=11) and (predominantly) toxin-negative cutaneous diphtheria (n=17) cases (unpublished data).

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, the toxin can cause a variety of systemic effects including myocarditis and neurologic complications. Invasive disease caused by *C. diphtheriae* occurs rarely, most commonly as a result of non-toxigenic strains and can include bacteremia, endocarditis, osteomyelitis or 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 carriers of toxigenic *C. diphtheriae*. Carriage can be eradicated by appropriate antibiotic treatment. Cutaneous diphtheria can cause secondary respiratory and cutaneous infections and may be a source of outbreaks. Cutaneous diphtheria lesions potentially act as silent reservoirs of disease.

5. Clinical presentation and risk factors for diphtheria

5.1. Respiratory diphtheria

The classic presentation of respiratory diphtheria is associated with extensive pseudomembranous pharyngitis, massive swelling of the tonsils, uvula, cervical lymph nodes, submandibular region, and anterior neck ('bull neck') [7]. 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 unvaccinated persons, persons with incomplete primary vaccination series, or more rarely, in persons who have been vaccinated as immunity wanes in older individuals especially those who did not receive booster doses during childhood [18]. However, disease in persons with prior vaccination may be mild, and systemic symptoms do not usually occur. *C. diphtheriae* isolates causing respiratory diphtheria are usually toxin producing.

5.1.1. Local symptoms and clinical findings

Pharyngeal infection commences with erythema, and progresses to isolated spots of grey and white exudate which may coalesce 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 area 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 most commonly from the effects of absorbed toxin, most importantly the heart and nervous system. The risk of developing cardiac and/or neurological toxicity is proportional to the severity of local infection. 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 (severe forms of heart block, AV dissociation and other arrhythmias that carry poor prognosis) can be detected in as many as two-thirds of patients. 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. 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 are primarily toxic neuropathies and 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 recovery may be slow with prolonged convalescence. Renal complications may develop as a direct effect of the toxin on the kidneys and may result in renal failure.

5.2. *Cutaneous diphtheria*

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 and is usually milder, and toxic manifestation are rare in vaccinated individuals. The types and appearance of cutaneous diphtheria are extremely variable [7]. *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 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. Cutaneous diphtheria is mostly due to toxin-negative *C. diphtheriae* although toxigenic strains have also been isolated from skin lesions and ulcers.

5.3 *Non-toxigenic C. diphtheriae*

Non-toxigenic *C. diphtheriae* typically causes chronic skin ulceration; less common manifestations include upper respiratory tract infections, or 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 with high morbidity and mortality.

6. Case definitions and classification of diphtheria

Why is surveillance necessary?

Diphtheria is caused by infection with toxin-producing strains of *Corynebacterium diphtheriae* or *C. ulcerans* or *C. pseudotuberculosis*. Diphtheria is spread via respiratory droplets or direct contact with infected skin lesions from an infected person.

Diphtheria has a high mortality rate. Notification is essential because additional cases can be prevented amongst contacts by early administration of antibiotics. Persons who are fully vaccinated are at lower risk of diphtheria.

Who must notify and when?

The clinician who suspects diphtheria should notify the case immediately. Healthcare workers should NOT wait for laboratory confirmation before notifying or treating cases.

Suspected case definition

A person who presents with an upper-respiratory tract illness characterised by sore throat, low-grade fever AND an adherent membrane of the nose, pharynx, tonsils, or larynx.

Probable case definition

A person who presents with an upper-respiratory tract illness characterised by sore throat, low-grade fever AND an adherent membrane of the nose, pharynx, tonsils, or larynx;

OR

a person who has an epidemiological link to a confirmed case, who has respiratory tract symptoms but no membrane;

OR

a person with a skin lesion

AND

C. diphtheriae or *C. ulcerans* or *C. pseudotuberculosis*

has been isolated from relevant specimens but toxigenicity status has not been confirmed.

Confirmed case definition

Any person with signs and symptoms consistent with diphtheria (respiratory and/or cutaneous)

AND

a positive culture for or PCR detection of *C. diphtheriae* or *C. ulcerans* or *C. pseudotuberculosis* from a clinical specimen which is confirmed to be *tox* gene positive by PCR or toxin-producing by ELEK testing.

Additional notes

Clinicians who suspect diphtheria should contact the **NICD 24-hour Clinician Hotline (0800 212 552)** for assistance with specimen collection and diagnosis. It is essential to: 1) collect a throat swab from suspected cases using the correct procedures, and 2) to complete a case investigation to provide authorities with information to identify contacts and implement prevention measures.

<https://www.nicd.ac.za/nmc-overview/notification-forms/>

7. Laboratory detection of *C. diphtheriae*

7.1. Specimen collection from suspected cases of respiratory or cutaneous diphtheria, and close/at-risk contacts

Please refer to pg. 22 for guidance on close and at-risk contacts

Swabs should preferably be collected prior to antibiotic treatment and taken from the nasopharynx, oropharynx and underneath the pseudomembrane (if present), or wound base in cutaneous ulcers (under the pseudo membrane if present). Pseudomembrane tissue should also be collected if possible and stored in saline (not formalin). Dacron, rayon or nylon-flocked swabs should be used and placed in Amies or Stuart transport medium (Fig. 1). Specimens must be transported to the laboratory, with ice packs, as soon as possible.

Please use the **specimen submission form** available at https://www.nicd.ac.za/wp-content/uploads/2023/05/CRDM-specimen-submission-form-v3_02-11-22.pdf

Please alert the laboratory that the specimens are for suspected diphtheria to ensure appropriate testing is performed. Following treatment, repeat swabs should be collected to ensure eradication.

For close and at-risk contacts, nasopharyngeal (or nasal) and oropharyngeal swabs should be collected prior to chemoprophylaxis. Following completion of chemoprophylaxis, swabs should be collected again from *C. diphtheriae*-positive contacts 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 specimens are appropriately protected. Droplet precautions are necessary, including a surgical mask. Eye and mask protection is 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 used for the transport of throat and nasal swabs

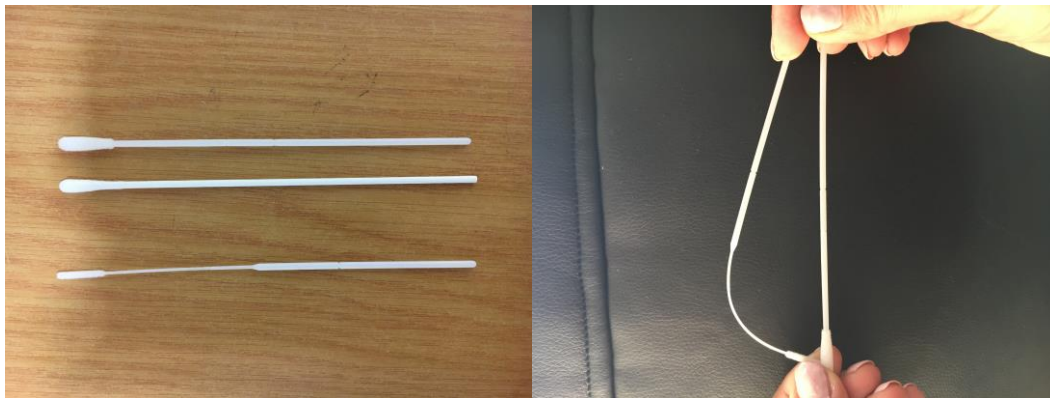


Figure 2A. Top two swabs may be used for throat. Bottom swab (thin/flexible shaft) to be used for nasopharyngeal specimen collection.

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 nasopharyngeal and oropharyngeal swabs from persons with suspected diphtheria or close 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. Through one nostril, insert the swab into the nose beyond the anterior nares.

6. 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. If the patient/individual resists, collect a mid-turbinate nasal swab instead.
7. Place the swab in Amies or Stuart transport medium and dispatch immediately to the laboratory for culture and PCR. In the absence of transport media, dry swabs may also be sent and should reach the laboratory without delay.

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 small Gram-positive 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. Rather, diagnosis relies on the detection of *C. diphtheriae* through culture or PCR detection [7,19].

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 O₂ 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. On blood agar, colonies appear similar to staphylococci.
4. Perform a Gram's stain of typical or suspect colonies on either plate. 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 of incubation on Hoyle's medium (~1mm in diameter, black matt colonies, bottom half of agar plate)



Figure 3B: Typical colonial appearance after 18 hours of 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 from *C. diphtheriae* bacterial colonies. Elek testing is available at the Centre for Respiratory Diseases and Meningitis (CRDM). Specimens and cultures can also be tested by PCR for the presence/absence of *C. diphtheriae* and the toxin gene [19]. In very rare cases, *tox* gene-bearing non-toxigenic *C. diphtheriae* has been described [20], and therefore the Elek test should ideally be performed on all *C. diphtheriae* isolates. Confirmed or suspected *C. diphtheriae* cultures should be submitted to the NICD for confirmation and toxigenicity testing. Isolates should be submitted as pure cultures heavily inoculated onto Dorset transport medium or other common agar slants or plates and submitted 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.

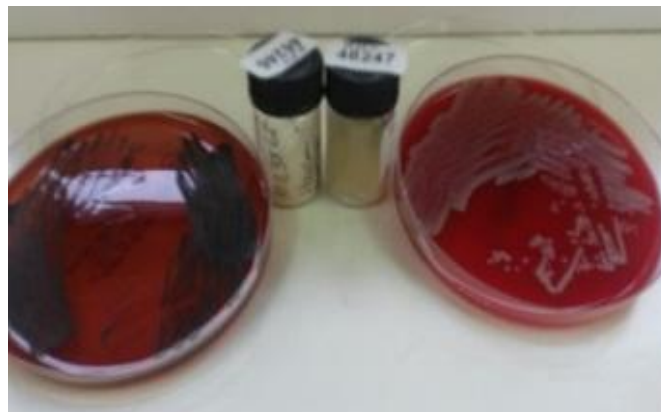
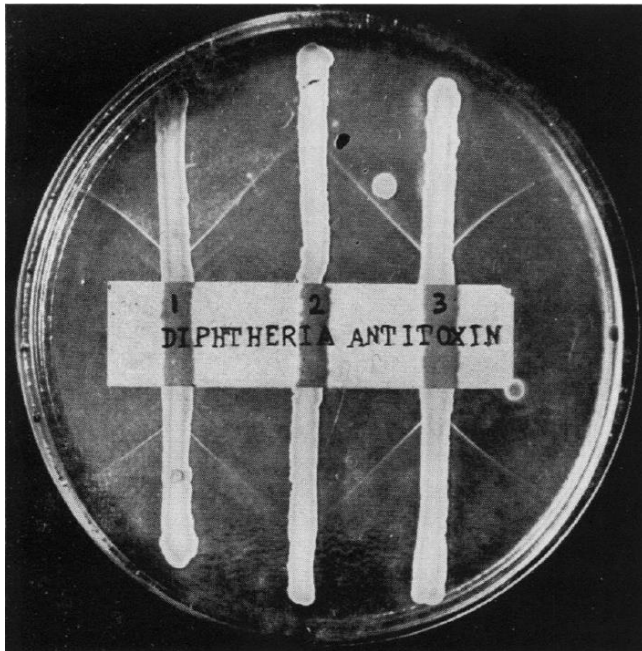


Figure 4: Submit plates with suspected *C. diphtheriae* colonies to NICD on Dorset transport media, or send the blood or Hoyle's agar plate (sealed in e.g. Parafilm M)

FIG. 5.—Plate photographed after prolonged incubation and several days at room temperature showing secondary lines. Strains 1 and 3 are virulent, 2 is avirulent. Strain 1 shows two fine lines developing between the toxin line and the filter strip.'



STEPHEN D. ELEK

J. clin. Path. (1949), 2, 250.

7.3. Transport of specimens to NICD

Culture plates, Dorset slopes, swabs and other clinical specimens (blood, tissue, pus swabs) should be transported without delay to:

Centre for Respiratory Diseases and Meningitis (CRDM), National Institute for Communicable Diseases (NICD), 1 Modderfontein Road, Sandringham, Johannesburg, 2192

Please use the **specimen submission form** available at:

https://www.nicd.ac.za/wp-content/uploads/2023/05/CRDM-specimen-submission-form-v3_02-11-22.pdf

For NHLS laboratories, please liaise 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/samples are sent to ensure that they receive appropriate priority, especially ahead of weekends/public holidays.

Additional information:

- Laboratory queries: Laboratory Manager: Mrs Linda de Gouveia (011-555-0327 lindad@nicd.ac.za) or Medical Scientist: Dr Mignon du Plessis (011-555-0387 mignond@nicd.ac.za)

- Clinical queries: Dr Anne von Gottberg (011-555-0316 annev@nicd.ac.za) or Dr Sibongile Walaza (011-386-6410 sibongilew@nicd.ac.za)
- After hours: **NICD Hotline (0800 212 552)**

8. Management and treatment of diphtheria

8.1 *Diphtheria antitoxin treatment (DAT)*

The mainstay of treatment is DAT. Disease course and outcome depend on how early from disease onset that antitoxin treatment is started. Approximately 2-3 days from onset of symptoms, the risk of complications and fatal outcome increases with each day DAT administration is delayed. If diphtheria is strongly suspected, treatment with DAT should be given immediately without waiting for laboratory results. The dose of DAT given varies depending on site and extent, time since onset and severity of infection. DAT should be considered for use in cases of probable or confirmed cases of toxigenic diphtheria. DAT is not recommended in asymptomatic carriers or close contacts. Clinicians are advised to contact their respective provincial CDCs regarding access to DAT; it may not be readily available due to global shortages.

8.2 *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 *C. diphtheriae*. In the absence of 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.

8.3 *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.

8.4 Antibiotic treatment

Antibiotic treatment is not a substitute for DAT treatment. Recommended antibiotics include macrolides (erythromycin, azithromycin or clarithromycin) or benzylpenicillin. Antibiotics eradicate the organism from the nasopharynx and prevent further transmission to others.

Elimination of the organism must be confirmed after antibiotic treatment is completed: two sets of nasopharyngeal/ mid-turbinate nasal and throat swabs must be collected for culture, taken at least 24 hours apart and more than 24 hours after completing antibiotic treatment. If the toxigenic strain persists, an additional 10 days of antibiotic treatment is indicated.

In symptomatic individuals, antibiotic therapy should be administered for 14 days [21] [2]:

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:

- Phenoxyethylpenicillin, 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 erythromycin
 - 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 (maximum 500mg/day)
 - Oral treatment for patients able to swallow
- Azithromycin, oral, 10 mg/kg daily (maximum 500mg/day)

Close and at-risk contacts:

1. Contacts should receive antibiotic therapy (penicillin or erythromycin) for 7 days.
2. If a contact is positive for toxigenic *Corynebacterium spp.*, then the contact should be treated as a case with an antibiotic course for two weeks (DAT is not needed for asymptomatic cases or cases without a pseudomembrane). Do a new investigation of contacts and implement proper case management, including isolation. This contact would now be classified as a laboratory-confirmed case.
3. If the contact is positive for non-toxicogenic *Corynebacterium spp.*, they should complete the course of antibiotics and be retested.
4. If the contact is negative for *Corynebacterium spp.*, antibiotics and monitoring can be stopped.

9. Control and prevention of diphtheria

Population-level vaccine coverage should be 80%-85%, to induce herd protection and reduce the threat of an outbreak [22]. Adherence to the Expanded Programme for Immunisation vaccination schedule is essential for the prevention of diphtheria and includes primary vaccinations with diphtheria toxoid-containing vaccine at 6, 10 and 14 weeks followed by a booster dose at 18 months, and at 6 and 12 years of age. The booster doses are essential for long term protection.

All persons diagnosed with confirmed or probable diphtheria should receive a booster dose of diphtheria-containing vaccine once they are clinically stable, as infection may 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. Children who have completed their primary diphtheria vaccination series plus routine booster/s, and adolescents and adults who have been previously immunised should 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, <i>Haemophilus influenzae type b</i> , 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, <i>Haemophilus influenzae type b</i> , 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 and reported to infection prevention and control practitioners at healthcare facilities where applicable. Suspected case should 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). On notification of a case, the following public health actions should be initiated immediately:

Step 1: Conduct a detailed case investigation

- a. Obtain detailed demographic, clinical and risk factor information. A case-investigation form (CIF) is available at <https://www.nicd.ac.za/diseases-a-z-index/diphtheria/>
- b. Complete the NMC form (available at [NOTIFICATION FORMS - NICD](#)) or complete using the App
- c. 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
- d. Compile a case and contact line list ([Diphtheria - NICD](#)) and apply case definitions

Step 2: Identify close and at-risk contacts

Close contacts include the following groups, who had contact with the suspected case during the 5 days prior to the start of symptoms. 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, intubated the patient or who were exposed to respiratory droplets (cough, sneezing etc.) without appropriate PPE (N95 mask) or have dressed the wounds of a cutaneous case without appropriate infection control procedures (droplet and contact precautions).

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 (within 5 days of onset of symptoms in the case):

- a. Friends, relatives, and caregivers who regularly visit the home

- b. School/pre-school class contacts
- c. Those who share the same room at work
- d. Other healthcare workers who have had direct/close contact with the case without adequate infection control procedures (droplet and contact precautions)

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

Collect nasopharyngeal/mid-turbinate nasal and oropharyngeal swabs for culture and PCR – this should ideally be done before chemoprophylaxis is administered (see pg. 13).

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 (see pg. 19-20 for details). 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.

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

Step 5: Isolation of positive case and disinfection of environment

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 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. If isolation is practically not feasible (e.g. high number of HCW contacts), then contacts should wear surgical masks.

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 address waning immunity in older children/adults. All unimmunised /incompletely immunised contacts should complete their primary vaccination and booster doses as per the EPI schedule.

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 and 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 vaccination 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. This is dependent on various factors – please refer to WHO guidelines [2] for more detailed information.

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