Department of Health and Wellness
Emergency and Clinical Services Support
Hilary Goeiman, Charlene A. Lawrence
Service Priorities Coordination (SPC): Communicable Disease Control (CDC)
Charlene.Lawrence@westerncape.gov.za | Tel: 021- 830-3727; 021-815-8660
Hilary.Goeiman@westerncape.gov.za | Tel: 021-815-8741

Western Cape Government

Urgent

TO:	**Chief Directors**	**Metro Health Services (MHS)**
		Rural Health Services (RHS)
		Strategy
	District Managers:	**MHS Substructures**
		Rural Districts
	Directors:	**Emergency Medical Services**
		Forensic Pathology Services
		Medicine Management, Laboratory & Blood Services
		Facilities Management: Provincial Environmental Health
		Communication
		Assurance
	Chief Executive Officers (CEOs):	**Central, Regional and District Hospitals**
	Managers:	**Private Hospitals and Private Clinics**
	Heads of Health / Executive Directors:	**Local Authorities/Municipalities/City of Cape Town**
		South African Military Health Services
	Managers:	**National Health Laboratory Services**
		Private Laboratories
		General Practitioners
	Regional Commissioner:	**Department of Correctional Services**
	Head of Department:	**Department of Basic Education**

CIRCULAR: H .....111...../2024

DIPHTHERIA ALERT: PREPAREDNESS & PUBLIC HEALTH RESPONSE: INCREASE IN THE IDENTIFICATION OF TOXIGENIC RESPIRATORY CASES IN THE CAPE TOWN METRO DISTRICT AND PROVINCE

This circular is an update of Circular H146/2023, issued on 15/11/2023.

Diphtheria is a highly contagious and potentially life-threatening bacterial disease. It is a vaccine-preventable disease, however a drop in vaccine coverage could potentially lead to the detection of cases. Diphtheria is preventable by vaccination given as part of the routine EPI schedule at 6, 10, 14 weeks of age, with booster doses given at 18 months, 6 years, and 12 years of age.

Diphtheria is a rare disease, and clinicians need to have a high index of suspicion to make an early diagnosis to commence appropriate treatment. Rapid contact tracing, testing, the administration of prophylactic antibiotics, and vaccination can contain outbreaks.

While diphtheria antitoxin is recommended as part of the treatment of patients with diphtheria, it is in short supply globally and limited supplies are available in South Africa. Clinicians involved in the care of patients with diphtheria will manage the appropriate use of diphtheria anti toxin - infectious disease specialists should be consulted with respect to this. Treatment, in the absence of anti-toxin, involves appropriate antibiotics and supportive care.

Diphtheria disease is a notifiable condition caused by infection with toxin-producing strains of *Corynebacterium diphtheriae* (*C. diptheriae* or rarely *C. ulcerans* or *C. pseudotuberculosis*) and presents most commonly as a membranous pharyngitis. Large neck glands (bull neck appearance) and low-grade fever are associated symptoms. A toxin produced by the bacterium causes necrosis of the tissues, resulting in respiratory obstruction, renal failure, neuropathy, and myocarditis, which if left untreated causes heart failure and death. The mortality due to respiratory diphtheria may be as high as 50% in the absence of antitoxin. Diphtheria may also present with cutaneous lesions caused by non-toxigenic or toxigenic strains. Although cutaneous diphtheria is generally less severe, cutaneous lesions may serve as a potential reservoir for the transmission of toxigenic and non-toxigenic *C. diphtheriae*.

Cutaneous infection with toxigenic strains may rarely be associated with systemic symptoms, such as myocarditis. 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*.

This alert serves to inform clinicians, healthcare workers or practitioners, laboratorians, district-and-sub-district public health officials in both the public and the private sector of:

- **An increase in toxigenic *Corynebacterium diphtheriae* cases that has been detected,** that includes a **localised diphtheria cluster linked to a school in the Cape Town District, and isolated deceased cases** in the West Coast and Cape Town districts respectively.
- The **targeted public health response measures/strategies** being undertaken to control the diphtheria cluster affecting incompletely immunised primary- school going children in the Cape Town District.
- **Advise on strategies to improve vaccination coverage** in the districts – i.e. vaccination in the primary series and especially at 6 and 12 years of age.
- **The Quick Reference Guide for Case Finding for Diphtheria** in the Western Cape – it includes the respiratory, and cutaneous clinical presentation of the disease.
- **The importance of detection of any clinical diagnosis of diphtheria, of notifying and investigating suspected cases, which includes laboratory confirmation – see definitions below.**
- The recommendation **to laboratories to routinely screen all oropharyngeal (OP) and nasopharyngeal (NP) swabs for *C.diphtheriae*. Swabs from abscess or cutaneous lesion should also be screened for *C. diphtheriae* if cutaneous diphtheriae is clinically suspected and/or if it is part of an *C. diphtheriae* outbreak investigation.**

1. SITUATIONAL UPDATE (27 AUGUST 2024)

- Nine laboratory confirmed toxigenic diphtheria cases have been identified from 1 June 2024 – 27 August 2024. This included a 3-year-old child, a 42-year and 38-year-old that demised; and a recent cluster of diphtheria cases linked to a primary school in the Cape Town Metropolitan District.
- A total of 6 cases of *Corynebacterium diphtheriae* have been identified, at a primary school in the Cape Town Metropolitan District in the Western Cape. The 9-year-old index case presented to a local hospital with a swollen neck, shortness of breath, difficulty swallowing, sore throat, membrane in mouth on the 2nd of August 2024. The case was laboratory confirmed on the 13th of August 2024. The case had an incomplete vaccination history (i.e. did not receive his 6-year-old Td vaccination). The child recovered after appropriate treatment with antitoxin and was subsequently discharged without any complications.

- A public health response was launched following the positive results that included contact tracing household/family, schools and consulting healthcare workers; the collection of swabs for diphtheria screening, provision of prophylaxis (antibiotics), and vaccination as per the guidelines. Contact tracing activities at the school led to the identification of two (2) positive school contacts (mild/asymptomatic), and 3 household/family contacts related to these positive school contacts. Contact tracing activities are ongoing
- In addition, a targeted vaccination campaign at the affected school/s and identified communities are underway.
- The Department of Health is working closely with the Department of Basic Education, and all partners to manage these cases, to ensure a multi-sectoral response, focusing on early diagnosis of cases, screening of contacts, treatment, and vaccination.
- Active case finding for respiratory and/or cutaneous (non-healing ulcers) disease is required. Any clinically suspected cases identified need to have laboratory samples/swabs collected and the clinical protocols should be followed.
- Healthcare workers and health facilities in the province have been urged to have a high index of suspicion for diphtheria. Ideally, suspected cases should be notified telephonically and then on the Notifiable Medical Condition (NMC) application. Appropriate specimens should be sent to the National Health Laboratory Services (NHLS) for testing.

2. RECOMMENDATIONS FOR THE MANAGEMENT AND PUBLIC HEALTH RESPONSE TO A LOCALISED CLUSTER/OUTBREAK OF DIPHTHERIA IN THE CAPE TOWN DISTRICT:

Clinicians, other healthcare workers, district/sub-district, and public health officials must be vigilant and report any clinical diagnosis of diphtheria (treatment should be started on clinical diagnosis, do not wait for laboratory confirmation), notify suspected cases, investigate, and ensure laboratory confirmation for all cases meeting the case definition of both the classical respiratory and cutaneous diphtheria presentation, for this cluster /outbreak specific area (Cape Town Metropolitan District), and all districts in the province.

A Quick Reference Guide for Case Finding for additional diphtheria cases in the Cape Town Metropolitan District, Western Cape Province, 9 November 2023, updated 27 August 2024 (Annexure 1) has been compiled for easy reference.

2.1 DIPHTHERIA GUIDELINES, REPORTING AND INVESTIGATION FORMS

All the below-mentioned documents can be found on the NICD website:
https://www.nicd.ac.za/diseases-a-z-index/diphtheria/

- Diphtheria: NICD Recommendations for Diagnosis, Management and Public Health Response (Revised May 2023),
- Notifiable Medical Conditions (NMC) Form,
- Diphtheria Case Investigation Form
- Diphtheria Contact Line List
- Diphtheria Alert to healthcare workers, May 2023
- Diphtheria Frequently Asked Questions, compiled December 2016
- NMC Case Definition Flipchart: Diphtheria
- **Provincial Information, Education and Communication (IEC material):** What you need to know about Diptheria, Facts about Diphtheria

2.2 DIPHTHERIA CASE DEFINITIONS FOR CLUSTERS/OUTBREAKS:

- Diphtheria is a notifiable medical condition in South Africa. Complete the NMC form (available at http://www.nicd.ac.za/index.php/nmc/notifiable-medical-conditions-list/)
- **Adapted diphtheria case definitions have been compiled that includes the respiratory and cutaneous clinical presentation of the disease. (Table 1).** All healthcare workers are also reminded of the general case definitions that are found in the Notifiable Medical Conditions Case Definition Flip Chart (Table 2)
- Obtain detailed demographic, clinical and risk factor information. A case-investigation form (CIF) is available. Submit both forms (CIF and NMC) to the provincial and the district CDC focal person as well as emailing to NMCSurveillanceReport@nicd.ac.za and outbreak@nicd.ac.za
- Compile a case and contact line list and apply case definitions.

Table 1: Case Definitions for the diphtheria cluster/outbreak in Cape Town Metropolitan District	
Suspected case	Individual of any age in any community (focusing specifically on shelters, homeless populations, prisons, schools) in the Cape Town Metropolitan district. **Any persons with upper respiratory-tract illness characterised by sore throat, low-grade fever AND an adherent membrane of the nose, pharynx, tonsils, or larynx.** Suspected cases must be notified and managed appropriately prior to laboratory confirmation.
Probable case	Individual of any age in any community (but also including in shelters and homeless population, prisons, schools) in the Cape Town Metropolitan with ANY of the following symptoms WITHOUT laboratory confirmation of C. diphtheriae: **A person who presents with an upper-respiratory tract illness characterized by sore throat, low grade fever AND an adherent (pseudo-) 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	**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.**
For case definitions of probable cases see Annexure 1: Quick Reference Guide for Case Finding for Diphtheria in the Cape Town Metropolitan District, updated 27 August 2024	

All public and private healthcare workers, laboratorians, and public health officials at district and sub-district levels are remined to report any cases meeting the case definition as stated below for respiratory diphtheria.

Table 2: Case Definitions for Respiratory Diphtheria (as in the NMC case definition flipchart)	
Suspected case	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	A person who presents with an upper-respiratory tract illness characterized by sore throat, low-grade fever AND an adherent membrane of the nose, pharynx, tonsils, or larynx, **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. diphtheria* or *C. ulcerans* or *C. pseudotuberculosis* has been isolated from relevant specimens but toxigenicity status has not been confirmed.
Confirmed case	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.
See NMC Case definition flipchart.	

2.3 PREPAREDNESS AND PUBLIC HEALTH RESPONSE MEASURES

- These measures listed below must be implemented by both **public and private healthcare providers, health practitioners, sub-district, and district health offices. See Annexure 1 and 2 for a quick reference guide and contact details.**

Table 3: Measures for implementation to ensure early detection and public health response to diphtheria cases.

	Objective	**Action**
1.	**Intensify surveillance, notification, report and investigation of suspected diphtheria cases**	✓ **All suspected/probable/confirmed cases should be reported IMMEDIATELY to:** o the Infection Prevention and Control (IPC) Practitioners at health care facilities where applicable, as well as o District and Provincial Communicable Disease Control Coordinators / focal persons, urgently. ✓ **Contact the Communicable Disease Control (CDC) sub-directorate telephonically** if a suspected case is detected at your facility or diphtheria (toxigenic or non-toxigenic *Corynebacterium diphtheriae*) is identified at the laboratory.**:** **Ms Charlene A. Lawrence/Janine Bezuidenhoudt/Washiefa Isaacs/Levani Naidoo** **Tel:** at 021-830-3727 or 021-815-8660 / 8790/ 8676 **Cell:** 072-356-5146, 082-327-0394, 064-742-4005, 060-508-0896 See Quick Reference Guide and Contact details.

		✓ **Inform the NICD 24-hour hotline, for use by health professionals (0800 212 552).** ✓ **Clinicians at referral health facilities e.g., Infectious Disease Specialist on call at Tygerberg Hospital; 021- 938-4911; Groote Schuur Hospital, 021-404-9111, Red Cross War Memorial Children's Hospital, 021-658-5111, may be contacted for further clinical advice or via Vula.** ✓ **Infection prevention and control measures and supportive care must be initiated.** ✓ **Clinicians are required to notify suspected cases of diphtheria while awaiting laboratory confirmation**. ✓ The attached Diphtheria Case Investigation Form (CIF) found at: https://www.nicd.ac.za/wp-content/uploads/2017/08/Suspected-Diphtheria-Case-Investigation-Form.pdf and Diphtheria Contact Line List at https://www.nicd.ac.za/wp-content/uploads/2017/08/SA_Diptheria_Contact_Line-List_2017.pdf, can be used. ✓ Obtain detailed demographic, clinical and risk factor information. Submit both NMC (paper-based or electronic) form found on the following website: https://www.nicd.ac.za/nmc-overview/notification-forms/ , to the provincial and the district CDC focal person as well as emailing to NMCSurveillanceReport@nicd.ac.za and outbreak@nicd.ac.za
2.	**Adequate clinical management of cases**	✓ Clinicians must collect samples from individuals with clinically suspected diphtheria. The samples are sent to the nearest laboratory for culture and then to the National institute for Communicable Diseases (NICD) for PCR and toxigenicity testing. ✓ **Isolation and treatment of the index case prior to confirmation - administration of diphtheria antitoxin (DAT) (where deemed appropriate by the attending clinician in consultation with an infectious disease specialist), antibiotics and immunisation** (booster dose for confirmed and probable cases once clinically stable, with vaccine appropriate for age and immunisation history). ✓ **See the attached guideline:** Diphtheria: NICD Recommendations for Diagnosis, Management and Public Health Response, Revised Version (May 2023), https://www.nicd.ac.za/wp-content/uploads/2023/06/NICD-guidelines_diphtheria_v4_2023_updated-after-review_2-JUN-2023_Final.pdf ✓ Early treatment with antitoxin as per national and WHO guidelines, prior to the toxin binding to cells, is extremely important, and **should be given based on clinical suspicion prior to laboratory confirmation** where feasible and appropriate based on infectious disease specialist advice. o https://iris.who.int/bitstream/handle/10665/375887/WHO-DIPH-Clinical-2024.1-eng.pdf
3.	**Public Health Response to a case or outbreak of diphtheria**	1. Conduct a detailed case investigation (demographic, clinical and risk factor information: case investigation form, case line list, case-contact line list 2. Identify close and at-risk contacts. 3. Conduct laboratory investigation of close contacts and eligible at-risk contacts o Isolation of *C. diphtheriae* on culture and toxigenicity testing (Elek test) 4. Administer chemoprophylaxis to close contacts and at-risk contacts.

		5. Monitor close and eligible at-risk contacts (prophylactic antibiotics, booster vaccination appropriate for age, throat swabs for diphtheria diagnosis) 6. Exclude close and eligible at-risk contacts in high-risk occupations. 7. Vaccinate close and eligible at-risk contacts. 8. Alert other healthcare facilities in the area 9. Conduct health promotion activities and health education 10. Selective vaccination campaigns targeting at-risk groups in response to an outbreak may be required. 11. **District and sub-district health authorities must put measures in place to improve the routine vaccination coverage in the primary series, and especially at 6 and 12 years of age.**

2.4 VACCINATION STRATEGIES TO CONTROL DIPHTHERIA IN THE CAPE TOWN METRO AND PROVINCE

The following vaccination activities are recommended in the affected areas to curb the spread and improve vaccination coverage in the province:

1. **Targeted Vaccination at the affected schools and communities in the Cape Town District**
   - Conduct an emergency diphtheria-containing vaccination campaign at the affected school/s and identified communities, with the support from local partners and health care facilities in the area.
   - This may include the use of mobile outreach sites to expedite the catch-up vaccination.
   - *Apply FIFO/FEFO for vaccine selection.

2. **Vaccination outreach in areas where positive diphtheria has been identified in the province**
   - In addition to contact tracing and follow-up activities, sub-districts where confirmed diphtheria cases have been identified must consider outreach in specific communities/sites, where low coverage and unvaccinated children have been identified.
   - This applies to the 4-hexavalent-doses, 6 and 12-year-old Td vaccination.

3. **Frontline staff (Emergency Medical Services, Emergency Centre)**
   - Frontline staff who were exposed to suspected /confirmed diphtheria cases must be screened, swabbed, given prophylaxis/antibiotics and vaccinated. Kindly refer to the close contact definitions in the national guidelines or consult the NICD hotline and the ID specialists on call at one of the tertiary hospitals.
   - Td vaccination is available for frontline staff who are unsure of their vaccination status or have concerns regarding their risk, through their local health facility.

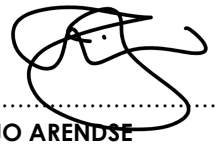
4. **Provincial-wide strategy to link Td vaccination to the national HPV campaign**
   - Provincially, the Td vaccination coverage for 6 and 12-year-olds have been sub-optimal and requires a concerted effort to improve immunisation coverage to prevent and control diphtheria cases, clusters and outbreaks.
   - The National HPV campaign is scheduled for September to October 2024 and includes a booster diphtheria-containing vaccine for all children in grade 5, with consideration to provide catch-up vaccinations for 6- and 12-year-olds who missed previous doses.
   - The province is in the process of switching from Td to Tdap through a phased process. FIFO/FEFO should be applied. Once the Td stock is depleted, providers may switch to Tdap.

NB! Td vaccine is available at health facility level within the province and should be utilised before the expiry date, October 2024. Further orders for Td vaccine should be placed timeously, to avoid stock out at facility level.

Kindly bring the content of this alert/circular to the attention of all healthcare workers at your facility, institution, sub-district, and districts - especially Emergency Centre Clinicians, Infection, prevention, and Control Practitioners; District/sub-district CDC Coordinators / equivalent, NHLS diagnostic laboratories; and Private Laboratories and Environmental Health Practitioners.

We trust on your continued support in the early detection, report, investigation, and control of communicable diseases in the Western Cape Province.

Yours sincerely.



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DR JO ARENDSE
CHIEF DIRECTOR: ECSS (Emergency & Clinical Services Support)
Western Cape Department of Health & Wellness

DATE: 29 August 2024

Annexure 1: Quick Reference Guide for Case Finding of additional Diphtheria Cases, Cape Town Metropolitan District, Western Cape, November 2023 (updated 27 August 2024)

Read in conjunction with the Diphtheria: NICD Recommendations for Diagnosis, Management and Public Health Response (Revised May 2023)

Diphtheria infection is caused by the organism, *Corynebacterium diphtheriae (C. diphtheriae).* Strains of *C. diphtheriae* include toxin-producing *C. diphtheriae* and non-toxin producing *C. diphtheriae.* Severe life-threatening disease is caused by toxin-producing strains, mostly infecting the upper respiratory tract. Non-toxin producing strain are associated with cutaneous lesions (rarely toxin-producing strains) and invasive disease, such as endocarditis and septic arthritis.

Diphtheria is a vaccine preventable disease but with disruptions to vaccine schedules and low vaccine coverage cases are likely to emerge. Diphtheria is highly contagious and may spread very quickly in populations in confined settings with close contact.

Suspected case of diphtheria:

Individual of any age in any community (focusing specifically on shelters, homeless population, prisons and schools) in the Cape Town Metropolitan District.

Suspected cases must be notified and managed appropriately prior to laboratory confirmation.

- **Any persons with upper-respiratory tract illness characterised by sore throat, low-grade fever AND an adherent (pseudo-) membrane of the nose, pharynx, tonsils, or larynx.**

Probable case of diphtheria:

Individual of any age in any community (but also focusing including in shelters and homeless population, prisons and schools) in the Cape Town Metropolitan with ANY of the following symptoms **WITHOUT** laboratory confirmation of *C. diphtheriae*:

- **A person who presents with an upper-respiratory tract illness characterized by sore throat, low grade fever AND an adherent (pseudo-) 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 of Diphtheria

- **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.**

Notification of cases:

1. Diphtheria is a category 1 notifiable medical condition and immediate reporting should be done electronically/paper-based within 24 hours of diagnosing a case.
2. Please complete the NMC form and case investigation form and submit to provincial & district CDC coordinators and to the NICD: NMCSurveillanceReport@nicd.ac.za and outbreak@nicd.ac.za
3. Notify the provincial and the district CDC focal person telephonically, and via emailing, to coordinate and support the investigation and response to cases.

Sample collection from individuals with suspected diphtheria:

1. **A throat swab** should be collected (ideally from below the membrane) using a Dacron, Rayon or nylon-flocked swab and placed in Amies or modified Stuart's transport medium with charcoal. This can be obtained from your local laboratory. The specimen should immediately be transported on ice to the laboratory for testing. The specimen should be clearly labelled: "***Suspected diphtheria***."
2. For cutaneous lesions: Collect samples from specific sites where infection is suspected e.g., tissue, pus swab from abscess or cutaneous lesion/non-healing ulcer. Using the same transport media as respiratory cases. The specimen should be clearly labelled: "***Suspected diphtheria***."
3. If suspected bacteraemia, collect at least 2 blood culture specimens at different times for blood culture.

Treatment of a diphtheria case

1. Isolate: Prevent transmission of *C. diphtheriae* by practicing contact and droplet precautions with appropriate PPE.
2. Alert the referring health facility/hospital clinician, Emergency Medical Services and the Infection Disease Specialist on Call, for clinical guidance.
3. Refer the patient (suspected or confirmed case) to the referral hospital for further management, transport the case alone with all staff wearing appropriate PPE.
4. Refer to the guidelines for treatment protocol, and/or contact the on call infectious disease specialist on https://www.nicd.ac.za/diseases-a-z-index/diphtheria/)

Management of contacts

1. Identify close and at-risk contacts by creating a line list and discuss with Western Cape Communicable Disease Control Coordinator (CDCC) - Ms Charlene A. Lawrence, 021-830-3727, 072-356-5146;
2. Identify if any respiratory and/or chronic skin lesions (may include scaling rash or ulcers with clearly demarcated edges) are present.
3. Collect an oropharyngeal swab and/or skin swab from contacts and complete contact line list

NICD Contact details: NICD Hotline: 0800 212 552

1. Clinical queries: Dr Anne von Gottberg (011-555-0316, annev@nicd.ac.za, Dr Sibongile Walaza (011-386-6410, sibongilew@nicd.ac.za), Dr Jocelyn Moyes jocelynm@nicd.ac.za 0828832044
2. Microbiology Laboratory Manager: Ms Linda de Gouveia (011-555-0327, lindad@nicd.ac.za)
   Molecular laboratory: Dr Mignon du Plessis (011-555-0387, mignond@nicd.ac.za)

Western Cape Department of Health and Wellness Contact Details (see Annexure 2):

- **Infectious Disease (ID) Specialist on call Tygerberg Hospital; 021- 938-4911; Groote Schuur Hospital, 021-404-9111, Red Cross Hospital, 021-658-5111,** for clinical management guidance for cases and contacts.
- **Western Cape CDC Team** – contact telephonically/email for guidance on case finding and contact tracing.

	Name	Designation	Tel/Cell	Email
1.	Ms Charlene Lawrence	Provincial CDC Coordinator	021- 830-3727, 072-356-5146	Charlene.Lawrence@westerncape.gov.za
2.	Ms Washiefa Isaacs	CDC: Provincial NICD NMC Surveillance Manager	072-310-6881	Washiefa.Isaacs@westerncape.gov.za
3.	Ms Janine Bezuidenhoudt	Provincial NICD Epidemiologist	021-815-8790, 082-327-0394	Janine.Bezuidenhout@westerncape.gov.za
4.	Ms Levani Naidoo	Provincial CDC Surveillance and Outbreak Response	021-815-8676, 060-508-0896	Levani.Naidoo@westerncape.gov.za

Annexure 2: Contact Details of Public Health Practitioners involved in Communicable Disease Control and Epidemic Preparedness and Response

Table 1. Public health officials responsible for Communicable Disease Control, Surveillance, Environmental Health, Pharmacy Services and CDC coordinators / equivalent, In the Western Cape, 5 July 2024 (not an extensive list of stakeholders)

	Province	Name	Designation	Tel/Cell	Email
1.	**Emergency and Clinical Services Support (ECSS)**	Dr Juanita Arendse	Chief Director	021-815-8612 (tel) 083-680-8719 (cell)	Juanita.Arendse@westerncape.gov.za
2.	**Service Priorities Coordination (SPC)**	Dr Hillary Goeiman	Director: SPC	021-815-8741 (tel) 083-333-1320 (cell)	Hilary.Goeiman@westerncape.gov.za
3.	**SPC: Communicable Disease Control**	Ms Charlene Lawrence	Provincial CDC Coordinator	021- 830-3727 (tel) 072-356-5146 (cell)	Charlene.Lawrence@westerncape.gov.za
4.		Ms Janine Bezuidenhoudt	Provincial NICD Epidemiologist	021-815-8663 (tel) 082-327-0394 (cell)	Janine.Bezuidenhoudt@westerncape.gov.za janineb@nicd.ac.za
5.		Ms Washiefa Isaacs	CDC: Provincial NICD NMC Surveillance Manager	072-310-6881(cell)	Washiefa.Isaacs@westerncape.gov.za washiefai@nicd.ac.za
6.		Ms Levani Naidoo	ASD: Outbreak Response	021-815-8676 (tel) 060-508-0896 (cell)	Levani.Naidoo@westerncape.gov.za
7.		Ms Farzanah Frieslaar	ASD: EPI Disease Surveillance	021-815-8740 (tel) 079-368-3693 (cell)	Farzanah.Frieslaar@westerncape.gov.za
8.		Mr. Francois Booysen	CDC: Administrative Officer	021-815-8661(tel) 061-600-3385 (cell)	Francois.Booysen@westerncape.gov.za
9.		Ms Felencia Daniels	CDC: Administrative Clerk	021-815-8660 (tel) 082-585-7295 (cell)	Felencia.Daniels@westerncape.gov.za
10.		Ms Sonia Botha	Provincial EPI Coordinator	021-815-8810 (tel) 083-576-7893 (cell)	Sonia.Botha@westerncape.gov.za
11.	**Pharmaceutical Service, Medicine Management, Laboratory and Blood Services Support**	Ms Kim Lowenherz	Director: Pharmacy Services	021-483-8702 (tel) 083-269-4308 (cell)	Kim.Lowenherz@westerncape.gov.za
12.		Ms Helen Hayes	Manager: Pharmaceutical Services	021-483-4567 (tel) 072-909-2838 (cell)	Helen.hayes@westerncape.gov.za
13.		Ms Yasmina Johnson	Pharmaceutical Services: Policy Specialist	021-483-6198 (tel) 084-417-5137 (cell)	Yasmina.Johnson@westerncape.gov.za
14.		Ms Caroline De Beer	Pharmaceutical Policy Specialist	021-483-2460 (tel) 084-250-2500 (cell)	Caroline.deBeer@westerncape.gov.za
15.	**Facilities Infrastructure Management**	Mr. Stanley Nomdo	Assistant Director: Environmental Health	021-918-1564 (tel) 072-133-5644 (cell)	Stanley.Nomdo@westerncape.gov.za
16.	**Assurance: Infection Prevention and Control**	Dr. Ziyanda Vundle	Public Health Specialist	082-862-4331 (cell)	Ziyanda.Vundle@westerncape.gov.za
17.	**Communication**	Ms Marika Champion	Director	074-011-2244 (tel) 021-483-3235 (cell)	Marika.champion@westerncape.gov.za
18.	**Disaster Medicine and Special Events**	Dr. Wayne Smith	Head of Disaster Medicine and Special Events	021-815-8819 (tel) 082-991-0760 (cell)	Wayne.Smith@westerncape.gov.za
19.	**Emergency Medical Services (EMS)**	Mr. Craig Wylie	Director: Emergency Medical Services	021-508-4517(tel) 078-800-5644(cell)	Craig.Wylie@westerncape.gov.za
20.	**Tygerberg Hospital**	Prof. Jantjie Taljaard	Infectious Disease Specialist	021-938-9645 (tel) 083-419-1452 (cell)	jjt@sun.ac.za
21.		Dr Arifa Parker	Lead IPC Clinician / ID Specialist, GSH	021-938-9520/4378 (tel) 083-218-0088 (cell)	aparker@sun.ac.za
22.		Prof. Helena Rabie	Paediatric Infectious Disease Specialists	021-938-9197 (tel) 084-515-6746 (cell)	hrabie@sun.ac.za
23.		Mr Mogamat Isaacs	TBH: Pharmacist	021-938-5225 (tel)	Mogamat.Isaacs2@westerncape.gov.za

24.	**Groote Schuur Hospital**	Prof. Marc Mendelson	Infectious Disease Specialists	021-404-5105 (tel) 082-684-5742 (cell)	Marc.mendelson@uct.ac.za
25.		Dr. Tari Papavarnavas	Lead IPC Clinician / ID Specialist, GSH	021-404-4456 (tel)	Tari.Papas@westerncape.gov.za
26.		Ms Vanishree Naicker	GSH: Pharmacist	021-404-3216 (tel)	Vanishree.Naicker@westerncape.gov.za
27.	**Red Cross Hospital**	Prof. Brian Eley	RCWMCH: Head of Paediatric Infectious Diseases	021-658-5321 (tel) 083-947-7637 (cell)	Brian.eley@uct.ac.za
28.		Mr Eddison Williams	RCWMCH: Pharmacist	021-658-5031 (tel)	Eddison.Williams@westerncape.gov.za
29.	**Forensic Pathology Services**	Ms Vonita Thompson	Director: Forensic Pathology Services	082-443-3009 (cell)	Vonita.thompson@westerncape.gov.za
30.	**National Health Laboratory Services (NHLS)**	Ms Nasima Mahomed	NHLS Area Manager	021-417-9376/7 (tel)	Nasima.Mahomed@nhls.ac.za
31.	**National Health Laboratory Services (NHLS) Groote Schuur Microbiology**	Dr. Amand Khumalo	Microbiologist	021-404-6727 (tel)	Amanda.Khumalo@nhls.ac.za
32.	**NHLS, Tygerberg Hospital Microbiology**	Prof. Andrew Whitelaw	Professor and Head: Division of Microbiology	021-938-4032 (tel) 082-375-6297(cell)	Andrew.Whitelaw@nhls.ac.za awhitelaw@sun.ac.za
33.	**Mediclinic Private Hospital Group**	Ms Christine Smedley	Infection Prevention and Control Officer, Mediclinic Southern Africa	021-809-1885 (tel) 083-987-8973 (cell)	Christine.Smedley@mediclinic.co.za
34.	**Netcare Private Hospital Group**	Ms Rileen Strauss	Regional Infection Prevention and Control Manager, Netcare Limited	021-590-4094 (tel) 072-378-6070 (cell)	Rileen.Strauss@netcare.co.za
	Rural Health Services (Districts)	**Name**	**Designation**	**Tel/Cell**	**Email address**
1.	**Rural Health Services Chief Directorate**	Dr. David Pienaar	Public Health Specialist	021-483-9901 (tel) 083-275-9333 (cell)	David.Pienaar@westerncape.gov.za
2.		Ms Eugenia Sidumo	Deputy Director: Professional Support Services	044-695-0047 (tel) 082-735-5463 (cell)	Eugenia.Sidumo@westerncape.gov.za
3.	**Cape Winelands**	Ms Surina Neethling	Deputy Director: Specialised Support Services	023-348-8120 (tel) 072-227-6058 (cell)	Surina.Neethling@westerncape.gov.za
4.		Ms Roenell Balie	Manager: Facility Based Services	023-348-8122 (tel) 082-397-4467 (cell)	Roenell.balie@westerncape.gov.za
5.		Mr Randall Humphreys	Cape Winelands District Municipality Environmental Health	023-348-2336 (tel) 082-824-2010 (cell)	humphreys@capewinelands.gov.za
6.		Mr Charles Williams	Pharmaceutical Services Manager	023-348 8115 (tel) 076-540-6656 (cell)	Charles.williams@westerncape.gov.za
7.	**Central Karoo**	Dr. Abraham Muller	Medical Manager: Central Karoo	023-414-8200 (tel) 078-214-3300 (cell)	Abraham.Muller2@westerncape.gov.za
8.		Ms Annalette Jooste	Deputy Director: Specialised Support Services	023-414-3590 (tel) 083-445-8106 (cell)	annalette.jooste@westerncape.gov.za
9.		Ms Janine Nel	Deputy Director: Comprehensive Health	023-414-3590 (tel) 083-708-1679 (cell)	Janine.Nel@westernccape.gov.za
10.		Mr Gerrit van Zyl	Central Karoo District Municipality Environmental Health	023-449-1000 (tel) 083-654-9688 (cell)	gerrit@skdm.co.za
11.		Mr Nathan Jacobs	Environmental Health	044-813-2926 (tel) 081-030-4557 (cell)	Nathan.Jacobs@westerncape.gov.za
12.		Ms A. Theron	Pharmaceutical Services Manager	023-414-8200 (tel) 082-334-3450 (cell)	Annatjie.Theron@westerncape.gov.za
13.	**Garden Route**	Mr Eugene Engle	Deputy Director: Specialised Support Services	044-803-2752 (tel) 083-441-8555 (cell)	Eugene.Engle@westerncape.gov.za
14.		Mr Nathan Jacobs	Environmental Health	044-813-2926 (tel) 081-030-4557 (cell)	Nathan.Jacobs@westerncape.gov.za

15.		Ms Gerda Terblanche	Assistant Manager: Nursing	044-803-2755/2700 (tel) 084-581-6648 (cell)	Gerda.Terblanche@westerncape.gov.za
16.		Mr. Johan Compion	Garden Route District Municipality	044-803-1501(tel) 082-803-5161 (cell)	jcompion@edendm.co.za
17.		Mr Jochemus Hattingh	Pharmaceutical Services Manager	044-803-2700 / 2756 (tel) 073-303-1574 (cell)	Jochemus.Hattingh@westerncape.gov.za
18.	**Overberg**	Ms Beatrice Groenewald	Child Health Coordinator	028-214-5852 (tel) 082-969-9297 (cell)	Beatrice.groenewald@westerncape.gov.za
19.		Ms Aletta Ludik	Assistant Manager: Facility Based Services	028-214-5851 (tel)	Aletta.Ludik@westerncape.gov.za
20.		Ms Petro Robertson	Deputy Director: Comprehensive Health	023-348-8142 (tel) 072-067-1309 (cell)	Petro.Robertson@westerncape.gov.za
21.		Ms Mashudu Mukoma	Overberg District Municipality, Environmental Health	028-425-1157 (tel) 064-890-4995 (cell)	Mmukoma@odm.org.za
22.		Ms Petro Robertson (Acting)	Pharmaceutical Services, Overberg	028-214-5828/023-348-8142 (tel)	Petro.Robertson@westerncape.gov.za
23.	**West Coast**	Ms Hildegard Van Rhyn	Clinical Program Coordinator	022-487-9354 (tel) 082-871-9709 (cell)	Hildegard.VanRhyn@westerncape.gov.za
24.		Ms Anne Kogana	Deputy Director: Comprehensive Health	022-487-9263 (tel) 066-046-6541 (cell)	Anne.Koganal@westerncape.gov.za
25.		Mr Andre Scott	Municipal Health Services Senior Manager	022- 433-8400 (tel) 082-557-7698 (cell)	health@wcdm.co.za
26.		Mr Christiaan Lintnaar	Pharmaceutical Services Manager	022-487-9209 (tel)	Christiaan.Lintnaar@westerncape.gov.za
	District: Cape Town Metropolitan District	**Name**	**Designation**	**Tel/Cell**	**Email address**
1.	**Metro Health Services (MHS) Chief Directorate**	Prof. Hassan Mahomed	Public Health Specialist (MHS)	021-815-8697 (tel) 082-334-5763 (cell)	Hassan.Mahomed@westerncape.gov.za
2.		Ms Anneline Janse Van Rensburg	Deputy Director: Comprehensive Health	021-815-8696 (tel) 082-897-2310 (cell)	Anneline.jansevanrensburg@westerncape.gov.za
3.	**MHS- Northern Tygerberg Substructure**	Ms Michelle Williams	Deputy Director: Professional Support Services	021-815-8882 (tel) 083-235-1155 (cell)	michelle.williams@westerncape.gov.za
4.		Ms Delaray Fourie	Deputy Director: Comprehensive Health Programmes	021-815-8879 (tel)	Delaray.fourie@westerncape.gov.za
5.		Ms Rayneze Saayman	Clinical Programme Coordinator: Facility Based Programmes	021-815-8888 (tel) 073-782-6854 (cell)	Rayneze.Saayman@westerncape.gov.za
6.		Ms Tasneem Parker	Pharmaceutical Services Manger	021-815-8876	Tasneem.Parker2@westerncape.gov.za
7.	**MHS- Klipfontein Mitchells Plain Substructure**	Ms Pearl Van Niekerk	Quality Assurance Manager	021-370-5000 (tel) 078-409-0030 (cell)	Pearl.Vanniekerk@westerncape.gov.za
8.		Mr. Mahboob Roomany	Pharmaceutical Services Manager	021-370-5000 (tel) 082-847-0334 (cell)	Mahboob.roomanay@westerncape.gov.za
9.	**MHS- Khayelitsha Eastern Substructure**	Ms Razia Vallie	Deputy Director: Professional Support Services	021-360-4633(tel) 076-375-1945 (cell)	Razia.Vallie@westerncape.gov.za
10.		Mr. Johan Van Niekerk	Pharmaceutical Services Manager	021-360-4641 (tel) 078-631-5125 (cell)	Johan.vanniekerk@westerncape.gov.za
11.	**MHS- Southern Western Substructure**	Ms Coleen van Diemen	Facility Based Manager	021-202-0900 (tel) 073-516-2809 (cell)	Coleen.VanDiemen@westerncape.gov.za
12.		Ms Helimamy Moeng	Pharmaceutical Services Manager	021-202-0989 (tel) 076-112-6294 (cell)	Helimamy.Moeng@westerncape.gov.za
13.	**City of Cape Town (CoCT)**	Dr. Natacha Berkowitz	Specialised Health: Epidemiologist-CDC Coordinator	021-400-6864 (tel) 083-406-6755 (cell)	Natacha.Berkowitz@capetown.gov.za
14.		Ms Bettie Leedo	Programme Manager: Environmental Health	072-658-3865 (cell)	Bettie.Leedo@capetown.gov.za

15.		Mr Mohamed Barday	Head: Pharmaceutical Services	021-444-5885 (tel) 082-702-2200 (cell)	Mohamed.Barday@capetown.gov.za
16.	**CoCT: Eastern**	Ms Sue-Ellen van Niekerk	Head: PPHC	021-444-4667 (tel)	SueEllen.Van Niekerk@capetown.gov.za
17.		Ms Lena Stofile	Head: Environmental Health, Area: East	021-444-2331 (tel)	Lena.Stofile@capetown.gov.za
18.	**CoCT: Khayelitsha**	Ms Babalwa Qukula	Head: PPHC	021-360-1153 (tel) 084-499-3949 (cell)	Babalwa.Qukula@capetown.gov.za
19.		Ms Yonela Mentese	Head Environmental Health, Area East:Khayelitsha	021-400-1920 (tel) 078-109-9467 (cell	Yonela.Mentese@capetown.gov.za
20.	**CoCT: Northern**	Ms Everin Van Rooyen	Head: PPHC	021-400-3917 (tel) 071-896-1674 (cell)	Everin.VanRooyen@capetown.gov.za
21.		Ms Jaquelene Peterson	Head Environmental Health: Northern Sub District	021-444-1729 (tel) 072-112-2574 (cell	Jacquelene.Peterson@capetown.gov.za
22.	**CoCT: Tygerberg**	Ms Marilyn Dennis	Head: PPHC	021-444-0899 (tel) 079-517-3318 (cell)	Marilyn.Dennis@capetown.gov.za
23.		Mr Andy Lucas	Head Environmental Health; Area Central Tygerberg	021-444-0879 (tel) 082-421-5805 (cell)	Andy.Lucas@capetown.gov.za
24.	**CoCT: Klipfontein**	Ms Stephanie Sirmongpong	Head: PPHC	021-444-0894 (tel) 084-792-7247 (cell)	Stephanie.Sirmongpong@capetown.gov.za
25.		Elroy Plaatjies	Head Environmental Health; Area Central	021-444-2332 (tel) 086-576-0834 (cell)	Elroy.plaatjies@capetown.gov.za
26.	**CoCT: Mitchells Plain**	Ms Marcelle Segels	Acting Head: PPHC	083-764-8267 (cell)	Marcelle.Segels@capetown.gov.za
27.		Ms Zanele Figlan	Head Environmental Health	021-400-4076 (tel) 083-700-2141(cell)	Ntombizanele.Figlan@capetown.gov.za
28.	**CoCT: Southern**	Ms Kelebogile Sannah Shuping	Head: PPHC	021-444-3261 (tel) 064-559-3526 (cell)	Kelebogile.Shuping@capetown.gov.za
29.		Mr. Anzil Sampson	Head: Environmental Health	021-444-3259 (tel) 082-533-8183 (cell)	Anzil.Sampson@capetown.gov.za
30.	**CoCT: Western**	Ms Melissa Stanley	Head: PPHC	021-444-1741 072-329-6361(cell)	Melissa.stanley@capetown.gov.za
31.		Mr Gavin Heugh	Head Environmental Health; Area: North	021-444-1739 (tel) 084-220-0141(cell)	Gavin.Heugh@capetown.gov.za

Table 6: Infection Prevention and Control (IPC) Practitioners / equivalent at Public and Private Hospitals in the Western Cape

	District	Name	Hospital and Designation	Tel/Cell	Email
1.	**Cape Town**	Ms Heidi Van Reenen	Groote Schuur Hospital: IPC Practitioner	021-404-44556	Heidi.VanReenen@westerncape.gov.za
2.		Ms Kholiwe Binase	Groote Schuur Hospital: IPC Practitioner	021-404-5246	Kholiwe.Binase@westerncape.gov.za
3.		Ms Maahirah Abrahams	Groote Schuur Hospital: IPC Practitioner	021-404-6182	Maahirah.Abrahams@westerncape.gov.za
4.		Ms Eunice van der Westhuizen	Tygerberg Hospital: IPC Practitioner	021-938-4582	Eunice.vanderWesthuizen@westerncape.gov.za
5.		Ms Sarah Booysen	Tygerberg Hospital: IPC Practitioner	021-938-5053	Sarah.Booysen@westerncape.gov.za
6.		Ms Magda Mocke	Tygerberg Hospital: IPC Practitioner	021-938-4911 021-938-5576	Magda.Mocke@westerncape.gov.za
7.		Ms Donita Erasmus	Tygerberg Hospital: IPC	021-938-5056	Donita.Erasmus@westerncape.gov.za
8.		Ms D Saal	Tygerberg Hospital: IPC	021-938-5057	Desire.Saal@westerncape.gov.za
9.		Ms Tamar Mc Farlane	Tygerberg Hospital: IPC	021-938 5053	Tamar.Mcfarlane@westerncape.gov.za
10.		Ms Shamiela January	Red Cross War Memorial Hospital: IPC Practitioner	021-658-5977	Shamiela.January@westerncape.gov.za
11.		Ms Marilyn Philander	New Somerset Hospital: QA Manager	021-402-6232	Marilyn.Philander@westerncape.gov.za
12.		Ms Michelle Charles-Jefthas	Karl Bremmer Hospital: IPC Practitioner	021-918-1984	Michelle.Charles-Jefthas@westerncape.gov.za
13.		Ms Magdalena Aucamp	Mowbray Maternity Hospital: IPC Practitioner	021-659-5549	Magdalena.Aucamp@westerncape.gov.za
14.		Ms Nomakhula Konza	Alexandra Hospital: IPC	021-503-5123	Nomakhula.Konza@westerncape.gov.za
15.		Ms Jessica Minnaar	Lentegeur Hospital: IPC	021-370-1463	Jessica.Minnaar@westerncape.gov.za
16.		Mr. Adrian Agulhas	Valkenberg Hospital	021-440-3231	Adrian.Agulhas@westerncape.gov.za

17.		Ms Valerie Nel	Stikland Hospital: IPC Practitioner	021-940-4400	Valerie.Nel@westerncape.gov.za
18.		Ms Jayaluxmi Anand	Eerste River Hospital: IPC Practitioner	021-902-8082/1	Jayaluxmi.anand@westerncape.gov.za
19.		Ms Leisl Pasquallie	Helderberg Hospital: IPC Practitioner / Clinical Programme Coordinator	021-850-4747	Leisl.Pasquallie@westerncape.gov.za
20.		Mr Sam Manga	Khayelitsha Hospital: IPC Practitioner	021-360-4320	Sam.manga@westerncape.gov.za
21.		Ms Francina Brown	Mitchells Plain District Hospital: Nurse Manager	021-377-2283/7578	Francina.brown@westerncape.gov.za
22.		Ms Bianca Tyutu	False Bay Hospital: Manager	021-832-5206	Bianca.Tyutu@westerncape.gov.za
23.		Ms Aletta Le Grange	Victoria Hospital: IPC Practitioner	021-799-1133	Alletta.leGrange@westerncape.gov.za
24.		Ms Marlene Van der Berg - Titus	Wesfleur Hospital: IPC Practitioner	021-572-8054/8148	Marlene.Vanderberg-Titus@westerncape.gov.za
25.		Ms Laticia Esbagh	Brooklyn Chest Hospital: IPC Practitioner	021-508-8330	Laticia.esbagh@westerncape.gov.za
26.		Capt. C Cloete	2 Military Hospital: IPC Practitioner	021-799-6184	2mhcovid@gmail.com cornel572@gmail.com
27.		Ms Hannelie Herselman	Mediclinic Cape Town: IPC & Patient Safety Manager	021-464-5603 072-463-8584	Hannelie.herselman@Mediclinic.co.za
28.		Ms Salome Nel	Mediclinic Constantiaberg: IPC Manager /Patient Safety Manager	021-799-2911 / 2139	Salome.nel@mediclinic.co.za
30.		Ms Michelle Vermeulen	Mediclinic Durbanville: IPC Manager	021-980-2499	Michelle.Vermeulen@mediclinic.co.za
31.		Ms Vidette Fourie	Mediclinic Milnerton: IPC Practitioner & Control Manager	021-529-9064 066-294-9118	Vidette.Fourie@mediclinic.co.za
32.		Ms Liezl Henning	Mediclinic Panorama: IPC Manager	021-938-3674	Liezl.Henning@mediclinic.co.za
33.		Ms Evelyn Thanthsa	Mediclinic Panorama: Infection Prevention and Control Manager	021-938-2671	Evelyn.Thanthsa@mediclinic.co.za
34.		Ms Claudine Page	Mediclinic Cape Gate: IPC Manager	021-983-5969	Claudine.Page@mediclinic.co.za
35.	**Cape Town**	Ms Teresa Van Heerden	Mediclinic Louis Leipoldt: IPC Manager	021-957-6165	Teresa.VanHeerden@mediclinic.co.za
36.		Ms Mzohona Nkala	Mediclinic Vergelegen / Strand: IPC Manager	021-850-6393	Mzohona.Nkala@mediclinic.co.za
37.		Ms Sheila Tredoux	Melomed Bellville: Quality Assurance Officer	021-950-8929	mbquality@melomed.co.za
38.		Ms Meriaan Whitlow	Melomed Bellville: IPC Practitioner	021-948-8131	mbipc@melomed.co.za
39.		Ms Nadeema Muller	Melomed Gatesville: IPC Practitioner	021-637-8100	mgipc@melomed.co.za
40.		Ms Dawn Baxter	Melomed Gatesville: Quality Officer	021-637-3118	mgquality@melomed.co.za
41.		Ms Roselin Linden	Melomed Mitchell's Plain: IPC Practitioner	021-392-3126	mpipc@melomed.co.za
42.		Ms Joyce Mogale	Melomed Tokai Hospital: IPC Practitioner	021-764-7500	mtipc@melomed.co.za
43.		Ms Madelaine Strydom	Netcare N1 City Hospital: IPC Practitioner	021-590-4094	Madelaine.strydom@netcare.co.za
44.		Ms Jacqueline Prince	Netcare: Chris Barnard Memorial Hospital: IPC Practitioner	021-441-0000 082-843-7606	Jacqueline.Prince@netcare.co.za
45.		Ms Danielle Claasen	Netcare: Chris Barnard Memorial Hospital: IPC Practitioner	021-441-0347	Danielle.Claasen@netcare.co.za
46.		Ms Laeticia Vass	Netcare: Kuilsriver Hospital: IPC	021-900-6687 072-585-9628	Letitia.Vass@netcare.co.za

47.		Ms R. Fakier	Netcare: UCT Academic: IPC Practitioner	021-442-1829 083 361 6867	Rushana.Fakier@netcare.co.za
48.		Ms P Khobo	Netcare: Blaauwberg Hospital: IPC Practitioner	021-554-9037 078-919-8834	Precious.Khobo@netcare.co.za
49.		Ms Margaret Tyandela	Lifehealth Care: Claremont and Kingsbury Hospital: (Acting) Infection Prevention Specialist	021-670-4032	Margaret.Tyandela@lifehealthcare.co.za
50.		Ms Patricia Curle	Life health Care: Vincent Palotti Hospital: IPC Specialist	021-506-5111/5503	Patricia.Curle@lifehealthcare.co.za
51.		Ms Enid Scott	Life health Care: Vincent Palotti Hospital: IPC Practitioner	021-506-5492	Enid.Scott@lifehealthcare.co.za
52.		Ms B Tumi	Rondebosch Medical Centre, Quality Assurance Coordinator	021-680- 5920 (Ext 1233)	ipc@rondeboschmc.com
53.		Ms Vicky Niemand	Busamed, Paardevlei Private Hospital: Risk Manager	021-840-6600	VickyN@Busamed.co.za
54.	**Cape Winelands**	Ms Laurette Pekeur	Worcester Hospital: IPC Practitioner	023-348-1146	Laurete.Pekeur@westerncape.gov.za
55.		Ms Yolanda Van Zyl	Paarl Hospital: IPC Practitioner	021-860-2532	Yolanda.vanZyl@westerncape.gov.za
56.		Ms Danelia Jacobs	Brewelskloof Hospital: Clinical Program Coordinator IPC & OHS	023-348-1313/37	Danelia.Jacobs@westerncape.gov.za
57.		Mr. Geoffrey Vermeulen	Ceres Hospital: Nursing Service Manager	023 316 9600	Geoffrey.Vermeulen@westerncape.gov.za
58.		Ms Cheray Jordaan	Ceres Hospital: IPC Practitioner / QA	023-316 9600/61	Cheray.Jordaan@westerncape.gov.za
59.		Ms Elizabeth Van Zyl	Montagu Hospital: Nursing Service Manager	023-614-8103	Elizabeth.VanZyl2@westerncape.gov.za
60.		Ms Sandra Kortje	Robertson Hospital: Nursing Service Manager	023-626-8519	Sandra.Kortje@westerncape.gov.za
61.		Ms Rene De Silva	Stellenbosch Hospital: Nursing Service Manager / IPC Practitioner	021-808-6135	Rene.Desilva@westerncape.gov.za
62.		Ms Johanna Webster	Mediclinic Worcester: IPC Practitioner	023-348-1608	Johanna.webster@mediclinic.co.za
63.		Ms Elizma De Klerk	Mediclinic Paarl: IPC Practitioner	021-807-8296	Elizma.DeKlerk@mediclinic.co.za
64.		Ms Karlien Pienaar	Mediclinic Stellenbosch: IPC Practitioner	021-861-2200	Karlien.pienaar@mediclinic.co.za
65.	**Central Karoo**	Mr. Tshokolo Ntombana	Beaufort West Hospital: Nursing Service Manager / IPC Practitioner	023-414-8212 023-414-8200	Tshokolo.ntombana@westerncape.gov.za
66.		Ms Nomnene Bhistoli	Nursing Service Manager: Laingsburg Hospital	023-814-2353	Nomnene.Bhistoli@westerncape.gov.za
67.		Ms Sonja Frieslaar	Nursing Service Manager, Prince Albert Hospital	023-541-1300	Sonja.Frieslaar@westerncape.gov.za
68.	**Garden Route**	Ms Ann Calitz	George Hospital : IPC Practitioner	044- 802-4397	Ann.Calitz@westerncape.gov.za
69.		Ms Jabulisile Mahlangu	Mossel Bay Hospital: Nursing Service Manager / IPC Practitioner	044-604-6104	Jabulisile.Mahlangu@westerncape.gov.za
70.		Ms Yolande De Wit-Stevens	Mossel Bay Hospital: IPC Practitioner	044-604-6142	Yolande.DeWit-Stevens@westerncape.gov.za
71.		Ms Florence Thomas	Oudtshoorn Hospital: IPC Practitioner	044-203-7463	Florence.Thomas@westerncape.gov.za
72.		Ms Anita Laubscher	Alan Blyth Hospital: Nursing Service Manager/ IPC Practitioner	028-551-1010	Anita.Laubscher@westerncape.gov.za
73.		Ms Toppa Strydom	Kannaland sub district: IPC Practitioner	028-551-1010	Uppertoppa.Strydom@westerncape.gov.za
74.		Mr. Pieter Moolman	Riversdal Hospital: Nursing Service Manager / IPC Practitioner	028-713-8643/8643	Pieter.Moolman@westerncape.gov.za

75.		Ms Glenda Seegar	Knysna Hospital: IPC Practitioner	044-302-8400	Glenda.Seeger@westerncape.gov.za
76.		Ms Hendriena Wilschut	Uniondale Hospital: (Acting) Nursing Service Manager / Infection Control Practitioner	044-814-1402	Hendriena.Wilschut@westerncape.gov.za
77.		Ms Wendy Burnett	Mediclinic George / Geneva: IPC Practitioner	044-803-2187	Wendy.Burnett@mediclinic.co.za
78.		Ms Andrie Wiese	Mediclinic Klein Karoo: Infection Control Practitioner	044-272-0111	Andrie.Wiese@mediclinic.co.za
79.		Mr Frank Crous	Mediclinic Plettenberg Bay: Nursing Service Manager/Infection Control Practitioner	044-501-5100/5312	Frank.Crouse@mediclinic.co.za
80.		Ms Bianca Rondganger (Wynand)	Knysna Private Hospital: QSSS/ Infection Prevention Specialist	044-302-5214	Bianca.wynand@lifehealthcare.co.za
81.		Ms Marianca Stols	Bayview Hospital: IPC Specialist	044-691-3718	Marianca.Stols@lifehealthcare.co.za
82.	**Overberg**	Ms Elaine Kleynhans	Mediclinic Hermanus: IPC Practitioner	028-313-0168	Elaine.Kleynhans@Mediclinic.co.za
83.		Ms Rosemary Davel	Caledon Hospital: Nursing Service Manager	028-212-1070	Rosemary.Darvel@westerncape.gov.za
84.		Anthea Klaasen	Hermanus Hospital: Nursing Service Manager	028-313-5221	Anthea.Klaasen@westerncape.gov.za
85.		Ms Nicole Adams	Otto Du Plessis Hospital: Nursing Service Manager	028-425-1239	Nicole.Adams@westerncape.gov.za
86.		Ms Florence Vermeulen	Swellendam Hospital: Nursing Service Manager	028-514-8419	Florence.Vermeulen@westerncape.gov.za
87.	**West Coast**	Ms Johanna De Nobrega	Nurse Manager: Vredenburg Hospital: IPC Practitioner	022-709-5099	Johanna.DeNobrega@westerncape.gov.za
88.		Mr. Niel Goeieman	Nurse Manager: Clanwilliam Hospital: IPC Practitioner	027-482-2166	Niel.Goeiman@westerncape.gov.za
89.		Mr Ndoisile Mphato	Nurse Manager: Citrusdal Hospital: Infection Control Practitioner	022-921-2153	Ndoisile.Mphato@westerncape.gov.za
90.		Ms Trudie Fredericks	Assistant Manager Nursing: Lapa Munik Hospital (Porterville): IPC Practitioner	022-931-2140	Trudie.fredericks@westerncape.gov.za
91.		Ms Trudie Fredericks	Nurse Manager: Radie Kotze Hospital (Piketberg): IPC Practitioner	022-913-1175	Trudie.fredericks@westerncape.gov.za
92.		Ms L Julius	Nurse Manager: Swartland Hospital: Infection Control Practitioner	022-487-9204	Loren.Julius2@westerncape.gov.za
93.		Mr Llewellon Wagenaar	Nurse Manager: Vredendal Hospital: Infection Control Practitioner	027-213-2039	Llewellon.Wagenaar@westerncape.gov.za
94.		Ms Gerda Karstens	West Coast Private Hospital, Life Health Care Group: IPC Practitioner	022-719-1030 Ext:210	Gerda.Karstens@lifehealthcare.co.za

Table 7: National Health Laboratories Services, NHLS Referral Laboratories in the Western Cape

	NHLS Laboratories	Designation / Person in charge	Telephone / Cell	Email
1.	Ms. N Mohamed	NHLS: Area Manager	021-417-9376/77	Nasima.Mohamed@nhls.ac.za
2.	Mr. I. De Villiers	Green Point Laboratory Manager, Lab Support services	021-417-9366	Izak.devilliers@nhls.ac.za
3.	Prof. A. Whitelaw Microbiologist, University of Stellenbosch, & NHLS	NHLS Microbiology, Tygerberg Hospital	021-938-4032 082-375-6297	awhitelaw@sun.ac.za / Andrew.Whitelaw@nhls.ac.za
4.	Dr. R. Hoffman Microbiologist	NHLS Microbiology, Tygerberg Hospital	021-938-4006	renah@sun.ac.za
5.	Dr. C. Pienaar Microbiologist	NHLS Microbiology, Tygerberg Hospital	021-938-4006/4032	Colette.Pienaar@nhls.ac.za
6.	Dr. A. Khumalo Microbiologist	NHLS Microbiology, Groote Schuur Hospital	021-406-6727	Amanda.Khumalo@nhls.ac.za

7.	Dr. E. Prentice Consultant Microbiologist	NHLS Microbiology, Groote Schuur Hospital	021-404-5282 084-589-9877	Elizabeth.Prentice@nhls.ac.za
8.	Dr. W. Dowling Microbiologist	NHLS Microbiology, Groote Schuur Hospital	021-404-5282	Wentzel.dowling@nhls.ac.za
9.	Dr. H. Tootla Microbiologist	NHLS Microbiology, Groote Schuur Hospital	021-658-5235	hafsah.tootla@nhls.ac.za

Table 8: National Health Laboratories Services, NHLS Laboratories in the Western Cape

	NHLS Laboratories	Laboratory Manager / Person in charge	Telephone / Cell	Email
1.	Paarl	Ms N. Singh	021-860-2746; 082-617-2813	Natasha.Singh@nhls.ac.za
2.	Vredendal	Ms J. Marcus	027-213-3924; 083-625-6310	Jacky.Marcus@nhls.ac.za
3.	Vredenburg	Ms M. Mouton	022-713-4468	Marianne.Mouton@nhls.ac.za
4.	Karl Bremer	Ms O. Max	022-719-1634; 073-762-5465	Odette.Max@nhls.ac.za
5.	Mitchells Plain	Ms M. Hill	021-371-7921; 082-605-9756	Marguerita.Hill@nhl.ac.za
6.	Worcester	Ms P. Dlakavu	023-348-1407/1401	Portia.Dlakavu@nhls.ac.za
7.	Helderberg	Ms M. Adams	021-852-3623; 076-489-1572	Moveen.adams@nhls.ac.za
8.	George	Ms A. Bench	044-874-2022	Anna.Bench@nhls.ac.za
9.	Mossel Bay	Ms D. Van Heerden	044-690-3745	Daneld.Vanheerden@nhls.ac.za
10.	Oudtshoorn	Mr. P. De Klerk	044-279-1104; 067-428-0601	Peter.Deklerk@nhls.ac.za
11.	Knysna	Ms S. Muller	044-382-0991	Samantha.Muller@nhls.ac.za
12.	Beaufort West	Mr. C. Brink	023-415-1447	Cornelius.Brink@nhls.ac.za
13.	Khayelitsha	Mr. L. Ramashoai,	021-360-4522/4521; 073-249-1949	Leneuwe.Ramashoai@nhls.ac.za
14.	Hermanus	Ms S. Van Wyk	028-312-1005; 082-328-1592	Sonja.Vanwyk@nhls.ac.za

Table 9: Contact details of Private Laboratories in Western Cape

	Private Laboratory	Name and Designation	Telephone	Email
1.	PathCare	Ms I. Howes; Head Office, (Enquiries)	021-596-3400/2130	howesi@pathcare.org
2.	PathCare	Dr. Jean Maritz; Clinical Virologist	021-596-3400	Jean.Maritz@pathcare.org
3.	Ampath	Dr. Clinton Van der Westhuizen; Pathologist	021 -596-5227	vanderwesthuizencl@ampath.co.za
4.	Lancet	Dr. J. Wojno; Pathologist	021-673-1700	Justyna.wojno@lancet.co.za

Table 10: Contact details of Regional Commissioner, Department of Correctional Services

	Name	Designation	Telephone / Cell	Email
1.	Ms G. Pienaar	Director: Development and Care, Western Cape Region	021-550-6006 072-447-6457	geraldine.pienaar@dcs.gov.za
2.	Mr. J. Shinga	(Act) Deputy Director: Regional Coordinator Health Care Services	021-550-6083 072-281-7595	jabo.shinga@dcs.gov.za
3.	Ms. C. McCree	Deputy Director: Regional Coordinator: HIV AND AIDS	021-550-6043 072-795-7200	claudia.mccree@dcs.gov.za

Table 11: Contact details of Department of Basic Education, Western Cape

	Name	Designation	Telephone / Cell	Email
1.	Daniels, B. Mr.	Director: Specialised Education Support Services	021-467-2027	Ignatius.DuPreez@westerncape.gov.za
2.	Kemp, R. Dr	Specialised Support Services: Provincial Social Work Manager	021-467-9259	Rochshana.Kemp@westerncape.gov.za
3.	Hassen, E. Mr.	Head of SLES: Metro Central Education District	021-514-6919	Enver.Hassen@westerncape.gov.za
4.	De Klerk, G. Ms.	Head of SLES: Metro South Education District	021-370-2090	Guilot.deKlerk@westerncape.gov.za
5.	Sonn, C. Ms.	Head of SLES: Metro North Education District	021-938-3063	Carola.Sonn@westerncape.gov.za
6.	Rustin, O. Ms	Head of SLES: Metro East Education District	021-938-3057	Olivia.Rustin@westerncape.gov.za
7.	Arendse, A. Mr.	Head of SLES: West Coast Education District	023-860-1209	Abre.Arendse@westerncape.gov.za
8.	Swart, S. Ms.	Head of SLES: Cape Winelands Education District	023-348-4658	Sura.Swart@westerncape.gov.za
9.	Crous, A	Head of SLES: Overberg Education District	028-214-7431	Annelien.Crous@westerncape.gov.za
10.	Le Grange, L. Ms	Head of SLES: Eden & Central Karoo Education Districts	044-803-8351	Lynn.LeGrange@westerncape.gov.za

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

DIPHTHERIA ALERT

An update for Physicians, Accident & Emergency practitioners and Laboratorians

Centre for Respiratory Diseases and Meningitis
National Institute for Communicable Diseases (NICD)
Office: 011 555 0395 / Fax: 0867 583 326

May 2023

Update: Two laboratory-confirmed cases of toxigenic *Corynebacterium diphtheria* disease were in identified in April 2023. One was in the Western Cape in a child and the other in an adult in KwaZulu-Natal. These cases are a reminder that a drop in vaccine coverage (likely due to the pandemic) may lead to more cases and that C. *diphtheriae* may be circulating undetected in other provinces. Diphtheria antitoxin is in short supply globally; the World Health Organization is working to secure additional supplies of antitoxin. Treatment in the absence of anti-toxin is appropriate antibiotics and supportive care.

Alert: All clinicians throughout the country are urged to have a high index of suspicion for diphtheria, to notify suspected cases and to send specimens to the laboratory for testing.

Guidelines for diagnosis, testing, and treatment on https://www.nicd.ac.za/diseases-a-z-index/diphtheria/

Suspected case definition:

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

An example of the adherent membrane of diphtheria is shown in the photograph on the right

Photo courtesy https://www.bestonlinemd.com/how-to-avoid-getting-diphtheria/

Specimen collection and transport

A throat swab should be collected (ideally from below the membrane) using a Dacron, Rayon or nylon-flocked swab and placed in Amies or modified Stuart's transport medium with charcoal. This can be obtained from your local laboratory. The specimen should immediately be transported on ice to the laboratory for testing. The specimen should be clearly labelled: "***Suspected diphtheria***."

For laboratory staff:

All laboratories are encouraged to screen throat and nose swabs for *C. diphtheriae*

Please send any suspected/confirmed isolates of Corynebacterium spp. to CRDM/NICD for identification/ confirmation and further characterisation. Please INCLUDE the original specimen/s (swab or tissue) for PCR testing.

Case notification

All suspected cases should be notified urgently to district or provincial communicable disease coordinators (CDCCs) as per notifiable medical condition notification procedures. In the event of a confirmed case, CDCCs will conduct contact tracing. This includes collection of throat swabs and administration of prophylactic antibiotics, with or without catch-up vaccination. https://www.nicd.ac.za/nmc-overview/notification-process/

Contact details

If any additional laboratory support is needed, please contact Linda de Gouveia on 011 555 0327 or lindad@nicd.ac.za, or Mignon du Plessis on 011 555 0387 or mignond@nicd.ac.za at the Centre for Respiratory Diseases and Meningitis, NICD.

Treatment of a case of diphtheria:

Treatment should be started prior to laboratory confirmation

- **Isolate:** prevent transmission of *C. diphtheriae* by practicing contact and droplet precautions.
- **Provide supportive care:** Provide oxygen, monitor with ECG and intubate or perform a tracheostomy if necessary.
- **Provide diphtheria antitoxin:** Dosage is according to severity of illness and weight of patient.
- **Treat with appropriate antibiotics.**

Advice regarding the clinical management of suspected cases, and preventive interventions including contact tracing may be directed to the NICD doctor-on-call on 080 021 2552 after hours. The NICD guidelines for diphtheria management and laboratory detection can be found at:

https://www.nicd.ac.za/diseases-a-z-index/diphtheria/

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

REVISED MAY 2023
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

Version 1.0 (7 May 2015):

J Thomas (NICD, DPHSR)
G Ntshoe (NICD, DPHSR)

Version 2.1 (22 March 2016):

Guidelines writing committee (in alphabetical order):

C Cohen, (NICD, CRDM)
L de Gouveia (NICD, CRDM)
M du Plessis, (NICD, CRDM)
K McCarthy (NICD, DPHSR)
K Mlisana (UKZN)
P Moodley (KZN DoH)
G Ntshoe (NICD, DPHSR)
A von Gottberg (NICD, CRDM)
N Wolter (NICD, CRDM)

Version 3.0 (28 May 2018) (in alphabetical order):

M. Archary (KZN)
C Cohen, (NICD, CRDM)
L de Gouveia (NICD, CRDM)
M du Plessis, (NICD, CRDM)
K McCarthy (NICD, DPHSR)
K Mlisana (UKZN)
P Moodley (KZN DoH)
G Ntshoe (NICD, DPHSR)
A von Gottberg (NICD, CRDM)
N Wolter (NICD, CRDM)

Version 4.0 (26 May 2023) (in alphabetical order)

J Bezuidenhoudt (NICD, WC)
C Cohen, (NICD, CRDM)
L de Gouveia (NICD, CRDM)
M du Plessis, (NICD, CRDM)
HD Tootla (NHLS GSH, WC)
A von Gottberg (NICD, CRDM)
S Walaza (CRDM, NICD)
N Wolter (NICD, CRDM)

Summary of changes:

Date reviewed	Reviewed by	Summary of changes
Version 2.0 September 2015	Guideline writing committee	Case definitions changed Laboratory diagnostics section updated References and 'quick reference guide' added
Version 3.0 May 2018	Guideline writing committee	Laboratory – sample collection, transport Treatment & prophylaxis Case definitions NMC reporting
Version 4.0 May 2023	Guideline writing committee	General update

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.

Contents

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):

- Clinical queries: Dr Anne von Gottberg (011-555-0316 annev@nicd.ac.za) or Dr Sibongile Walaza (011 386 6410 sibongilew@nicd.ac.za)
- Laboratory Manager: Mrs Linda de Gouveia (011-555-0327 lindad@nicd.ac.za)
- Medical Scientist: Dr Mignon du Plessis (011-555-0387 mignond@nicd.ac.za
- After hours: **NICD Clinician Hotline (0800 212 552)**

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 CO_2 for 48 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, 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 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 become 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 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 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

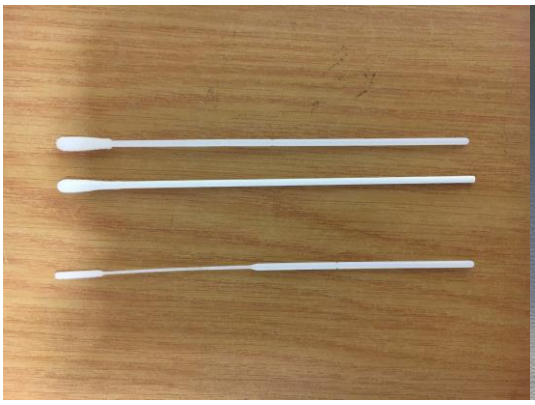


Figure 2A. Top two swabs may be used for throat. Bottom swab (thin/flexible shaft) to be used for nasopharyngeal specimen collection.

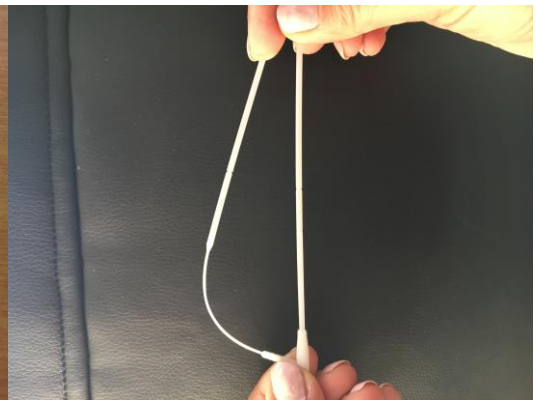


Figure 2B. Note difference in flexibility of shaft. Nasopharyngeal swab = thin/flexible shaft Throat swab = no flexibility.

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 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. 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.

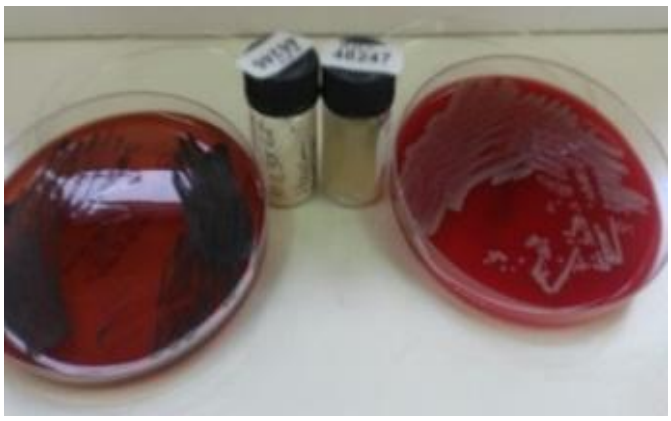
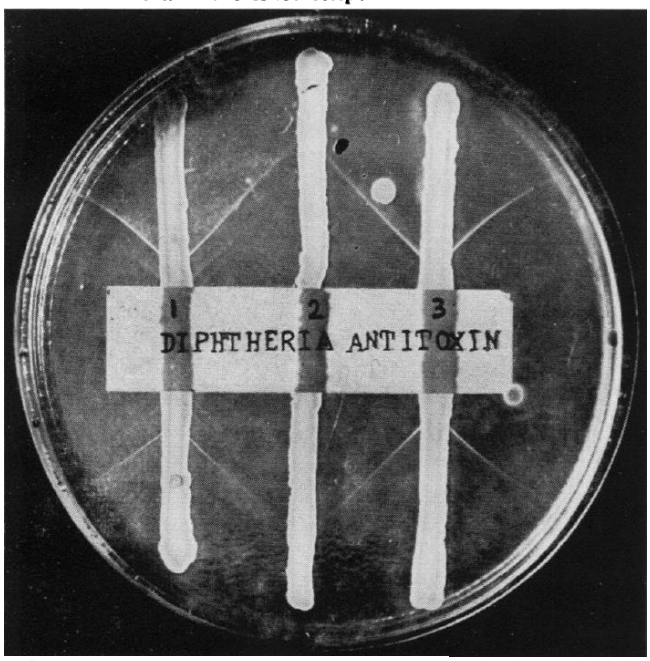


Figure 4: Submit plates with suspected *C. diphtheriae* colonies to NICD on Dorset transport media, or send the blood or Hoyle's agar plate (sealed in e.g. Parafilm M)

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:

- 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 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-toxigenic *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, *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 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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DIPHTHERIA INVESTIGATION FORM

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***				
6 weeks ☐	Date received		**6 years** ☐	Date received			
10 weeks ☐	Date received		**12 years** ☐	Date received			
14 weeks ☐	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**					
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:							

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Division of the National Health Laboratory Service

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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DIPHTHERIA CONTACT LINE LIST

health
Department: Health
REPUBLIC OF SOUTH AFRICA

Confirmed 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/yyyy									

***Types of Contact:**
1 = Had direct physical contact with the body of the case (alive or dead)
2 = Slept or spent time in the same household or room as the case

Completed by: **Surname and name:**_____ **Cell number :**_____ **Date:**_____

Diphtheria
Frequently asked questions

1. What is diphtheria?

Diphtheria is a contagious and potentially life-threatening bacterial infection. It is caused by infection with a toxin-producing strain of *Corynebacterium diphtheriae* or more rarely *Corynebacterium ulcerans* or *Corynebacterium pseudotuberculosis*. It occurs in two forms- respiratory diphtheria and cutaneous diphtheria.

2. Who can get diphtheria?

Children who are not immunized or who did not receive complete the Expanded Programme of Immunization (EPI) schedule, are at increased risk of getting diphtheria. Adults may also be at risk of contracting diphtheria if the organism is present in the community because adult immunity following vaccination wanes with time. Susceptible persons living in crowded conditions are at increased risk of getting the disease.

3. Where does diphtheria occur in South Africa?

Diphtheria is an uncommon disease in South Africa. Since the implementation of diphtheria immunization in South Africa in the 1950s, only sporadic cases of diphtheria, 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). An outbreak of diphtheria in KwaZulu-Natal Province involving 15 confirmed cases occurred during March to June 2015. Two cases of diphtheria were identified also from KwaZulu-Natal Province in 2016.

4. How is diphtheria transmitted?

C. diphtheriae spreads from person to person through contact with respiratory droplets or hand-to-mouth contact with secretions from an infected person's mouth, nose, throat or skin. Sometimes, persons can carries the microorganism in their throat but have no symptoms. These persons can also spread the organism through respiratory droplets. Less frequently, the infection can be transmitted through close contact with skin lesions in a person with the cutaneous form of the illness. Prolonged close contact is normally required for the infection to be transmitted to others. Diphtheria caused by *C. ulcerans* or *C. pseudotuberculosis* can also spread through contaminated milk or close contact with infected animals (e.g. through working on a farm or as a veterinarian).

5. How does diphtheria affect animals?

Humans are the only known natural host for *C. diphtheriae*. *C. ulcerans* and *C. pseudotuberculosis* are zoonoses and cause mastitis and lymphadenitis in cattle.

6. What are the signs and symptoms of diphtheria?

Symptoms of respiratory diphtheria usually start 2 to 5 days after exposure, although the incubation period can be longer (range 1 to 10 days). Initial signs and symptoms include fever, malaise, chills, loss of appetite, sore throat, nausea and vomiting. Within days, a whitish/greyish pseudomembrane may form over the throat and tonsils that can make it hard to swallow and breathe. Typically the membrane is adherent to the pharynx and cannot be dislodged. The 'membrane' is actually necrotic tissue. The infection can also cause the lymph glands and tissue on both sides of the neck to swell (bull neck). Complications of diphtheria include respiratory obstruction, and myocarditis with cardiac arrest or cardiac failure. The cutaneous form of diphtheria often presents as a non-healing ulcer with a dirty grey membrane.

7. How is diphtheria diagnosed?

Respiratory diphtheria is first suspected clinically in a patient with pharyngitis by the presence of an adherent pharyngeal pseudomembrane and fever, with or without a bull neck. The diagnosis is confirmed by culture of the organism from a pharyngeal or wound swab. Clinicians should label the swab 'suspected diphtheria'. The laboratory will plate the organism onto selective media. Once the organism has been identified as *C. diphtheriae*, it will be subjected to PCR testing for the *tox* gene, which is responsible for toxin production, and to ELEK testing, to determine if toxin production is 'switched on'.

8. How is diphtheria treated?

Patients should be given diphtheria antitoxin (DAT) to neutralize the diphtheria toxin. The decision to give diphtheria antitoxin is based on clinical diagnosis, and should not wait for laboratory confirmation. Antibiotics have not been demonstrated to affect healing of local infection. However, they are used to eliminate *C. diphtheriae* from the nasopharynx and prevent its spread to others.

9. How can diphtheria be prevented?

Diphtheria is prevented by immunisation with diphtheria containing vaccine. In South Africa, the Expanded Program on Immunisation (SA-EPI) schedule includes 6 doses of diphtheria vaccine. The primary series of vaccination is given in 3 doses at 6, 10 and 14 weeks of age using diphtheria toxoid given in combination with other antigens. Boosters are given at 18 months and 6 and 12 years of age respectively. Following exposure to a case of diphtheria, contacts (persons sharing meals or living in the same house, or caring for infected children, or health care workers who have conducted CPR, or procedures involving contact with respiratory secretions) should receive chemoprophylaxis, booster vaccination and should have a throat swab to determine carriage status.

10. Where can I find out more information?

Guidelines and other useful resources are available on the NICD website: www.nicd.ac.za. For more information contact:

- Medical/clinical related queries: contact NICD Hotline number +27 (0) 82 883 9920 (for use by healthcare professionals only)
- Laboratory related queries
  - Centre for Respiratory Diseases and Meningitis: (Linda de Gouveia 011-555-0327 lindad@nicd.ac.za , Mignon du Plessis 011-555-0387 mignond@nicd.ac.za or Nicole Wolter 011-555-0352 nicolew@nicd.ac.za
- Results enquiries: Centre for Respiratory Diseases and Meningitis laboratory (011-555-0315/7/8)

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Notifiable Medical Conditions (NMC) Case Notification Form

{Section 90 (1) (j), (k) and (w) of National Health Act, 2003 (Act no. 61 of 2003)}

This form must be **completed immediately** by the health care provider who diagnosed the condition ***Please mark applicable areas with an X***

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Health facility name *(with provincial prefix)*	Health facility contact number	Health district
Patient file/folder number	Patient HPRS-PRN	Date of notification y y y y - m m - d d

Patient demographics				**Patient residential address**
First name				Street/dwelling unit/building/ERF number
Surname				Street name, building, location description
S.A ID number				Sub-place, suburb, village, postal area
Passport/other ID number				Town/city Post code:
Citizenship				**Employer/educational institution address**
Date of birth	y y y y - m m - d d			Institution name
Age	Years	Months (if less than 1yr	Days (if less than 1 month)	Street name, building, location description
Gender	Male	Female		Sub-place, suburb, village, postal area
Is patient pregnant?	Yes	No	Unknown	Town/city Post code:
Contact number				Contact number

Medical conditions details						
Name of NMC diagnosed			History of possible exposure to NMC in the last 60dys		No Yes Unknown	
Method of diagnosis	Clinical signs and symptoms ONLY		Rapid test	X-ray	Laboratory confirmed	Other:
Clinical symptoms relating to the NMC						
Treatment given for the NMC						
Date of diagnosis	y y y y - m m - d d			Date of symptom onset	y y y y - m m - d d	
Patient admission status	Outpatient	Discharged		Inpatient	Ward name	
Patient vital status	Alive	Deceased		Date of death	y y y y - m m - d d	

Travel history in the last 60 days			
Did patient travel outside of usual place of residence?	Yes	No	*If yes, complete the travel details below*
Place travelled from	Place travelled to	Date patient left usual place of residence	Date patient returned to usual place of residence
Country/Province/Town	Country/Province/Town	y y y y - m m - d d	y y y y - m m - d d
Country/Province/Town	Country/Province/Town	y y y y - m m - d d	y y y y - m m - d d

Vaccination history *for the NMC diagnosed above (complete only for vaccine preventable NMC)*				
Vaccination status	Not vaccinated	Up-to-date	Unknown	Date of last vaccination y y y y - m m - d d

Specimen details			**Notifying health care provider's details**	
Was a specimen collected?	Yes	No	First name	
Date of specimen	y y y y - m m - d d		Surname	
Specimen barcode/lab number			Mobile number	
			SANC/HPCSA number	Notifier's signature

The top copy (white) must be sent to NMCsurveillanceReport@nicd.ac.za or fax to 086 639 1638 or NMC hotline 072 621 3805 and to the sub-district/district office. The middle copy (blue) must be attached to the patient referral letter or patient file. The bottom copy (pink) must remain in the booklet

Category 1: Immediate reporting telephonically followed by written or electronic notification within 24hrs of diagnosing a case

DIPHTHERIA

Why is surveillance necessary?	Who must notify and when?	Suspected case definition	Probable case definition	Confirmed case definition
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 not at risk of diphtheria.	The clinician who suspects diphtheria should notify the case immediately. Healthcare workers should NOT wait for laboratory confirmation before notifying cases.	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.	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. diphtheria or C. ulcerans or C. pseudotuberculosis* has been isolated from relevant specimens but toxigenicity status has not been confirmed.	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 hotline (082-883-9920) 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. See resources below.

Additional resources

A case-investigation form (CIF), frequently asked questions document (FAQ), Guidelines for the management and public health response to diphtheria (2018), and specimen collection guidelines are available at http://www.nicd.ac.za/diseases-a-z-index/diphtheria/

Clinical management of diphtheria

Guideline

2 February 2024

World Health Organization

Clinical management of diphtheria: guideline, 2 February 2024

WHO/Diph/Clinical/2024.1

Suggested citation. Clinical management of diphtheria: guideline, 2 February 2024. Geneva: World Health Organization; 2024 (WHO/DIPH/Clinical/2024.1). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Contact

cmtm@who.int

Sections

1. Summary of the guideline

Clinical question: What is the role of antibiotics and diphtheria antitoxin (DAT) in the treatment of diphtheria?

Context: This clinical practice guideline has been rapidly developed recognizing the global increase in diphtheria outbreaks. Outbreaks of diphtheria in Nigeria, Guinea and neighbouring countries in 2023 have highlighted the urgent need for evidence-based clinical practice guidelines for the treatment of diphtheria. Given the sporadic nature of outbreaks, many clinicians in the affected regions have never managed acute diphtheria and its related complications. The diphtheria case definition is provided in the WHO document: Diphtheria: Vaccine Preventable Diseases Surveillance Standards*(1)*.

Scope: This guideline focuses on the clinical management of respiratory diphtheria and does not provide advice on vaccination.

See WHO Laboratory manual for the diagnosis of diphtheria and other related infections *(2)*.

New recommendations:

- In patients with suspected or confirmed diphtheria, WHO recommends using macrolide antibiotics (azithromycin, erythromycin) in preference to penicillin antibiotics [Strong recommendation, low certainty evidence].

- In patients with suspected or confirmed diphtheria, WHO recommends not to perform routine sensitivity testing prior to administration of diphtheria antitoxin (DAT) [Strong recommendation, moderate certainty evidence].

- In patients with suspected or confirmed symptomatic diphtheria, WHO suggests an escalating dosing regimen for diphtheria antitoxin (DAT) which is based on disease severity and time since symptom onset, in comparison with a fixed dose for all patients [conditional recommendation, very low certainty evidence].

Characteristic of diphtheria disease	Dose of diphtheria antitoxin (IU)
• Laryngitis **or** pharyngitis **and** • Duration < 48 hours	20 000
• Nasopharyngeal disease (extensive pseudomembrane) **and** • duration < 48 hours	40 000
One or more of: • Diffuse swelling of the neck • Any disease ≥ 48 hours • Severe disease (respiratory distress, shock)	80 000

About this guideline: This guideline was developed according to standards and methods for trustworthy guidelines. These guidelines are based on the synthesis of the available evidence on the health effects of interventions, and the grading of the certainty of that evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. The synthesized and graded evidence on the health effects of interventions, as well as any evidence on contextual factors, is used to develop an evidence-to-decision (EtD) framework for each recommendation *(3)*. The judgement on the different factors in the EtD framework (including the certainty of evidence) facilitates the determination of the strength and direction of each recommendation *(4)*.

Expert input is important for the interpretation of the evidence, and the development of guidance may rely on expert opinion, particularly in areas where the evidence is currently weak, scarce or absent. For example, the DAT dosing recommendations presented in the guidelines are based on a consideration of the evidence gained from observational data as well as the technical knowledge and experience of the Guideline Development Group (GDG). Details of contributors are available online here.

Update and access: The living guideline is written, disseminated, and updated on an online platform (MAGICapp, https://app.magicapp.org/#/guideline/7759), with a user-friendly format and easy-to-navigate structure that accommodates dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations updated within the guideline. This format should also facilitate adaptation, which is strongly encouraged by WHO, to contextualize recommendations from a health care system perspective to maximize country impact.

A planned update is already ongoing to address clinical questions related to the prevention of infection in close contacts of people with diphtheria.

Broader context:
The guideline closely aligns with the WHO Health Emergencies Programme goal of strengthening preparation, preparedness, response and resilience in response to health emergencies, particularly the ability of member states to provide safe and scalable care *(5)*.

2. Abbreviations

AMR	antimicrobial resistance
AST	antibiotic sensitivity testing
DAT	diphtheria antitoxin
DOI	declaration of interest
DST	drug sensitivity testing
ETD	evidence to decision
GDG	guideline development group
SAE	serious adverse event
WHO	World Health Organization

3. Introduction

What triggered this guideline?

Despite the implementation of diphtheria vaccination early last century there has continued to be outbreaks of diphtheria in regions where vaccine coverage is not optimal. Vaccine coverage has been negatively impacted by the COVID-19 pandemic, population displacement, and structural disruption of health systems. There is now a prolonged outbreak of diphtheria in multiple countries in West Africa and sporadic outbreaks in all WHO regions. Although diphtheria is both preventable and treatable, successful treatment depends on rapid recognition of the clinical syndrome as well as rapid implementation of the appropriate treatment, which includes the timely administration of the appropriate antibiotics and DAT. Access to DAT has been a challenge due to limited global supply and rapid distribution systems.

The WHO Clinical management of diphtheria guideline aims to provide, in a single reference, the latest evidence-based recommendations to support clinicians in their efforts to provide acute treatment for diphtheria. This guideline responds to direct requests from clinicians and health ministries of affected countries. Currently, clinicians in countries affected by the outbreak have limited or no clinical experience managing patients with diphtheria and limited access to antimicrobial susceptibility testing.

What are the guideline's objectives?

- To provide evidence-based and context-sensitive recommendations on the appropriate choice(s) for diphtheria clinical management including the use of diphtheria antitoxin (DAT) and antibiotics.
- To support the adaptation by WHO Member States of these evidence-based guidelines into national diphtheria policies for the clinical management of diphtheria.
- To inform the clinical research agenda by identifying knowledge gaps which limit our capacity to produce evidence-based recommendations.

Who is this guideline for?

The primary audience for the guideline is clinicians treating patients with diphtheria. The guideline is also intended for use by health managers at facility or jurisdiction level to develop local tools or protocols to assist clinicians in managing patients with diphtheria and orient procurement and allocation of recommended treatments. Furthermore, the guideline is intended to guide researchers and research funders to address the highlighted evidence gaps and uncertainties.

4. Clinical characterization

Clinical characterization

Respiratory diphtheria is caused by strains of *Corynebacterium diphtheriae*, which have affinity for the upper respiratory tract (nose and throat) and produce a toxin which causes local disease and, in severe cases, airway compromise and systemic complications. Diphtheria occurs when the bacterial toxin inflames the epithelial mucosal, causing an exudate which can have a characteristic greyish-white “pseudomembrane” in the pharynx, nasopharynx, tonsils, or larynx (or a combination of these). The fibrinous pseudomembrane can lead to respiratory obstruction. The toxin disrupts protein synthesis and causes cell death leading to the breakdown of the epithelium, and subsequent spread to local lymph nodes can cause a swollen neck. Spread of the toxin in the blood can affect the myocardium (heart), kidneys, and nervous system. *C. diphtheriae* can also cause skin and wound infections. Cutaneous disease is not further discussed in this guideline.

The severity of diphtheria is described in previous WHO operational guidance.

- Mild disease: localized laryngeal or pharyngeal disease of 2 days duration;
- Severe/extensive disease: duration of 3 or more days, or diffuse neck swelling (the so called “bull neck”), or respiratory distress, or hemodynamic instability”*(6)(7)*.

A recent systematic review suggests the case fatality ratio in unvaccinated individuals infected with toxin-producing strains is 29% *(8)*. Case fatality ratios in resource-limited settings are highly variable but, in some outbreaks, can be as high as 50% *(9)(10)*.

Transmission: Diphtheria spreads from person to person mostly through the air, and less frequently by direct contact. The incubation period is usually from 2 to 5 days.

Current treatments include:

- neutralization of unbound toxin with DAT;
- antibiotics to prevent further bacterial growth;
- monitoring and supportive care to prevent and treat complications, e.g. airway obstruction, myocarditis. In patients with imminent airway obstruction, urgent airway intervention may be lifesaving. The possible options include basic airway manouevres, endotracheal intubation, cricothyroidotomy (needle or surgical approach), and tracheostomy. The risks and benefits of each approach will depend on the experience of the treating medical personnel.

5. Recommendation for antibiotics treatment

Antibiotics are used to prevent further bacterial growth and toxin production reducing the risk from further organ damage, and to reduce bacterial transmission to others. Historically, penicillins have been used (including benzylpenicillin, procaine penicillin and penicillin V), but macrolides have also been employed (for example, erythromycin or azithromycin). Antimicrobial resistance prevalence amongst strains of *C. diphtheriae* occurs to both classes, and is variable by region and over time. Local resistance patterns can therefore only be known by bacterial susceptibility testing. Recent studies have demonstrated increased resistance to penicillin over the macrolide class of antibiotics *(11)*. Antibiotics are also used to prevent the development of diphtheria in close contacts of infectious patients; WHO recommendations on this topic are under development.

Strong recommendation for

In patients with suspected or confirmed diphtheria, WHO recommends using macrolide antibiotics (azithromycin, erythromycin) in preference to penicillin antibiotics [Strong recommendation, low certainty evidence].

Remarks:

- Antibiotics should be administered alongside DAT and should not be delayed.
- Recent evidence suggests that there is increasing resistance to penicillins and less resistance to macrolide antibiotics. Local antimicrobial susceptibility testing is vital to ensure the ongoing appropriate use of antibiotics. Advice on laboratory testing in outbreaks is available here.
- The choice of macrolide will depend on availability and feasibility.

Practical info

Macrolide antibiotics include azithromycin and erythromycin. Parenteral administration of macrolide antibiotics is possible; however, it is typically indicated for where oral administration is not possible, such as when patient is unable to swallow oral medications. The choice of macrolide will be based on availability and feasibility. Dosing recommendation are as follows:

- **Azithromycin:** administer orally or intravenously once a day.
  - For children: 10 – 12 mg/kg once daily (maximum 500 mg per day).
  - For adults: 500 mg once daily.
- **Erythromycin**: administer orally or intravenously every six hours.
  - Dose (children and adults): 10 – 15 mg/kg every 6 hours, maximum 500 mg per dose or 2 grams a day.

Penicillin antibiotics

We are providing practical information on penicillin for the scenario where macrolide antibiotics are not available and susceptibility testing demonstrates sensitivity to penicillin. Penicillin can be given orally or parentally (intravenous or intramuscular). Parenteral administration is used primarily to achieve adequate tissue concentrations, especially in patients with severe disease.

- **Procaine benzyl penicillin (penicillin G)**: administer by intramuscular injection**.**
  - Dose (children and adults): 50 mg/kg once daily. Maximum is 1.2 g per day.
- **Aqueous benzyl penicillin (penicillin G)**: administer by intramuscular injection or slow intravenous infusion.
  - Dose (children and adults): 100 000 units/kg per day in divided dose of 25 000 IU/kg every 6 hours. Maximum is 4 MIU or 2.4 g per day.
- **Phenoxymethylpenicillin V:** administer orally.
  - Dose (children and adults): 50 mg/kg per day in divided doses administered every 6 hours (each dose 10 – 15 mg/kg. Maximum 500 mg per dose).

In a diphtheria outbreak it is important that antibiotic stewardship and monitoring are implemented particularly in relation to any changes in antibiotic resistance, which can be determined by antibiotic sensitivity testing.

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

In patients with suspected or confirmed diphtheria, the GDG deemed the use of antibiotics to be the standard of care over no antibiotics. The use of macrolides, compared with penicillins, probably does not affect mortality or rate of serious side-effects, but erythromycin may increase the rate of gastrointestinal side-effects. The treatment effect of macrolide antibiotics, compared with penicillin antibiotics, is very uncertain for the outcomes of rate of myocarditis, hospitalization, need for airway intervention, new cases of diphtheria, or treatment failure. However, the point estimate of treatment failure favurs macrolides over pencillins.

The treatment burden of penicillins is substantially greater than that of azithromycin, including the need for more frequent doses of penicillins generally, and the need for intravenous administration of benzylpenicillin specifically. Though the risk of antibiotic resistance was uncertain and dependent on local resistance patterns the panel noted that current data suggests that the risk of penicillin resistance is higher than macrolide resistance, therefore suggesting potential benefits of macrolide therapy.

In the circumstances where antitoxin is unavailable and unlikely to be accessible in a short period, there is a speculative benefit of dual antibiotic treatment. In such cases, where bacteriological susceptibility is unknown, clinicians might choose, pending susceptibility data, to treat concurrently with both macrolide and beta-lactam antibiotics.

Certainty of the Evidence

Low

The evidence summary for the prioritized outcomes were largely informed by one randomized clinical trial (n=86) which compared penicillin (benzylpenicillin followed by penicillin V) with erythromycin for the treatment of diphtheria.

Certainty of evidence was rated as: moderate for mortality (rated down for imprecision), very low for myocarditis (rated down for imprecision and risk of bias), very low for hospitalization and airway intervention (rated down for imprecision and indirectness), very low for new cases of diphtheria (rated down for imprecision and indirectness) and very low for treatment failure (rated down for risk of bias, imprecision, and indirectness). The certainty of evidence was rated as: moderate for serious side-effects (rated down for risk of bias), low for gastrointestinal side-effects (rated down for risk of bias, imprecision), high for burden of treatment, and very low for antibiotic resistance.

Values and preferences

No substantial variability expected

Patients place a high value on receiving fewer doses and oral drug treatment, rather than multiple doses and parenteral drug administration, and to a lesser extent on the speculative possibility of greater effectiveness with macrolide treatment. The panel felt that considerations of antimicrobial resistance were as or more important than individual patient considerations.

Resources

Important issues, or potential issues not investigated

The resources required to routinely use penicillin antibiotic treatment, with frequent intramuscular or intravenous dosing, are substantially greater than with a daily, oral treatment such as azithromycin.

The availability and reliability of microbiological susceptibility testing for isolates to guide therapy will not always be available in a timely fashion , particularly in outbreak settings. Therefore, clinicians should administer the antibiotic with the lowest probability of resistance.

Equity

Important issues, or potential issues not investigated

The GDG discussed at length the availability of both pencillin and macrolide antibiotics, and how there were no significant equity-related concerns as to accessibility of the two treatments in most settings. Treatment burden being higher with penicillins led considerations for preference of macrolides, which has equity implications for accessing health care resources.

The GDG discussed data on diphtheria resistance to beta-lactam and/or macrolide antibiotics, and the possibility of widespread use of macrolides in worsening antimicrobial resistance, and worsening health equity longer term. The agreed

values and preferences statement heavily weighed on the considerations of the GDG, where antibiotic resistance was seen as, or more important than, individual patient considerations. The GDG made a strong recommendation for the use of macrolides, given the feasibility of implementation and the likely limited impact of macrolide usage in diphtheria outbreaks on wider resistance patterns.

Acceptability

Important issues, or potential issues not investigated

The GDG remarked that intravenous dosing may be appropriate for patients who are severely ill and admitted to hospital, or who may be unable to tolerate orally administered medications. In addition, some panelists commented on the potential for concomitant use of penicillin and macrolide antibiotics for severely ill patients when susceptibility patterns are unknown, and particularly during the early phases of outbreaks when DAT may be unavailable.

There are known gastrointestinal side-effects of macrolides, which may impact acceptability of the recommendation, but these are not serious *(12)*.

The acceptability of implementation was a primary consideration in making recommending administration of macrolides, specifically oral azithromycin rather than intravenous or intramuscular penicillin.

The current WHO AWaRe antibiotic book does not list diphtheria as an indication for azithromycin, and this was noted *(13)*.

Feasibility

Important issues, or potential issues not investigated

The feasibility of implementing macrolide antibiotics, compared with penicillin antibiotics, is very high. For patients who are severely ill, feasibility considerations are less relevant, as intravenous routes of administration may be preferred and are available for either antibiotic. Treatment of severely ill patients largely focused on the potentially high burden of resistance to beta-lactam antibiotics.

In a diphtheria outbreak it is important that antibiotic stewardship and monitoring are implemented particularly in relation to any changes in antibiotic resistance, which can be determined by antibiotic sensitivity testing.

Justification

When moving from the evidence to a recommendation the GDG emphasized the relative treatment burden of penicillins and macrolides. The GDG discussed the known and variable epidemiology of antibiotic resistance in *Corynebacterium diphtheriae*, in addition to no compelling adverse clinical consequences of macrolide use.

Typically, WHO does not make strong recommendations with low certainty evidence. One exception is when low evidence suggests equivalence or benefit of a therapy (in this case macrolides equivalent or superior to penicillins) and there is high certainty evidence of less harm with that therapy. In this case, we have high certainty evidence of the higher burdens associated with penicillin parenteral therapy multiple times a day.

The GDG made a strong recommendation for the use of macrolides, given the feasibility of implementation and the likely limited impact of macrolide usage in diphtheria outbreaks on wider resistance patterns.

Clinical question/ PICO

Population: Persons with suspected or confirmed diphtheria
Intervention: Macrolide antibiotic
Comparator: Penicillin antibiotic

Summary

Full summary of the evidence synthesis is available here. *(14)*

Outcome Timeframe	**Study results and measurements**	**Comparator** Penicillin	**Intervention** Macrolide	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Mortality 10 days	Relative risk 1 Based on data from 86 participants in 1 studies. [1] (Randomized controlled)	10 per 1000 Difference:	10 per 1000 **0 fewer per 1000** CI 95%	Moderate Due to serious imprecision. [2]	The choice of antibiotic probably does not affect mortality.
Myocarditis	Based on data from 86 participants in 1 studies. [3] (Randomized controlled)	68 per 1000 Difference:	0 per 1000 **68 fewer per 1000** (CI 95% 166 fewer — 29 more)	Very low Due to serious imprecision, Due to serious risk of bias [4]	We are very uncertain if the choice of antibiotic affects the rate of myocarditis.
Treatment failure as inferred from non-clearance of colonisation at day 8 (higher value suggests more treatment failure) [5]	Relative risk Based on data from 238 participants in 1 studies.	160 per 1000 Difference:	80 per 1000 **80 fewer per 1000** (CI 95% 173 fewer — 8 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [6]	We are uncertain if choice of antibiotic affects the rate of treatment failure.
Serious side effects	Based on data from 86 participants in 1 studies. [7] (Randomized controlled)	0 per 100 Difference:	0 per 100 **0 fewer per 100** CI 95%	Moderate Due to serious risk of bias [8]	The choice of antibiotic probably does not affect the rate of serious side effects.
Gastrointestinal side effects	Relative risk Based on data from 86 participants in 1 studies. [9]	23 per 1000 Difference:	191 per 1000 **167 more per 1000** (CI 95% 18 more — 318 more)	Low	Erythromycin may increase the rate of gastrointestinal side effects.
Hospitalization + airway intervention as inferred from time to membrane clearance [10]	Measured by: Time to membrane clearance Lower better Based on data from 86 participants in 1 studies. (Randomized controlled)	3 days (Median)	3 days (Median) CI 95%	Very low Due to very serious indirectness, Due to serious imprecision [11]	We are very uncertain if the choice of antibiotic affects the rate of hospitalization or need for airway intervention.

Outcome Timeframe	**Study results and measurements**	**Comparator** Penicillin	**Intervention** Macrolide	**Certainty of the Evidence** (Quality of evidence)	**Summary**
New cases of diphtheria as inferred from time to bacteriological clearance by culture	Measured by: Time to bacteriological clearance by culture Lower better Based on data from 86 participants in 1 studies. (Randomized controlled)	2 days (Median)	2 days (Median) CI 95%	Very low Due to serious imprecision, Due to very serious indirectness [12]	We are very uncertain if the choice of antibiotic affects the rate of new cases of diphtheria.

1. Primary study[15]. **Baseline/comparator:** No studies available.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
3. Primary study[15]. **Baseline/comparator:** Primary study[15].
4. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting. **Imprecision: serious.** Only data from one study.
5. undefined
6. **Risk of Bias: serious.** Selective outcome reporting. **Indirectness: serious.** Direct comparisons not available. **Imprecision: serious.** Only data from one study.
7. Primary study[15]. **Baseline/comparator:** Control arm of reference used for intervention[15].
8. **Risk of Bias: serious.** Selective outcome reporting.
9. Primary study[15]. **Baseline/comparator:** Control arm of reference used for intervention[15].
10. undefined
11. **Indirectness: very serious.** Direct comparisons not available. **Imprecision: serious.** Only data from one study.
12. **Indirectness: very serious.** Direct comparisons not available. **Imprecision: serious.** Only data from one study.

6. Recommendations for diphtheria antitoxin (DAT)

Diphtheria antitoxin (DAT) is the standard of care for treatment of diphtheria cases. DAT has a significant impact on mortality,and has been used since the late 19th century. The relative mortality reduction based on systematic review is 76% (RR 0.24 [95% CI 0.22–0.28]), and it is more effective when administered earlier *(8)*.

There is a global shortage of DAT due to the limited number of manufacturers and their capacity.

6.1 Mechanism of action of diphtheria antitoxin (DAT)

DAT targets the diphtheria toxin released from the pathogen. Diphtheria toxin binds to cells through the heparin-binding epidermal growth factor-like growth factor precursor (pro-HB-EGF). After binding, the toxin is internalized by endocytosis during which it is processed into constituent subunits. The active subunit A is released from the endosome and inhibits ADP-ribosylating elongation factor 2 (EF-2), which terminates protein synthesis thereby eliciting cell death.*(16)* DAT is most effective in neutralizing extracellular toxin, and once toxin is internalized DAT is ineffective in preventing its intracellular consequences.

Antibody concentrations, and anti-toxin neutralizing activity by cytotoxicity assays, have been assayed in serum from four patients receiving diphtheria antitoxin for suspected diphtheria (but who did not have diphtheria).*(17)* The minimum effective dose of DAT has not been formally determined in humans, and doses employed in the management of diphtheria assume that duration of disease and/or severity roughly indicate the amount of circulating toxin.

6.2 Diphtheria antitoxin sensitivity testing: rationale

DAT is derived from the serum of horses exposed to diphtheria toxoid. Due to the potential for immediate allergic reactions to infusions of DAT, some manufacturers have recommended sensitivity testing, an incremental exposure of the patient to small doses of DAT during a period of observation. If no adverse events are noted, the full dose is given. If there is evidence of a reaction to DAT, desensitization using progressive administration of escalating doses can be performed in an effort to enable allergic patients to receive treatment.

In many outbreaks, sensitivity testing has not been performed. Reasons have included: perceived poor predictive value of the procedure for adverse reactions to the full DAT dose; the significant potential delay in life saving treatment where resources and severely limited; the relative safety to medically manage DAT reactions, where the risk of not giving antitoxin is significant.*(18)* The need for DAT sensitivity testing was reviewed in this guideline and a recommendation provided.

6.3 Recommendation on DAT sensitivity testing

Strong recommendation against

In patients with suspected or confirmed diphtheria, WHO recommends not to perform routine sensitivity testing prior to administration of diphtheria antitoxin [Strong recommendation, moderate certainty evidence].

Remarks:

- Due to the risk of allergic reaction, ensure sufficient trained staff and equipment are available and the patient is cared for in an area where they can be monitored closely.

Practical info

WHO recommends not to perform routine sensitivity testing prior to administration of diphtheria antitoxin.

In the 2017-18 diphtheria outbreak in Bangladesh in a crowded camp of Rohingya migrants, patients were administered antihistamines and weight-based corticosteroids 30 minutes prior to DAT infusion.*(18)* Oral chlorphenamine and intravenous hydrocortisone were used. We found no diphtheria-specific literature comparing prophylactic strategies. Implementers of this guideline might consider indirect evidence from snakebites given equine-derived antitoxin. The largest RCT for snakebite (n = 1,007) found rates of adverse events to the antitoxin in those treated with either steroid, or antihistamine, or both, were similar to placebo.*(20)*

In case serious allergic reaction occurs, ensure sufficient trained staff and equipment are available and the patient is being cared for in area where they can be monitored closely. This includes:

- Monitoring equipment: pulse oximeter, blood pressure monitoring, thermometer.
- Emergency medicines: adrenaline (1:1000), salbutamol, intravenous antihistamine (e.g. chlorphenamine), corticosteroid (e.g. prednisolone, hydrocortisone), intravenous fluid (Ringer's lactate or 0.9% w/v saline), oxygen supply and delivery devices.
- Emergency equipment: age appropriate equipment for airway management and suction, oxygenation (bag valve mask and oxygen), and cardiovascular support (intravenous cannulae and giving sets).

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

In patients with suspected or confirmed diphtheria who will receive diphtheria antitoxin therapy (DAT), giving DAT without routine sensitivity testing probably reduces mortality compared with performing allergy testing and desensitization. This benefit results because routine sensitivity testing will lead to an appreciable number of patients who will not receive DAT due to a test result suggestive of allergy, and because desensitization is either not available or not usually successful. When routine sensitivity testing is not employed, patients will receive DAT and therefore the benefit of reduced mortality. This is true even for the vast majority of those who experience allergy in whom reactions are clinically manageable, allowing complete DAT administration.

Certainty of the Evidence

Moderate

The evidence on routine sensitivity testing before DAT is from single-arm interventions reporting rates of adverse events related to antitoxin use. The decision analysis undertaken by the methods incorporated evidence from 14 single-arm studies, and provided moderate certainty evidence that routine sensitivity testing increases mortality.

Values and preferences

No substantial variability expected

Patients place a high value on avoiding death, and a lower value on avoiding severe adverse events resulting from treatment.

Resources

No important issues with the recommended alternative

Not performing routine sensitivity testing on all patients recommended to receive DAT is resource-saving, both in terms of the time and the materials required for sensitivity testing and desensitization.

Equity

No important issues with the recommended alternative

The GDG provided insight that not routinely performing sensitivity testing for all patients recommended to receive DAT may increase accessibility and timeliness to receive DAT.

Acceptability

Important issues, or potential issues not investigated

The GDG commented on the available data on time-to-DAT for improved outcomes for severely ill patients, and the impact that routine sensitivity testing may have on delays to administering DAT.

The GDG also commented on the available protocols in place to routinely administer antihistamines and/or corticosteroids prior to DAT administration. The GDG does not provide specific recommendations for these, but strategies used in one outbreak are summarized in "Practical info".

Feasibility

Important issues, or potential issues not investigated

The GDG commented on the complexity of performing routine sensitivity testing, particularly in outbreak settings with large numbers of patients and varied providers.

Justification

When moving from the evidence to a strong recommendation against performing routine sensitivity testing in patients recommended to receive DAT, the GDG emphasized the moderate certainty evidence in the mortality benefit. Although there remains concerns about the possibility of a systemic allergic response during the administration of DAT, the GDG recommended to not routinely perform sensitivity testing, given the high value placed on avoiding death.

Clinical question/ PICO

Population: Persons with suspected or confirmed diphtheria for whom diphtheria antitoxin is indicated

Intervention: Sensitivity testing performed prior to administration of diphtheria antitoxin

Comparator: Sensitivity testing not performed prior to administration of diphtheria antitoxin

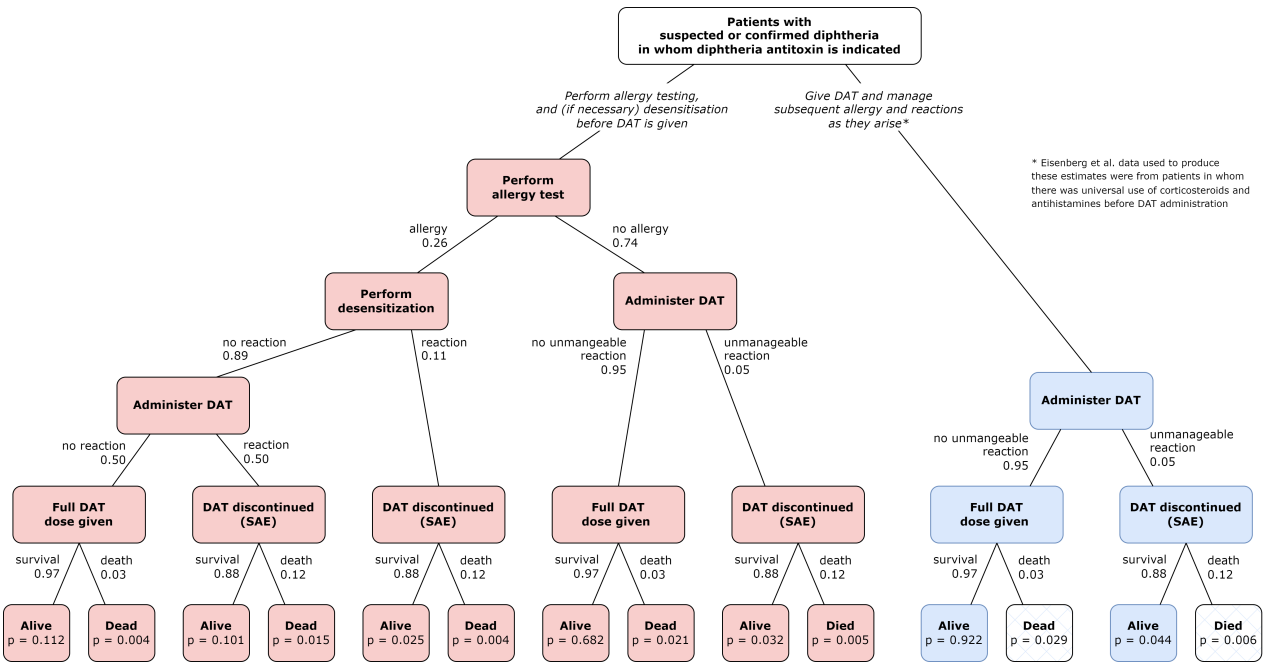
Summary

Full summary of the evidence synthesis is available here. *(14)*

A decision tree was created from assumptions based on Eisenberg *et al*.*(18)*

Mortality was modeled at 12.5% without diphtheria antitoxin (DAT), and 3% with DAT, by applying the relative risk ratio of 0.24.*(8)* Key assumptions were that: 1) incomplete administration of diphtheria antitoxin had no clinical benefit; 2) complete administration of DAT is attained in 95% of cases where given with concurrent antihistamine and corticosteroid administration; 3) Serious adverse events (SAE) associated with DAT occur at 3% (anaphylaxis); 4) Serious adverse events associated with DAT administration have trivial (zero) mortality.*(18)*

Figure: Outcome probabilities based on alternative strategies



Red boxes (left side of diagram) represent the probability tree where allergy testing and (where necessary) desensitisation is performed before DAT is administered.

Blue boxes (right side of diagram) represent the probability tree where DAT is given, and allergies are treated as they arise (with no allergy testing, and no desensitisation).

Outcome Timeframe	**Study results and measurements**	**Comparator** No sensitivity testing	**Intervention** Sensitivity testing	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Mortality	Relative risk 0.74 (Observational (non-randomized))	47 per 1000 Difference:	35 per 1000 **12 fewer per 1000** CI 95%	Moderate	Giving DAT without allergy testing probably reduces mortality compared with performing allergy testing and desensitization.

6.4 Recommendation on DAT dose

Conditional recommendation for

In patients with suspected or confirmed symptomatic diphtheria, WHO suggests administration of a single dose of diphtheria antitoxin with choice of dose based on disease severity and time since symptom onset, in comparison with a fixed dose for all patients [Conditional recommendation, very low certainty evidence].

Characteristic of diphtheria disease	Dose of diphtheria antitoxin (IU)
• Laryngitis **or** pharyngitis **and** • Duration < 48 hours	20 000
• Nasopharyngeal disease (extensive pseudomembrane) **and** • Duration < 48 hours	40 000
One or more of: • Diffuse swelling of the neck • Any disease ≥ 48 hours • Severe disease (respiratory distress, shock)	80 000

Remarks:

- DAT must be administered as soon as possible as early administration of DAT is associated with improved clinical outcomes. *(8)* Early treatment may reduce overall DAT usage by avoiding the higher doses required once disease has progressed.

Practical info

Pre-medication

Steroids and antihistamines have been used in some outbreak settings, the largest of which reported very low rates of adverse events (3% with no deaths). However, indirect evidence from antitoxin administration in other diseases treated (snake bite), did

not find significant difference in reduction of adverse events when antihistamines were given.*(20)* Pre-medication should not delay administration of DAT, and where they are considered standard, doses for antihistamines can be used.

DAT should be administered in a monitored setting.

In rare cases, a serious allergic reaction may occur. Clinical settings should have trained staff, equipment, emergency medicines, equipment and protocols available to manage anaphylaxis or other serious adverse events. This includes:

- Monitoring equipment: pulse oximeter, blood pressure monitoring, thermometer.
- Emergency medicines: adrenaline (1:1000), salbutamol, intravenous antihistamine (e.g. chlorphenamine), corticosteroid (e.g. prednisolone, hydrocortisone), intravenous fluid (Ringer's lactate or 0.9% w/v saline), oxygen supply and delivery devices.
- Emergency equipment: age-appropriate equipment for airway management and suction, oxygenation (bag valve mask and oxygen), and cardiovascular support (intravenous cannulae and giving sets).

See posters for more details:

- **WHO/Diph/DAT/Poster_A/2024.1:**

https://iris.who.int/bitstream/handle/10665/375883/WHO-Diph-DAT-Poster_A-2024.1-eng.pdf

- **WHO/Diph/DAT/Poster_B/2024.1:**

https://iris.who.int/bitstream/handle/10665/375884/WHO-Diph-DAT-Poster_B-2024.1-eng.pdf

- **WHO/Diph/DAT/Poster_C/2024.1:**

https://iris.who.int/bitstream/handle/10665/375885/WHO-Diph-DAT-Poster_C-2024.1-eng.pdf

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is very low certainty on the impact of different diphtheria antitoxin dosing regimens on mortality. However, the current standard of care – escalating dosing regimens – is well established in clinical practice globally. The main adverse consequence of excess dosing of DAT is consumption of a scarce resource. Dose-related adverse clinical events are not well-described. The benefit of escalating DAT dosing reflects theoretical assumptions of higher circulating amounts of diphtheria toxin in severe or late disease. The GDG felt that recommending a change in practice would require compelling evidence of the benefits of such a change; that evidence does not exist.

Certainty of the Evidence

Very low

The evidence summary for DAT dosing is from a series of observational case series and one quasi-randomized clinical trial. Overall, the certainty of the evidence for the outcome of mortality is deemed as very low, down-rated for risk of bias, imprecision, and inconsistency.

Values and preferences

Substantial variability is expected or uncertain

Where the optimal dose of diphtheria antitoxin is uncertain, patients place a high value on receiving a dose that is sufficient, but might reduce the total number of patients who could be treated. The GDG acknowledges the substantial variability in these values and preferences that are likely to exist.

Resources

Important issues, or potential issues not investigated

DAT availability is a worldwide concern, and every effort must be made to ensure that manufacturing and distribution capacity for DAT matches global needs. The GDG discussed the increased resources required to provide varied dosing regimens, with higher doses provided to patients with more severe disease, or those who present later in their illness. However, given the importance patients will place in the possible benefits of improving the outcomes of very unwell patients, as articulated in the values and preferences statement, the GDG recommends a varied dosing regimen.

The GDG also discussed the importance of providing early dosing to patients so as to avoid deterioration and requiring higher doses later, incorporating evidence on positive association of time-to-DAT with clinical outcomes.

The administration of a second dose in patients with progressive disease was not discussed.

Equity

Important issues, or potential issues not investigated

Equity in this situation demands a dose regimen that the majority of patients would choose given the extreme uncertainty. The panel, in keeping with the values and preference statement, believes the choice would be to maximize the likelihood that those most at risk of adverse outcomes receive a sufficient dose.

The WHO strongly advocates for increasing the supply of DAT so that all patients who require this therapy have access to it. This will require an increase in production of DAT which could be facilitated by increasing the numbers of suppliers with WHO pre-qualification.

Acceptability

No important issues with the recommended alternative

The current standard of care – varied dosing regimens – is acceptable across care settings. The increased dose comes with increased volume of administration, which may require some added clinical monitoring, particularly in small children.

Feasibility

No important issues with the recommended alternative

Varied dosing regimens are the current standard of care, and their administration is feasible across care settings. A conditional recommendation allows for flexibility for practitioners who might therefore incorporate alternative dose regimens based on their clinical judgement.

Justification

When moving from the evidence to a conditional recommendation for varied dosing of DAT compared with fixed dosing regimens in patients with suspected or confirmed symptomatic diphtheria, the GDG emphasized the very low certainty evidence of a mortality benefit, compared with fixed dosing regimens. Although there remain concerns about the possibility of excess dosing of DAT in periods of scarcity, a varied dose regimen is the current standard of care and reflects the values and preferences statement.

Clinical question/ PICO

Population: Persons with suspected or confirmed diphtheria for whom diphtheria antitoxin is indicated
Intervention: Escalating doses of diphtheria antitoxin
Comparator: Fixed dose diphtheria antitoxin

Outcome Timeframe	**Study results and measurements**	**Comparator** Low dose	**Intervention** Higher dose	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Mortality (quasi-randomized trial)	Relative risk 0.92 (CI 95% 0.38 — 2.24) Based on data from 50 participants in 1 studies. [1] (Observational (non-randomized))	27 per 100 Difference:	29 per 100 **2 fewer per 100** (CI 95% 27 fewer — 23 more)	Very low Due to very serious risk of bias and serious imprecision [2]	We are very uncertain which diphtheria antitoxin dosing regimen most effectively reduces mortality
Mortality (observational)	Based on data from 1,631 participants in 5 studies. [3] (Observational (non-randomized))	No comparative data available Low mortality (1%) in studies which have given modest DAT doses (Eisenberg)		Very low Due to serious risk of bias and serious inconsistency [4]	We are very uncertain which diphtheria antitoxin dosing regimen most effectively reduces mortality

1. Primary study. 22/26 [85%] had severe disease in low dose arm; 20/24 [83%] had severe disease in the higher dose arm. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [19],
2. **Risk of Bias: very serious. Imprecision: serious.**
3. Systematic review **Supporting references:** [21], [22], [23], [18], [24], [10],
4. **Risk of Bias: serious. Inconsistency: serious.**

7. Methods: how this guideline was created

These emergency guidelines have been developed in accordance with the *WHO Handbook for guideline development*).*(4)*

General approach

The production of the guideline has included the following steps:

1. Identification of guideline scope and priority questions
2. Evidence identification and synthesis
3. Consideration of the evidence by the GDG
4. Formulation of recommendations
5. Review of draft guidelines (internal and external)
6. Approval by the WHO Guideline Review Committee

Step 1: Identification of guideline scope and priority questions

Important questions were identified through clinical networks responding to current and recent outbreaks of diphtheria (notably Nigeria 2023 and Bangladesh 2018). Existing guidance from WHO was reviewed by the technical team. *(6)* The WHO Steering Committee and the Guideline Review Committee reviewed and revised this list, and determined the priority and scope of the initial guideline.

Step 2: Evidence identification and synthesis

Questions were codified using a PICO framework (identifying the population, intervention, comparator and outcomes of interest), and refined by the methodologist, technical team and clinical chair. Outcomes of interest were focused on those most believed to be most important to patients, agreed by the GDG.

Systematic review was undertaken according to a pre-defined protocol and search strategy as per the attached appendix.

Evidence certainty was assessed using GRADE methodology *(4)*.

Step 3: Consideration of the evidence by the GDG

GDG members were selected for global geographical representation, gender balance, and appropriate technical and clinical expertise. The technical unit collected and managed written statements of declarations of interests (DOI). There were no relevant conflicts of interest. Additionally, during the first meeting, the WHO Secretariat described the DOI process and GDG members were asked to verbally update any other DOI; no verbal conflicts were declared. Web searches did not identify any additional interests that would likely affect members' independence.

The GDG members are listed online here, and were convened in online meetings on 28 November 2023 and 11 December 2023.

Step 4: Formulation of recommendations

Deliberations on the direction and strength of recommendations were facilitated by the methodologist and clinical chair. *A priori* voting rules informed procedures if the GDG failed to reach consensus by discussion; The chair was not eligible to vote in this setting. For the current recommendations, voting was not necessary.

The following factors informed the formulation of recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables including effect estimates and confidence intervals or narrative summaries);
- quality/certainty of the evidence;
- values and preferences of patients;
- resources and other considerations (including considerations of feasibility, applicability, equity).

When possible, we used research evidence to inform discussion around these key factors. If not available, discussion of these factors was informed by expert opinion of both external and GDG members.

Benefits and harms
The guideline used recently prioritized patient-important outcomes from other WHO guidelines which related to those with severe and critical illness.*(?)*

Values and preferences

There was insufficient information to provide the GDG with an evidence-based description of patient experiences or values and preferences regarding treatment decisions for diphtheria treatment. The GDG therefore relied on their own judgments of what well-informed patients would value after balancing the benefits, harms, and burdens of treatment. In addition to individual patient perspectives, the GDG considered a population perspective in which feasibility, acceptability, equity and cost were important considerations.

Specific deliberations on values and preferences and associated feasibility and resource-related considerations are presented for each recommendation.

Step 5: Review of draft guidelines (internal and external)

An external review group reviewed the final guideline document to identify, correct and clarify errors, contextual issues, and implications for implementation.

The guideline was then reviewed and approved by the WHO Guideline Review Committee.

8. How to access and use the guideline

This guideline from WHO will be updated periodically.

How to access the guideline:

- WHO website in PDF format. This is a full read out of the MAGICapp content for those without reliable web access. It can also be downloaded directly from MAGICapp (see cogwheel on top right).
- MAGICapp online in multilayered formats: (https://app.magicapp.org/#/guideline/7759). This is the fullest version of the guideline, as detailed below.

How to navigate this guideline

The guideline is written, disseminated, and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation. It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline.

The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting information pertinent to applying the recommendations in practice. End-users will also need to understand what is meant by strong and conditional recommendations (displayed immediately below) and certainty of evidence (the extent to which the estimates of effect from research represent true effects from treatment).

For each recommendation additional information is available through the following tabs:

- ***Research evidence:*** Readers can find details about the research evidence underpinning the recommendations as GRADE summary of findings tables and narrative evidence summaries
- **Evidence to decision*:*** The absolute benefits and harms are summarized, along with other factors such as the values and preferences of patients, practical issues around delivering the treatment as well as considerations concerning resources, applicability, feasibility, equity and human rights. These latter factors are particularly important for those adapting the guidelines for the national or local context.
- ***Justification:*** Explanation of how the GDG considered and integrated evidence to decision factors when creating the recommendations, focusing on controversial and challenging issues.
- ***Practical information:*** For example, dosing, duration and administration of drugs, or how to apply tests to identify patients in practice.
- ***Decision aids:*** Tools for shared decision-making in clinical encounters.

Additional clinical training, tools, and resources are also available:

- WHO OpenWHO.org training course on Clinical care of diphtheria (https://openwho.org/)
- WHO Facility Estimator tool to support estimation of required medicines and equipment for treatment areas (https://partnersplatform.who.int/essentialitemsestimator).

This guideline from WHO is also used to inform the activities of the WHO Prequalification of Medicinal Products.

9. Uncertainties, emerging evidence and future research

There is a need for high-quality clinical trials in all aspects of the clinical management of diphtheria.

- Determination of the minimal clinically effective dose of DAT according to disease severity.
- Scaling up capacity for routine antimicrobial susceptibility testing and surveillance for resistance across regions, particularly during outbreaks.
- Investigation of third-line antibiotic therapies or combination therapies for increasing resistance across diphtheria isolates.
- The initiation of randomized controlled trials to investigate novel therapies for diphtheria that may reduce the reliance on DAT.
- Efficacy of premedication with DAT administration.

In addition standardized clinical data collection to better describe disease characterization, evolution and impacts of treatments including adverse event.

10. Authorship, contributions and acknowledgements

WHO would like to thank the collaborative efforts of all those involved to make this process rapid, efficient, trustworthy and transparent.

WHO Steering Committee

The committee includes representatives from WHO departments at regional offices and headquarters, including specialty technical input.

Janet Diaz (Lead, Clinical Management Team, Health Emergencies Programme, headquarters), Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Team for COVID-19 Response, Health Emergencies Programme, headquarters), Ekanem Blessing (Nigeria WHO Country Office), Anindya Bose (Surveillance and Risk Assessment, headquarters), Lisa Carter (Public Health Laboratory Strengthening, headquarters), Chad Centner (Antimicrobial Resistance, headquarters), Laxmikant Chavan (Nigeria WHO Country Office), Shalini Desai (Immunization, headquarters), Sergey Eremin (Antimicrobial Resistance, headquarters), Luca Fontana (Health and Technical Logistics, Health Emergencies Programme, headquarters), Musa Yahya Hindiyeh (Immunization, headquarters), Benedikt Huttner (Antimicrobial Resistance, headquarters), Chiori Kodama (WHO Regional Office for the Eastern Mediterranean, Health Emergencies Programme), Lusubilo Fedrick Malakbungu (Antimicrobial Resistance, headquarters), Daniel Marcano Zamora (Antimicrobial Resistance, headquarters), Mick Mulders (Immunization, headquarters), Takeshi Nishijima (WHO Regional Office for the Western Pacific/Health Emergencies Programme), Joshua Ofoli (Nigeria WHO Country Office), Mie Okamura (Nigeria WHO Country Office), Dina Pfeifer (WHO Regional Office for Europe, Health Emergencies Programme), Kamara Rashidatu Fouad (WHO Regional Office for Africa, Health Emergencies Programme), Andreas Reis (Health Ethics & Governance Department, headquarters), Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Pan American Health Organization), Raghu Sriram (Antimicrobial Resistance, headquarters), Lisa Stevens (Public Health Laboratory Strengthening, headquarters), Pushpa Wijesinghe (WHO Regional Office for South-East Asia Region, Health Emergencies Programme), Victoria Willet (Infection, Prevention and Controle, Health Emergencies Programme, headquarters), Were Wilson (Maternal, Newborn, Child and Adolescent Health Department, Health Emergencies Programme, headquarters), Philip Dwamo Zorto (Nigeria WHO Country Office).

Project officer: Julie Viry (Clinical Management Team, Health Emergencies Programme, headquarters).

The WHO Steering Committee is fully responsible for decisions on guidance production and convening the GDG.

Guideline Development Group (GDG)

Umma Idris Abdullahi (Federal Medical Centre, Jigawa State, Nigeria), Hamed Hassan Adetola (Ministry of Health and Sanitation, Sierra Leone), Andrew Argent (University of Cape Town, South Africa), Lucille Blumberg (National Institue for Communicable Diseases, South Africa), Victoria Chu (University of California, United States of America), Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam), Androulla Efstratiou (Health Security Agency, United Kingdom), Daniela Garone (MSF International Office, Belgium), Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada), Hans-Jorg Lang (Alliance for International Medical Action, Senegal), Madonna Matar (Notre Dame de Secours University Hospital, Lebanon), Ziad Memish (King Saud Medical City, Ministry of Health and College of Medicine Alfaisal University, Saudi Arabia), Regina Oladokun (Ibadan University College Hospital, Nigeria), Kobus Preller (Cambridge University Hospitals NHS Foundation Trust, United Kingdom), Shalini Sri Ranganathan (University of Colombo, Sri Lanka), Gentle S Shrestha (Tribhuvan University Teaching Hospital, Nepal), Salma Ali Suwaid (Murtala Muhammad Specialist Hospital, Kano State), Sridhar Venkatapuram (King's College London, United Kingdom), Nicholas White (Mahidol University, Thailand).

Methodologist: Gordon Guyatt (McMaster University, Canada).

Clinical Chair: Srinivas Murthy (University of British Columbia, Canada).

Technical advisor: Andrew Owen (Liverpool Tropical School of Medicine, United Kingdom).

Systematic reviewers: Lindsay Keegan (University of Utah, United States of America), Steven McGloughlin (Clinical Management Team, Health Emergencies Programme, headquarters), Jamie Rylance (Clinical Management Team, Health Emergencies Programme, headquarters), Shaun Truelove (Johns Hopkins Bloomberg School of Public Health, United States of America).

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DIPHTHERIA

FACT SHEET FOR HEALTHCARE WORKERS

What is diphtheria?

Diphtheria is a contagious and potentially life-threatening bacterial infection caused by toxin-producing strains of *Corynebacterium diphtheriae* or more rarely *Corynebacterium ulcerans* or *Corynebacterium pseudotuberculosis*.

What are the symptoms?

- Symptoms usually begin two to five days (range 1 - 10 days) after exposure to the diphtheria bacteria. The symptoms will depend on the site of infection, but the most severe form of diphtheria affects the throat and tonsils.
- The first symptoms are usually a sore throat, loss of appetite and a mild fever. Within 2-3 days, a membrane forms over the throat and tonsils that can make it hard to swallow and breathe. The infection can also cause the lymph glands and tissues on both sides of the neck to swell ("bull neck").
- The toxin formed by the diphtheria bacteria can spread via the bloodstream and cause inflammation of the heart muscle and the nerves which can be fatal.
- Death occurs in 5-10% of cases of diphtheria.
- Sometimes diphtheria can cause small skin sores that form larger ulcers, commonly on the legs.

How is it spread?

- Diphtheria bacteria can live in the mouth, nose, throat or skin on infected individuals.
- The bacteria is normally spread from person to person in respiratory droplets. These droplets are created by coughing or sneezing. Rarely, diphtheria spreads from close contact with discharges from an infected person's mouth, nose, throat or skin.
- Without antibiotic treatment, people with diphtheria are infectious for up to 4 weeks from the onset of symptoms. Some people become carriers and are infectious for longer.
- Corynebacterium ulcerans infection is occasionally associated with consumption of unpasteurised milk or contact with animals.

Who is at risk?

- Anyone who comes in contact with diphtheria during its infectious period who has not had diphtheria in the past, or has not been fully immunised is at risk.
- Susceptible persons living in crowded conditions are at increased risk of getting the disease.

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DIPHTHERIA

FACT SHEET FOR HEALTHCARE WORKERS

How is it prevented?

- Diphtheria vaccination protects against the disease. It is part of the routine vaccination schedule as a primary series at 6,10 and 14 weeks with boosters at 18months as well as 6 and 12 years.
- At 6, 10 & 14 weeks and 18 months it is provided as a combined vaccine against diphtheria, tetanus, acellular pertussis, inactivated polio vaccine , Haemophilus Influenzae type b and Hepatitis B vaccine (Hexavalent vaccine).
- At 6 years and at 12 years of age it is given in combination with tetanus (Td vaccine).
- A high vaccination rate in the community is important to protect the population from resurgence of this disease.

How is it diagnosed?

- A doctor can suspect diphtheria based on a clinical examination when the membrane is seen in the throat, this membrane is usually grey or whitish and importantly it is adherent to the tissues below.
- Special laboratory tests to confirm the diagnosis. Throat and nose swabs need to be sent for culture and toxin production.
- If the diagnosis is suspected, it is important to contact the Department of Health and notify the case and obtain advice on the procedure to confirm the diagnosis.

How is it treated?

- Diphtheria infection is treated with antibiotics and antitoxin.

What is the public health response?

- Laboratories, hospitals, school principals and directors of childcare centres are required to report/notify suspected cases of diphtheria to the Department of Health.
- Public health officials and the Communicable Diseases Control unit will investigate cases and their contacts to identify possible sources of infection and prevent further spread.
- Cases are isolated until they are not infectious. All contacts are put on prophylactic treatment and may require booster doses of diphtheria vaccine if not immunised/ not fully immunised.

Please consult the National Diphtheria guidelines, Frequently Asked Questions and provincial circulars for further information.

**Source: Adapted from KZN Department of Health Diphtheria Factsheet*

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DIPHTHERIA

WHAT YOU NEED TO KNOW

"Protect your child against vaccine preventable diseases. Vaccinate today."

What is diphtheria?

Diphtheria is a vaccine preventable serious disease caused by a toxin (poison) made by a bacteria. It causes a thick coating in the back of the nose or throat that makes it hard to breathe or swallow.

What are the symptoms of diphtheria?

Diphtheria starts with a sore throat, mild fever and chills. Next, there is swelling of the throat followed by the diphtheria toxin making a thick coating on the back of the nose or throat and swelling of the neck. The coating may be white or greyish.

How does diphtheria spread?

Diphtheria spreads when an infected person coughs or sneezes. A person can spread the disease for up to two weeks after infection. Prolonged close contact is necessary for the infection to be spread.

How can it be prevented?

Through routine vaccination of children with diphtheria vaccine, in combination with other vaccines (Hexavalent) at the age of 6 weeks, 10 weeks, 14 weeks, 18 months, Td vaccine as booster dose at 6 years and 12 years. **The vaccine is available for FREE in all Western Cape healthcare facilities. It is recommended that all children get the vaccine.**

Who is at risk?

Any person who is not vaccinated against diphtheria can get the disease. Diphtheria mostly affects children, but any age group can be affected.

What can be done if symptoms appear?

Please visit your nearest healthcare facility urgently for assessment. If diphtheria is suspected – laboratory tests will be done.

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WITSEERKEEL
WAT JY MOET WEET

“Beskerm jou kind teen siektes wat deur entstowwe voorkom kan word. Gaan vandag vir inenting.”

Wat is witseerkeel?
Witseerkeel is ’n ernstige siekte wat veroorsaak word deur ’n gifstof wat deur bakterieë gemaak word. Dit lei tot ’n dik laag agter in die neus wat dit moeilik maak om asem te haal of te sluk.

Wat is die simptome van witseerkeel?
Witseerkeel begin met ’n seer keel, ligte koors en kouekoors. Dan swel die keel op en dit word gevolg deur die witseerkeel-gifstof wat ’n dik laag maak agter in die neus of keel en die nek wat opswel. Die laag kan wit of gryserig wees.

Hoe word witseerkeel versprei?
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Hoe kan witseerkeel voorkom word?
Deur kinders in te ent met die witseerkeel-entstof in kombinasie met ander entstowwe (Hexavalent) wanneer hulle 6 weke, 10 weke, 14 weke en 18 maande oud is en die Td-entstof as versterkdosis wanneer hulle 6 jaar en 12 jaar oud is. **Die entstof is GRATIS by alle klinieke beskikbaar. Dokters beveel aan dat alle kinders die entstof kry.**

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IPHEPHA ELENZELWE

ULUNTU ELINENKCAZELO NGEDIPTHERIA

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Yintoni idiphtheria?

Idiphtheria sisifo esinobuzaza kakhulu esibangelwa yityhefu (ipoyizini) eyenziwa ziintsholongwane. Yenza into engqindilili apha ngasemva empumlweni okanye emqaleni ebangela ukuba kube nzima ukuphefumla okanye ukuginya.

Zintoni iimpawu zediphtheria?

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Isasazeka njani idiphtheria?

Idiphtheria isasazeka xa umntu onayo ekhohlela okanye ethimla. Umntu onayo angathi ayisasaze into engangeveki ezimbini emva kokuba umntu esulelekile.

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Namphi na umntu ongagonyelwanga idiphtheria angasifumana esi sifo kwaye ikakhulu sichaphazela abantwana, kodwa namphi na umntu singamchaphazela.

Yintoni enokwenziwa xa zinokuthi iimpawu zayo zibonakale?

Yiya kwikliniki ekufutshane kuwe wenziwe uvavanyo. Xa irhaneleka idiphtheria - kuyakwenziwa iimvavanyo naselebhu.

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Witseerkeel word versprei wanneer ’n persoon wat die siekte het, hoes of nies. ’n Persoon kan ander mense aansteek vir tot twee weke nadat hulle daarmee aangesteek is. Verlengde noue kontak is nodig vir die infeksie om te versprei.

Hoe kan witseerkeel voorkom word?

Deur kinders in te ent met die witseerkeel-entstof in kombinasie met ander entstowwe (Hexavalent) wanneer hulle 6 weke, 10 weke, 14 weke en 18 maande oud is en die Td-entstof as versterkdosis wanneer hulle 6 jaar en 12 jaar oud is. **Die entstof is GRATIS by alle klinieke beskikbaar. Dokters beveel aan dat alle kinders die entstof kry.**

Wie is vatbaar vir witseerkeel?

Enige persoon wat nie teen witseerkeel ingeënt is nie, kan die siekte kry. Witseerkeel tas meestal kinders aan, maar enige ouderdomsgroep kan aangetas word.

Wat kan gedoen word as die simptome voorkom?

Gaan asseblief dringend na jou naaste kliniek om ondersoek te word. Indien daar ‘n vermoede is dat dit witseerkeel is, sal laboratoriumtoetse gedoen word.

Kom ons maak gesondheidsorg **BETER TESAME.**

Wes-Kaapse Regering
Gesondheid en Welstand
VIR JOU

CITY OF CAPE TOWN
ISIXEKO SASEKAPA
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Making progress possible. Together.

DIPHTHERIA

WHAT YOU NEED TO KNOW

"Protect your children now; vaccinate against vaccine preventable conditions"

What is diphtheria?

Diphtheria is a serious disease caused by a toxin (poison) made by a bacteria. It causes a thick coating in the back of the nose or throat that makes it hard to breathe or swallow.

What are the symptoms of diphtheria?

Diphtheria starts with a sore throat, mild fever and chills. Next, there is swelling of the throat followed by the diphtheria toxin making a thick coating on the back of the nose or throat and swelling of the neck. The coating may be white or greyish.

How does diphtheria spread?

Diphtheria spreads when an infected person coughs or sneezes. A person can spread the disease for up to two weeks after infection. Prolonged close contact is necessary for the infection to be spread.

How can it be prevented?

Through vaccination of children with diphtheria vaccine, in combination with other vaccines (Hexavalent) at the age of 6 weeks, 10 weeks, 14 weeks, 18 months, Td vaccine as booster dose at 6 years and 12 years. **The vaccine is available for FREE in all Western Cape health facilities. It is recommended that all children get the vaccine.**

Who is at risk?

Any person who is not vaccinated against diphtheria can get the disease. Diphtheria mostly affects children, but any age group can be affected.

What can be done if symptoms appear?

Please visit your nearest health facility urgently for assessment. If diphtheria is suspected – laboratory tests will be done.

Let's make our health care **BETTER TOGETHER.**

Western Cape Government
Health and Wellness
FOR YOU

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IPHEPHA ELENZELWE
ULUNTU ELINENKCAZELO NGEDIPTHERIA

“Khusela abantwana bakho ngoku; masikhusele abantwana bethu kwezo meko zinokukwazi ukukhuselwa lugonyo.”

Yintoni idiphtheria?
Idiphtheria sisifo esinobuzaza kakhulu esibangelwa yityhefu (ipoyizini) eyenziwa ziintsholongwane. Yenza into engqindilili apha ngasemva empumlweni okanye emqaleni ebangela ukuba kube nzima ukuphefumla okanye ukuginya.

Zintoni iimpawu zediphtheria?
Idiptheria iqala ngomqala obuhlungu, ifiva nokuxhaxha. Okulandelayo, kukudumba komqala okulandelwa yityhefu yediphtheria eyenza ubungqindilili apha emva empumlweni okanye emqaleni nokudumba kwentamo. Obu bungqindilili bungaba mhlophe okanye bubegreyi. Obu bungqindilili benza kube nzima ukuphefumla okanye ukuginya.

Isasazeka njani idiphtheria?
Idiphtheria isasazeka xa umntu onayo ekhohlela okanye ethimla. Umntu onayo angathi ayisasaze into engangeveki ezimbini emva kokuba umntu esulelekile.

Ikhuselwa njani idiphtheria?
Ewe ikhuselwa ngokugonywa kwabantwana abanediptheria ichiza lidityaniswe kunye namanye amachiza angala(Hexavalent) kumntana obudala buziveki ezi-6, ezili-10, iinyanga ezili-14, ezili-18, ichiza iTd lisetyenziswa njengebhusta kwabaminyaka mi-6 neli-12 ubudala. **Ichiza lifumaneka MAHALA kwikliniki zonke. Oogqirha bakhuthaza ukuba bonke abantwana balifumane ichiza.**

ngubani ochaphazelekayo yile meko ekufuneka sigxininisise kuye?
Namphi na umntu ongagonyelwanga idiphtheria angasifumana esi sifo kwaye ikakhulu sichaphazela abantwana, kodwa namphi na umntu singamchaphazela.

Yintoni enokwenziwa xa zinokuthi iimpawu zayo zibonakale?
Yiya kwikliniki ekufutshane kuwe wenziwe uvavanyo. Xa irhaneleka idiphtheria - kuyakwenziwa iimvavanyo naselebhu.

MASENZE NGCONO UNONOPHELO LWEZEMPILO
NGOKUBAMBISANA

URhulumente weNtshona Koloni
IMpilo neMpilontle
NGOWAKHO

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