

Diphtheria outbreaks

Comprehensive guidance for the
public health preparedness and
response in the WHO African Region

February 2024



African Region

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WHO:AFRO/EPR:2024-02

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Designed in Brazzaville, Congo

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Executive summary

Background and rationale. The WHO African Region is grappling with a resurgence of diphtheria, a rare and deadly disease, with five active outbreaks currently ongoing in Guinea, Mauritania, Niger, Nigeria and South Africa. Angola, Central African Republic, Chad, Congo, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Madagascar, Mali, Somalia and South Sudan have been identified as the most vulnerable countries to the disease, raising concerns about potential disease transmission. Despite significant progress in access to health care, many Member States have historically had insufficient vaccination coverage against diphtheria, which was further reduced during the COVID-19 pandemic. WHO aims to understand the risks of other Member States and prioritize outbreak-preventive measures.

To address these issues and in accordance with its mandate to provide guidance to Member States on health policy matters, the WHO Regional Office for Africa (AFRO) has developed a comprehensive guideline for public health preparedness and response to diphtheria outbreaks. This document provides updated operational recommendations that have been reviewed by subject-matter experts and are based on available evidence systematically assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology and field experience (from the Western Pacific Region, for example). This technical guide focuses on key response pillars as well as readiness for vulnerable countries, addresses potential disease transmission and provides guidance on health policy matters for Member States.

Although the global diphtheria disease burden decreased by over 80% between 1980 and 2018, recent outbreaks highlight the public health threat of respiratory diphtheria, which causes substantial morbidity among unprotected populations. At least eight countries in the world, including five in the WHO African Region, are currently reporting outbreaks, namely: Guinea, Mauritania, Niger, Nigeria and South Africa. WHO AFRO is supporting these countries to effectively respond to the outbreaks, including by strengthening coordination, actively and promptly identifying cases, ensuring the provision of diphtheria antitoxin (DAT) and antibiotics, and supporting catch-up vaccination campaigns. The majority of cases are children and young adults who are not fully vaccinated against diphtheria.

About 20 other countries in the WHO African Region have been identified as vulnerable and at increased risk of diphtheria outbreaks, taking into consideration risk factors such as vaccination coverage in children under 15 years, active outbreaks of arboviruses (dengue, chikungunya, yellow fever, etc.) reported currently, neighbouring countries with outbreaks, the percentage of the population with access to hand-washing facilities, and the Global Health Security's (GHS) epidemic preparedness score. Given that the diphtheria risk is mainly concentrated in the African Region, mostly in at-risk areas in hard-to-reach or conflict-affected areas, WHO AFRO is offering assistance for the effective implementation of readiness activities.

According to this recent preliminary mapping of diphtheria vulnerability in the WHO African Region, the following categorization has been suggested for prioritization of countries.

- Tier 1. Emergency response–active outbreaks, including ongoing diphtheria outbreaks and low vaccination coverage: Guinea, Mauritania, Niger, Nigeria and South Africa.
- Tier 2. High priority readiness/“response mode”–very low coverage or likely multiple subnational hotspots with low coverage: Angola, Central African Republic, Chad, Ethiopia, Mali and Somalia.
- Tier 3. Medium priority readiness–low vaccination coverage: Congo, Democratic Republic of the Congo, Equatorial Guinea, Madagascar and South Sudan
- Tier 4. Preparedness: Algeria, Benin, Cameroon, Côte d’Ivoire, Gabon, Liberia and Mozambique.

The disease. Diphtheria is caused by *Corynebacterium diphtheriae*, a club-shaped facultative anaerobic species that exists in four biotypes (*gravis*, *mitis*, *belfanti* and *intermedius*). *Corynebacterium* is a genus of gram-positive bacteria. *C. diphtheriae* is transmitted through **respiratory droplets, close physical contact**, contagious cutaneous diphtheria lesions, contaminated clothing and objects. The incubation period for respiratory diphtheria is 2 to 5 days. However, disease can develop for as long as 10 days after exposure and the case fatality rate is estimated at 5–10%. The basic reproduction rate is six to seven secondary cases. Risk factors include overcrowding, poor hygiene and absent or incomplete immunization.

The exotoxin produced by *C. diphtheriae* is by far the most important pathogenic factor associated with the organism. The toxin (poison) inhibits cellular protein synthesis and causes local cellular destruction of the mucous membrane. A fibrinous exudate, along with accumulated debris, hardens to form a characteristic leather-like pseudomembrane. Absorption of toxin into the bloodstream leads to systemic manifestations by affecting various organs such as the heart, nerves and kidneys. Morbidity and mortality due to toxigenic *C. diphtheriae* are mediated by the diphtheria toxin. Diphtheria has various clinical manifestations depending on the anatomical site, with the most common form being respiratory/pharyngeal and tonsillar diphtheria. Complications include the absorption of diphtheria toxin into the bloodstream, leading to toxic damage to organs such as the heart, kidneys and peripheral nerves.

Case definitions and classification. Suspected cases of diphtheria are characterized by upper respiratory tract illnesses such as pharyngitis, nasopharyngitis, tonsillitis or laryngitis and an adherent pseudomembrane. Some countries may expand the suspected case definition to include mild cases without a pseudomembrane, non-healing ulcers in people with a travel history to endemic or diphtheria-affected countries, and a bull-neck appearance caused by swollen anterior cervical lymph nodes, inflammation and surrounding tissue oedema. Final diphtheria case classification includes: (a) laboratory-confirmed cases; (b) epidemiologically linked confirmed cases; (c) clinically compatible confirmed cases; and (d) discarded cases (not a diphtheria case, final diagnosis to be specified).

- Laboratory-confirmed cases are individuals with *C. diphtheriae* isolated by culture and positive for toxin production, regardless of symptoms. Toxigenicity must be confirmed by the phenotypic Elek test, and polymerase chain reaction (PCR) can complement surveillance.
- Laboratory-confirmed cases may be further classified into three subcategories based on the type of surveillance occurring in the country.
- Epidemiologically linked confirmed cases meet the definition of a suspected case and are linked epidemiologically to a laboratory-confirmed case.
- Clinically compatible confirmed cases meet the definition of a suspected case but lack both confirmatory laboratory test results and epidemiologic linkage to a laboratory-confirmed case.

- A discarded case is a suspected case that meets either criterion: a non-toxigenic *Corynebacterium spp.* but a negative Elek test or a negative PCR for the diphtheria toxin gene.

Specimen collection, storage, transport and diagnosis. To detect *C. diphtheriae*, collect two swabs (throat and nasal) from suspected cases at first contact using a polyester, calcium alginate, dacron, nylon or flocked swabs tipped applicators. (Do not use cotton as it can inhibit PCR reactions.) Ideally, collect samples before starting antibiotics. For pharyngeal swabs, examine the pharynx, depress the tongue, and rub vigorously over the membranes. For nasal swabs make sure that the swab is inserted in the nasal cavity. Please, also note that the swab shaft is a bit thick and will cause discomfort when entering the patient's nasal cavity. For cleared skin lesions, press the swab tightly into the lesion and transport it to the laboratory for culture. Store and transport samples promptly, labelled with unique identifiers and sources, placed in appropriate media (Amies transport medium or Stuart medium), or place dry swabs in silica gel sachets. Transport swabs immediately (within 24 hours) to the laboratory at room temperature. If there are delays in the transport, place the samples at 2–8°C, and pseudomembrane samples should be collected and sent to the laboratory. Key diphtheria laboratory analyses to be performed include, but are not limited to: (1) isolation of *C. diphtheriae* by culture; (2) toxicity testing and biotyping for diagnosis and confirmation of toxin production; and (3) antimicrobial sensitivity testing. A diphtheria diagnosis is confirmed through culture and toxin production using immunoprecipitation reactions. Primary culture on blood tellurite medium and selective culture on cystinase medium are used to examine clinical specimens. Toxigenicity testing and biotyping are also necessary.

Outbreak response. A single laboratory-confirmed case of diphtheria and/or two cases epidemiologically linked to at least one laboratory-confirmed case is/are considered an outbreak and trigger(s) a public health response. The main objectives of response include preventing and minimizing the spread of cases, preventing complications and deaths through early diagnosis and proper management, assisting public health workers in risk assessment, identifying high-risk areas, implementing appropriate public health control measures, and raising community awareness about diphtheria and its prevention..

At the beginning of an outbreak, it is crucial to test all suspected cases, clinically compatible cases and those with an epidemiological link to better characterize the outbreak and guide case management. However, due to limited sample collection and transport resources, it would be unrealistic to test all cases when the outbreak is already characterized and antimicrobial sensitivity has been determined. Therefore, defining sample collection criteria and prioritizing newly affected areas will be advisable. Laboratory confirmation and treatment with antibiotics and DAT for severe cases. The choice of antibiotics should be guided by the results of the antimicrobial sensitivity tests. Administering DAT neutralizes the toxin and reduces complications and mortality. Adverse reactions to DAT include hypersensitivity reactions, febrile reactions and serum sickness. Vaccination is crucial for preventing cases and stopping outbreaks. Preparedness for diphtheria outbreaks includes understanding the main areas of risk, ensuring good preparatory outbreak response coordination, rapidly detecting and assessing diphtheria-related events, and understanding existing DAT supplies.

WHO ADVICE

- Control of diphtheria is based on the primary prevention of disease by ensuring high population immunity through vaccination and the secondary prevention of spread by the rapid investigation of close contacts to ensure prompt treatment of those infected.
- Early reporting and case management of suspected diphtheria cases are crucial to initiate timely treatment of cases and management of contacts.
- Epidemiological surveillance ensuring early detection of diphtheria outbreaks should be in place in all countries, and all countries should have access to laboratory facilities for reliable identification of toxigenic *C. diphtheriae*.
- To ensure effective diphtheria case management, optimal quantities of DAT should be procured and prepositioned by anticipation at both the global and regional levels based on in-depth vulnerability mapping.
- Vaccination is key to preventing cases and outbreaks.
- Adequate clinical management involves administering antibiotics and DAT to neutralize the toxin and reducing complications and mortality.
- Advice when implementing the following infection prevention and control measures in health care settings.
 - Always apply standard precautions, with a focus on hand hygiene, wearing personal protective equipment and environmental cleaning and disinfection.
 - At screening point or triage, immediately isolate patients with symptoms of upper respiratory tract infection until examined and, if suspected, house and treat them with patients with a similar diagnosis. Segregate the isolation area from other patient-care areas.
 - Maintain 1-metre distances between patients. Keep patient-care areas well ventilated.
 - Avoid patient movement or transport out of the isolation area. If movement is necessary out of isolation area, have the patient use a medical mask, and cover any wounds or lesions on the patient's body.
- Case management should be carried out following WHO guidelines. In addition, high-risk populations such as children under 5 years of age, schoolchildren, the elderly, people in close contact with diphtheria cases and health care workers should be vaccinated as a priority.
- Effective coordination and community engagement are crucial for a successful response to the outbreak.
- Antibiotics for prophylaxis (penicillin or erythromycin, dependent on antibiotics sensitivity patterns) are indicated for close contacts of confirmed cases for 7 days. If the culture is positive for toxigenic *C. diphtheriae*, then all the contact individuals should be treated as a case with an antibiotic course for 2 weeks (DAT is not needed for asymptomatic cases or cases without a pseudomembrane).
- Although travellers do not have a special risk of diphtheria infection, it is recommended that national authorities remind travellers going to areas with diphtheria outbreaks to be appropriately vaccinated in accordance with the national vaccination scheme established in each country prior to travel. A booster dose is recommended if more than 5 years have elapsed since their last dose.
- Countries with active outbreaks should document progress against defined WHO performance standards for Grade 2 and Grade 3 diphtheria outbreaks or any related emergencies.

I. Background

EPIDEMIOLOGY

Respiratory diphtheria is a life-threatening bacterial disease caused by toxin-producing strains of *C. diphtheriae*. Throughout history, diphtheria has been one of the most feared infectious diseases globally, which has caused devastating epidemics, mainly affecting children. During major diphtheria epidemics in Europe and the United States of America (USA) in the 1880s, the case-fatality rates of respiratory diphtheria reached 50% in some areas. Case-fatality rates in Europe dropped to about 15% during World War I, mainly as a result of widespread use of DAT treatment. Diphtheria epidemics also ravaged Europe during World War II, resulting in about 1 million cases and 50 000 deaths in 1943. Diphtheria toxoid-based vaccines became available in the late 1940s in Europe and North America and were shown to reduce outbreaks in vaccinated populations. In the 1970s, before these vaccines became easily accessible and used worldwide, an estimated 1 million cases of diphtheria, including 50 000–60 000 deaths, occurred each year in low- and middle-income countries. After the establishment of the Expanded Programme on Immunization (EPI) in 1974, with diphtheria vaccine as one of the original six EPI vaccines, the incidence of diphtheria decreased dramatically worldwide. The total number of reported diphtheria cases was reduced by >90% during the period 1980–2000.

Respiratory diphtheria, once a major cause of childhood morbidity and mortality worldwide, is now rare in countries with high coverage of the diphtheria toxoid-containing vaccine (DTCV). The global diphtheria disease burden has declined by more than 80%, from 97 511 reported cases in 1980 to 16 651 cases in 2018. However, recent outbreaks highlight the public health threat of respiratory diphtheria, causing substantial morbidity among unprotected populations. The largest outbreak of the recent past was reported in the Russian Federation and former Soviet Republics in the 1990s, with over 170 000 cases and 5000 deaths reported during 1990–1998. In 2017, some 8819 cases of diphtheria were reported worldwide, the highest since 2004. According to the most recent estimate, 86% of children worldwide receive the recommended three doses of diphtheria-containing vaccine in the infant schedule, leaving 14% with no or incomplete vaccination. There are pockets of unvaccinated children in all countries, and case-fatality rates exceeding 10% have been reported, particularly where DAT is unavailable. In regions with temperate climates, most cases occur during the cold season, while in warmer climates, transmission takes place throughout the year.

A recent review of diphtheria epidemiology showed that the true burden of disease is likely greater than reported. The majority of cases occur in adolescents and adults, reflecting the decline in incidence due to increasing vaccination coverage in children. In the United States, from 1996 to 2018, 14 cases were reported, with five cases of diphtheria-like illness caused by *C. ulcerans*. DAT requests for suspected cases have declined, suggesting surveillance of this condition might be warranted. Global coverage with the third dose of diphtheria, tetanus and pertussis vaccine (DTP3) is suboptimal, whereas achieving high DTP3 coverage and implementing recommended booster doses are necessary to decrease diphtheria incidence. Collection and use of data on subnational and booster dose coverage, enhanced laboratory capacity and case-based surveillance would improve data quality.

The control of diphtheria is based on primary prevention of disease by ensuring high population immunity through vaccination, and secondary prevention of spread by the rapid investigation of close contacts to ensure prompt treatment of those infected.

DIPHThERIA IN THE WHO AFRICAN REGION, 2013–2023

Diphtheria is uncommon in the African Region. Of the 97 438 cases reported globally between 2013 and 2022, a total of 29 163 (29.9%) were reported in the African Region (mean: 2916 cases per year; median: 1812 cases per year [min 1: max 11 400]). Even though sporadic cases may have been missed due to suboptimal surveillance systems and a lack of specialized laboratory diagnostic capacity in some countries, a few cases have been identified. High regional vaccination coverage with DTP3 is thought to be largely responsible for the Region's previously low incidence of disease. According to WHO/UNICEF estimates of National Immunization Coverage (WUENIC) for the period 2013–2022, coverage with the first dose of diphtheria, tetanus and pertussis vaccine (DTP1) and DTP3 was 77–83% (average: 80.5%) and 70–77% (average: 73%), respectively. Again, in Africa, from 2019 to 2022, approximately 29 million children did not receive their first dose of DTP. Coverage of 80–85% is required to control the threat of outbreaks (WHO Position, 2017).

From 1 January to 20 December 2022, a total of 910 diphtheria cases were reported to WHO AFRO through the International Health Regulations (IHR) system or directly to the Vaccine-Preventable Diseases (VPDs) Programme of the Regional Office. The cases were reported in decreasing order by Niger (736), Madagascar (92), Democratic Republic of the Congo (44), Burkina Faso (34) and Algeria (4). DTP3 coverage is low in most African countries.

Since the beginning of July 2023 (epidemiological week 26), at least five countries in the African Region (Guinea, Mauritania, Niger, Nigeria and South Africa) have recorded an unusual increase in cases of diphtheria and are experiencing ongoing active outbreaks.

As of 12 November 2023, a total of **21 641 suspected cases of diphtheria and 775 deaths** were reported in Guinea, Mauritania, Niger, Nigeria and South Africa. Among these suspected cases, **12 351 have been confirmed either by laboratory testing, epidemiological linkage or by clinical compatibility**.

Table 1. Number of total suspected and confirmed cases and deaths reported by countries in the WHO African Region, 1 January to 12 November 2023

Country	Total suspected cases	Total deaths	CFR (%)	Confirmed cases			
				Lab. Confirmed	Epi-linked	Clinically compatible	Total confirmed
Nigeria	18 239	572	3.1	288	219	10 707	11 214
Guinea	1 017	69	6.8	21	92	768	881
Niger	2 286	128	5.6	123	-	104	227
Mauritania	20	5	25.0	-	-	20	20
South Africa	79	1	1.2	9	-	-	9
TOTAL	21 641	775	3.6	441	311	11 599	12 351

WHO support for these five countries includes, but is not limited to, establishing an incident management system (IMS) to strengthen coordination, case identification and contact management, procuring DAT and antibiotics, as well as organizing catch-up vaccination campaigns of a diphtheria-containing vaccine with supplemental or booster doses required in all populations. Most of the cases are children and young adults who are not fully vaccinated against diphtheria (59.2% of confirmed cases in Nigeria and 100% of cases in Niger). The routine immunization coverage is 62%, 50%, and 47% in Nigeria, Niger and Guinea, respectively. This outbreak calls for urgent action to reach the unvaccinated children (zero dose) and to implement catch-up interventions to increase coverage to the recommended 85% in all countries of the Region.

Preliminary diphtheria vulnerability mapping in the WHO African Region (November 2023)

WHO has conducted a diphtheria vulnerability mapping and prioritized countries taking into consideration the diphtheria risk, including active outbreaks with low vaccination coverage and the risk according to vaccination coverage; it has also prioritized countries bordering an outbreak country and any countries with subnational ‘hotspots’ that need to be targeted.

According to a recent preliminary mapping of diphtheria vulnerability in the WHO African Region that has not yet been published, the suggested countries for prioritization can be categorized as below.

- **Tier 1. Emergency Response**—active outbreaks, including ongoing diphtheria outbreaks, and low vaccination coverage: **Guinea, Mauritania, Niger, Nigeria and South Africa.**
- **Tier 2. High priority readiness/“response mode”**—very low coverage or likely multiple subnational hotspots with low coverage: **Angola, Central African Republic, Chad, Ethiopia, Mali and Somalia.**
- **Tier 3. Medium priority readiness**—low vaccination coverage: **Congo, Democratic Republic of the Congo, Equatorial Guinea, Madagascar and South Sudan.**
- **Tier 4. Preparedness: Algeria, Benin, Cameroon, Cote d’Ivoire, Gabon, Liberia and Mozambique.**

It is crucial to note that the large majority of diphtheria risk is concentrated in the African Region, with most at-risk areas located in hard-to-reach and/or conflict-affected areas.

PATHOGEN AND DISEASE

Corynebacterium is a genus of gram-positive bacteria. Various species of the genus *Corynebacterium* exist. Diphtheria is caused by *C. diphtheriae*, a club-shaped facultative anaerobic species that exists in four biotypes (*gravis*, *mitis*, *belfanti* and *intermedius*). The four biotypes differ slightly in their colonial morphology and biochemical parameters, but no consistent differences have been found in the prevalence or the severity of disease caused by the different types. The most important virulence factor of *C. diphtheriae* is the diphtheria exotoxin. This is encoded by a highly conserved sequence of the *tox* gene of the β -corynebacteriophage, which is integrated in the circular bacterial chromosome. The exotoxin consists of two fragments: A and B. Following attachment mediated by the non-toxic B fragment and penetration of the host cell, the highly toxic fragment A is detached, and inhibits protein synthesis leading to cell death. Outside the host cell, the exotoxin is relatively inactive.

In addition to the bacterial exotoxin, cell-wall components such as the O- and K-antigens are important in the pathogenesis of the disease. The β -corynebacteriophage can infect nontoxicogenic strains of two other species of *Corynebacterium*, *C. ulcerans* and *C. pseudotuberculosis*, which leads to production of the diphtheria toxin and transformation to a toxigenic strain. Both are zoonotic agents without documented human-to-human transmission. Humans are the natural host for *C. diphtheriae*, although it has been occasionally isolated from cattle (15) and horses. Humans are the reservoir for *C. diphtheriae*. In outbreaks, high percentages of children are found to be transient carriers.

Transmission

Transmission of *C. diphtheriae* occurs from person to person through respiratory droplets (like from coughing or sneezing) and close physical contact. Transmission may also occur via contagious cutaneous diphtheria lesions, as has been documented in some areas of the tropics and under conditions of poor hygiene. It may also be spread by contaminated clothing and objects. Cutaneous diphtheria is more common in warmer climates and in settings with poor hygiene and overcrowding. The basic reproduction rate for diphtheria is six to seven secondary cases. The risk factors for diphtheria transmission/outbreaks include overcrowding, poor hygiene and absent or incomplete immunization, including booster doses. Transmission of nontoxicogenic *C. diphtheriae* to susceptible individuals frequently results in transient asymptomatic pharyngeal carriage or mild clinical disease. Infection can cause respiratory or cutaneous diphtheria and in rare cases lead to systemic diphtheria.

Temporal pattern

In temperate areas, diphtheria most frequently occurs during winter and spring.

Incubation period

The incubation period for respiratory diphtheria is 2 to 5 days; however, disease can develop for as long as 10 days after exposure.

Pathogenesis

The exotoxin produced by *C. diphtheriae* is by far the most important pathogenic factor associated with the organism. The toxin (poison) inhibits cellular protein synthesis and causes local cellular destruction of the mucous membrane. A fibrinous exudate along with accumulated debris harden to form a characteristic leather-like pseudomembrane. Absorption of toxin into the bloodstream leads to systemic manifestations by affecting various organs such as the heart, nerves and kidneys. Morbidity and mortality due to toxigenic *C. diphtheriae* are mediated by the diphtheria toxin.

Clinical features

The disease has an insidious onset, although symptoms are initially non-specific and mild. Throughout the course of the disease, the patient temperature does not usually exceed 38.5 °C (101.3 °F). The onset is usually relatively slow and characterized by mild fever, a sore throat, and an exudative pharyngitis initially with progression of symptoms over 2 to 3 days. In classic cases, the exudate organizes into a pseudomembrane that gradually forms in the nose, pharynx, tonsils or larynx. The pseudomembrane is typically asymmetrical, greyish white in appearance and is firmly attached to the underlying tissue. Attempts to remove the pseudomembrane result in bleeding at the site. The pseudomembrane may extend into the nasal cavity and the larynx causing obstruction of the airways, which is a medical emergency that often requires tracheotomy. Anterior cervical lymph nodes become markedly enlarged and in some patients, there is considerable inflammation

and oedema of surrounding tissues (“bull-neck” appearance) with greater morbidity and mortality. Depending on the anatomical location, respiratory disease may be nasal, pharyngeal, or laryngeal, or any combination of these. Pharyngeal diphtheria is the most common form. Together, aural, vaginal, conjunctival and cutaneous diphtheria account for approximately 2% of cases.

The clinical manifestations can be classified depending on the anatomical site of the disease.

- **Respiratory/pharyngeal and tonsillar diphtheria:** This is the most common form of the disease seen in unimmunized populations. At the very onset of symptoms, the pharynx on examination shows no membrane. About a day after onset, small patches of exudate appear in the pharynx. Within 2 or 3 days, the patches of exudate spread and become confluent and may form a membrane that covers the entire pharynx, including the tonsillar areas, soft palate and uvula (Fig. 1). Efforts to dislodge the pseudomembrane result in bleeding. Anterior cervical lymph nodes become markedly enlarged and tender. In patients with severe disease, the lymph node swelling is associated with considerable inflammation and oedema of the surrounding soft tissues, giving rise to the so-called “bull-neck” appearance (Fig. 2).



Fig. 1. Typical grey-white adherent membrane of the tonsils and pharynx



Fig. 2. The “bull-neck” appearance



Fig. 3. Diphtheria skin lesion (US CDC)

- **Respiratory/laryngeal diphtheria** Laryngeal diphtheria occurs in 25% of cases, and in 75% of these instances the pharynx is involved. This form of diphtheria may occur at any age but is particularly likely to occur in children younger than 4 years old. Laryngeal diphtheria is marked by an insidious onset with gradually increasing hoarseness and stridor. The diagnosis is often missed or delayed when the pharynx is not simultaneously involved. Laryngeal diphtheria is associated with higher morbidity and mortality as a result of airway obstruction and greater degree of toxin absorption from the extensive membrane.
- **Respiratory/nasal diphtheria** Nasal diphtheria is characterized by mucopurulent (containing both mucus and pus) nasal discharge that may be blood-tinged. A white membrane usually forms on the nasal septum. Isolated nasal diphtheria is uncommon (about 2% of the cases) and can be missed as the symptoms are similar to the common cold.
- **Cutaneous (skin) diphtheria** Cutaneous diphtheria is an indolent skin infection that often occurs at the sites of burns or other wounds and may act as a source of respiratory infection in others (Fig. 3). *C. diphtheriae* replicates on the surface of the mucous membrane but can also manifest as a cutaneous form. This form of diphtheria occurs rarely, most commonly as a result of non-toxigenic strains though cases of cutaneous diphtheria caused by toxin producing *C. diphtheriae* have been reported. Cutaneous diphtheria is not reported in the WHO/UNICEF Joint Reporting Form on Immunization (JRF), but occasional information is available through published data.

- **Other sites** Together, aural, vaginal, conjunctival and cutaneous diphtheria account for approximately 2% of cases.

Complications

Absorption of diphtheria toxin into the bloodstream results in toxic damage to organs such as the heart, kidneys and peripheral nerves. The extent of toxin absorption in respiratory disease depends largely on the anatomical site of infection, extent of the mucosal lesions and duration of untreated illness.

- The major threat from laryngeal diphtheria is respiratory obstruction. Pseudomembranes may advance to the larynx or into the tracheobronchial tree, resulting in life-threatening respiratory obstruction or pneumonia. Sloughing of pseudomembranes can lead to asphyxia and death. Children are particularly prone to obstruction because of their small airways.
- Severe acute systemic toxicity with myocardial involvement can occur between the third and seventh day of illness, often classified as early myocarditis and carrying a poor prognosis. The electrocardiography (ECG) changes such as ST-T wave changes, QTc prolongation or first-degree heart block can be detected in as many as two thirds of patients. More frequently, late myocarditis usually appears in the second or third week of illness, when the local symptoms of diphtheria in the respiratory tract are resolving and the patient is otherwise improving. Myocarditis is typically associated with arrhythmia and cardiomyopathy.
- Neurologic complications are primarily toxic peripheral neuropathies and occur in 15–20% of the cases. They usually begin 2 to 8 weeks after onset of the illness. Paralysis of eye muscles, limbs and diaphragm can occur, usually during the fifth to sixth week after onset. Diaphragmatic paralysis can be serious, and may require mechanical ventilation.
- Other complications of diphtheria include pneumonia, otitis media, renal failure, encephalitis, cerebral infarction and pulmonary embolism.

Period of communicability

A person is infectious as long as virulent bacteria are present in respiratory secretions (usually 2 weeks and seldom more than 4 weeks) without antibiotics. In rare cases, chronic carriers may shed organisms for 6 months or more. Effective antibiotic therapy, for example, penicillin or erythromycin, promptly terminates shedding.

Differential diagnosis

Respiratory diphtheria should be clinically differentiated from other causes of membranous pharyngitis or stridor.

Table 2. Differential diagnosis of pharyngitis

Differential diagnosis of pharyngitis	
Group A streptococcus	Fever, no coughing, tonsillar exudate and follicles, tender anterior deep cervical lymph nodes
Epstein-Barr virus (EBV)	Fever, pharyngitis, adenitis, hepatomegaly, splenomegaly
Adenovirus	Fever, pharyngitis, adenitis
Vincent's angina	Acute onset of painful bleeding gums, ulcers and sluffing of the gingiva
Oral candida	White/yellow patches on the inner cheeks, tongue, roof of the mouth, and throat; gelatinous mass can be removed Cracking and redness at the corners of the mouth
Differential diagnosis of stridor	
Viral croup	Barking cough, respiratory distress, hoarse voice
Retropharyngeal abscess	Soft tissue swelling in back of the throat, difficulty in swallowing, fever
Epiglottitis	Stridor, septic, little or no cough, drooling of saliva, inability to drink
Ludwig's angina	Swelling and pain of submandibular space, neck and oral base, stridor, septic, fever
Anaphylaxis	History of allergen exposure, wheeze, shock, urticaria and oedema of lips and face

Source: reproduced from the presentation in OpenWHO course on clinical management of respiratory diphtheria and WHO operational protocol for clinical management of diphtheria.

Outbreaks

A single laboratory-confirmed case of diphtheria should trigger a public health response. Two epidemiologically linked cases, of which at least one is laboratory-confirmed, is considered an outbreak of diphtheria.

In countries endemic for diphtheria, the disease occurs mostly as sporadic cases or in small outbreaks.

Factors observed to influence outbreaks:

- susceptible population (zero-dose (not vaccinated) and under-immunized children)
- change in biotype
- rapid urbanization (decreased hygiene and overcrowding)
- population movement increase (for example migration or refugee camps).

Diagnosis

Clinical diagnosis of diphtheria usually relies on the presence of pseudomembranous pharyngitis. Although laboratory investigation of suspected cases is recommended for case confirmation, treatment should be started immediately without waiting for the laboratory results. Material for culture should be obtained by swabbing the edges of the mucosal lesions, placed in appropriate transport media (Amies or Stuart media in ice packs; or dry swabs in silica gel sachets) and followed by prompt inoculation onto blood agar and tellurite containing media, for example, Tinsdale media. Suspected colonies may be tested for toxin production using the modified Elek immunoprecipitation test for detection of toxin; this standard assay takes 24–48 hours. A positive culture with toxin-producing *C. diphtheriae* confirms the etiologic diagnosis. Diphtheria toxin gene (*tox*) can be detected directly in *C. diphtheriae* isolates using polymerase chain reaction (PCR)

techniques. However, in some cases the presence of tox gene does not confirm production of toxin; positive PCR results should therefore be confirmed with an immunoprecipitation test.

Treatment

Intravenous or intramuscular administration of equine-derived DAT (polyclonal IgG antibody) is highly effective and is the gold standard for diphtheria treatment. Diphtheria toxin that has already entered the host cells is unaffected by DAT. Therefore, to reduce complications and mortality DAT should be administered as soon as possible after disease onset, preferably intravenously in serious cases. The entire therapeutic dose should be administered at one time. The amount of antitoxin recommended varies between 20 000 and 100 000 units, with larger amounts recommended for persons with extensive local lesions and with longer interval since the onset. The dose is the same for children and adults. Adverse events such as anaphylaxis may occur.

Global access to DAT is limited as most manufacturers have ceased production and episodes of delayed or non-availability of equine DAT have been reported recently in Europe and elsewhere. Novel approaches to passive immunization include the development of monoclonal antibodies to diphtheria toxin, and the development of recombinant modified diphtheria toxin receptor molecules to bind diphtheria toxin. Efficacy of monoclonal antibodies has been demonstrated in preclinical models but clinical development will take several more years. Antibiotics (penicillin or erythromycin) eliminate the bacteria and toxin production, prevent further transmission to uninfected individuals and limit carriage that can persist even after clinical recovery. Treatment should be continued for 2 weeks. Airway management is crucial for patients with impending respiratory difficulty or the presence of laryngeal membranes. Interventions to prevent the risk of sudden asphyxia involve tracheotomy or mechanical removal of tracheobronchial pseudomembranes and/or intubation, ventilator and possibly extracorporeal membrane oxygenation (ECMO) where available. Patients should also be monitored continuously for the development of cardiac complications.

Post-exposure prophylaxis

For susceptible exposed individuals, active immunization with diphtheria toxoid-containing vaccine is strongly recommended. Swabs should be taken from contacts and the samples cultured for *C. diphtheriae*, and a course of penicillin or erythromycin should be administered for 7 days. DAT is not recommended for post-exposure prophylaxis, as evidence regarding its benefit is limited. During outbreaks, vaccination records of all contacts of each case should be reviewed. Unvaccinated contacts should receive a full course of diphtheria toxoid-containing vaccine and under-vaccinated contacts should receive the doses needed to complete their vaccination series.

Naturally acquired immunity

Immunity to disease depends mainly on the presence of diphtheria antitoxin antibodies (IgG). Cell-mediated immunity may also play a role. In general, there is a good correlation between clinical protection and the level of diphtheria antitoxin antibodies in the blood, regardless of whether this results from disease or from vaccination. When measured using a toxin neutralization test, a diphtheria antibody concentration of 0.01 international units (IU)/mL is considered to be the minimum level required for some degree of protection. Antibody levels of 0.1 IU/mL or higher confer full protection and levels of 1.0 IU/mL or higher are associated with long-term protection against diphtheria. Rarely, diphtheria has been reported in persons having higher than protective levels of antibodies. Occasionally, protective immunity does not develop after recovery from the disease. Individuals recovering from diphtheria should therefore receive a complete course of diphtheria

toxoid vaccination during convalescence. Transplacental maternal antibodies provide passive immunity to the newborn infant during the first few months of life.

Diphtheria vaccines

Diphtheria toxoid-containing vaccines are among the oldest vaccines in current use. The first approaches to active immunization against diphtheria were based on a mixture of toxin and antitoxin. Such vaccines were widely used in the USA in 1914. In 1923, diphtheria toxoid vaccine was developed by formaldehyde detoxification of diphtheria toxin. In 1926, a more immunogenic alum-precipitated diphtheria toxoid was developed. In the 1940s diphtheria toxoid, tetanus toxoid and pertussis antigens were combined in the diphtheria tetanus-pertussis vaccine (DTP) used widely throughout the world. A systematic review of evidence indicates that two primary doses result in substantially lower antitoxin titres than three doses in the primary series. However, this difference does not persist during the second year of life and after boosting, nor does it appear to impact clinical protection. The review also found that booster vaccination during the second year of life after a two-dose or three-dose primary series substantially increases antitoxin titres. With regard to the effect of the length of the interval between primary doses, evidence suggests that an accelerated schedule (2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) results in two-fold lower antibody titres when measured after the third dose or during the second year of life, as compared to a longer schedule (with an interval of around 6 months between the second and third doses). On immunological grounds, an interval of 6 months between the second priming dose and the third dose (2p+1) results in more durable protection than three doses administered at 1-month intervals (3p+0). However, the purpose of early vaccination of infants with three doses of DTP-containing vaccine at intervals of 4–8 weeks is to ensure early protection against pertussis, given that severe disease and mortality from pertussis are almost entirely limited to the first weeks and months of life. Vaccination has led to significant decreases in diphtheria incidence worldwide, and is also responsible for the development of herd protection. At the population level, it is believed that vaccine coverage of 80–85% must be maintained in order to maintain herd protection/ community protection and reduce the threat of an outbreak. Since non-immune individuals living in highly vaccinated populations can develop respiratory diphtheria, every person should be adequately protected by vaccination.

II. WHO recommendations

2.1 SURVEILLANCE OF DIPHTHERIA

Surveillance for diphtheria should be national and facility based; and because the disease is relatively rare in the African Region, surveillance should also be case based. All health care providers identifying cases should be required to report those cases. Ideally, laboratory testing of all suspected cases should be conducted for case confirmation. Case-based surveillance may not be possible during large outbreaks, when laboratory testing of all suspected cases becomes logistically challenging.

The objectives of diphtheria surveillance are to: (1) monitor disease burden and define transmission patterns; (2) identify outbreaks to trigger investigation and prevent further cases; and (3) determine appropriate vaccine policy in the country, such as the need to introduce booster doses or change the vaccine formulation.

Improving surveillance by focusing mainly on respiratory diseases caused by toxigenic *Corynebacterium* species

Surveillance systems for diphtheria, including laboratory diagnostic capacity, must be adequate to prevent missed cases. Clinicians should collect and send clinical specimens of suspected cases for laboratory **confirmation of toxigenic diphtheria**. Antimicrobial sensitivity testing of all *C. diphtheriae* isolates is also encouraged due to the broad resistance to common antibiotics. Laboratories should be equipped with appropriate materials and submit isolates of potentially **toxigenic** *C. diphtheriae* to a reference or specialist laboratory for confirmation. A revised WHO manual has been published to guide laboratory workers in diagnosing diphtheria cases and treatment options. Countries are encouraged to adhere to WHO-recommended surveillance standards for diphtheria, which focus primarily on classic respiratory diphtheria. Non-respiratory presentations are less common, making up approximately 2% of all diphtheria cases. Asymptomatic and mild respiratory cases are usually identified through contact tracing. Expanded diphtheria surveillance may be conducted to include other anatomical sites.

Using data for decision-making

To improve vaccination policies and strategies, use case descriptions to guide changes and inform corrective actions. Monitor case fatality ratios to identify causes such as poor case management, lack of antibiotics and delayed treatment. Determine age-specific incidence rates, geographical areas and seasons of diphtheria cases to understand risk groups and periods. Assess the impact of control efforts, identify vaccine failures and modify vaccination policies. Detect outbreaks and implement control measures, including outbreak response with vaccination and catch-up vaccination. Investigate outbreaks to understand epidemiology and ensure proper case management. Ensure a high percentage of cases with laboratory testing (> 80%). Use surveillance data, immunization coverage data and serosurvey data to identify areas of poor programme performance.

Increased awareness and case investigation

WHO AFRO would like to alert all clinicians, particularly those responsible for the health of asylum seekers, refugees and other newly arriving migrants, to the potential presence of cutaneous and respiratory diphtheria. Clinicians examining or caring for patients presenting with skin lesions such as ulcers or a sore throat are encouraged to consider the possibility of diphtheria.

The risk of spread of the disease is higher in closed and crowded spaces as is often the case in asylum seeker centres. In contrast, the risk of spread to the general community is low primarily because of high vaccination coverage against diphtheria. A clinician should notify public health authorities of any suspected diphtheria case within 24 hours in order to arrange for DAT to be given to the case. Surveillance officers should investigate the case within 48 hours of report regardless of the case's vaccination status. With case-based surveillance, a case investigation form should be completed for every case and close contacts identified. All suspected diphtheria cases should be isolated and have two specimens collected (a nasal and a pharyngeal swab over and around edges of the pseudomembrane) prior to antibiotic treatment. Cases should then be treated promptly without waiting for laboratory confirmation.

Diphtheria case definitions and final classification

Suspected case definition for case finding

For case finding, the definition of a suspected case of diphtheria is an illness of the upper respiratory tract characterized by the following:

- pharyngitis, nasopharyngitis, tonsillitis or laryngitis;
AND
- adherent pseudomembrane of the pharynx, tonsils, larynx and/or nose. A diphtheria pseudomembrane is an exudate that is greyish, thick, firmly adherent and patchy to confluent. Dislodging the pseudomembrane is likely to cause profuse bleeding.

Some countries can choose to expand the suspected case definition to include the following:

- mild cases without a pseudomembrane;
- non-healing ulcers in a person with a travel history to countries with endemic disease or countries with diphtheria outbreaks;
- a bull-neck appearance caused by swollen anterior cervical lymph nodes, inflammation and surrounding tissue oedema.

Final case classification

- **Laboratory-confirmed case.** A laboratory-confirmed case is a person with *C. diphtheriae* isolated by culture and positive for toxin production, regardless of symptoms. Toxigenicity must be confirmed by the phenotypic Elek test in all instances. Polymerase chain reaction (PCR) can complement surveillance and may qualify as laboratory-confirmed after reviewing the epidemiology and clinical manifestations of the case. Laboratory-confirmed cases may be further classified into three subcategories based on the type of surveillance occurring in the country.
 - » Laboratory-confirmed classic respiratory diphtheria cases meet the suspected case definition and are laboratory-confirmed as defined above.
 - » Laboratory-confirmed mild respiratory/asymptomatic diphtheria cases have some

respiratory symptoms such as pharyngitis and tonsillitis, but no pseudomembrane, or no symptoms (usually identified via contact tracing).

- » Non-respiratory laboratory-confirmed diphtheria cases have a skin lesion or non-respiratory mucosal infection (for example, eye, ear or genitalia) from which *C. diphtheriae* is isolated by culture and tests positive for toxin production.
- **Epidemiologically linked (confirmed) case.** An epidemiologically linked case meets the definition of a suspected case and is linked epidemiologically to a laboratory-confirmed case. In this situation, a person has had intimate respiratory or physical contact with a laboratory-confirmed case within the 14 days prior to the onset of sore throat.
- **Clinically compatible (confirmed) case.** This type of case meets the definition of a suspected case and lacks both a confirmatory laboratory test result and epidemiologic linkage to a laboratory-confirmed case. A clinically compatible confirmed diphtheria case may include symptoms like pharyngitis, nasopharyngitis, tonsillitis, laryngitis, greyish pseudomembrane, bull-neck appearance or non-healing ulcers in a person with a travel history to an endemic or diphtheria-affected (ongoing outbreak) country.
- **Discarded case (not a diphtheria case, final diagnosis to be specified).** A discarded case is a suspected case that meets either of these criteria:
 - » *C. diphtheriae* but negative Elek test (non-toxigenic *C. diphtheriae*) OR
 - » negative PCR for the diphtheria toxin (tox) gene.
- **Classifying asymptomatic or mild cases.** Sometimes during outbreak investigations in which household contacts are investigated, a person may be identified with *Corynebacterium* and have evidence of toxigenicity but does not meet the suspected case definition because the person is asymptomatic or has only mild disease. These persons should still be reported as laboratory-confirmed cases, given that their treatment and public health response is the same as other laboratory-confirmed cases.

Fig. 4. Diphtheria final case classification

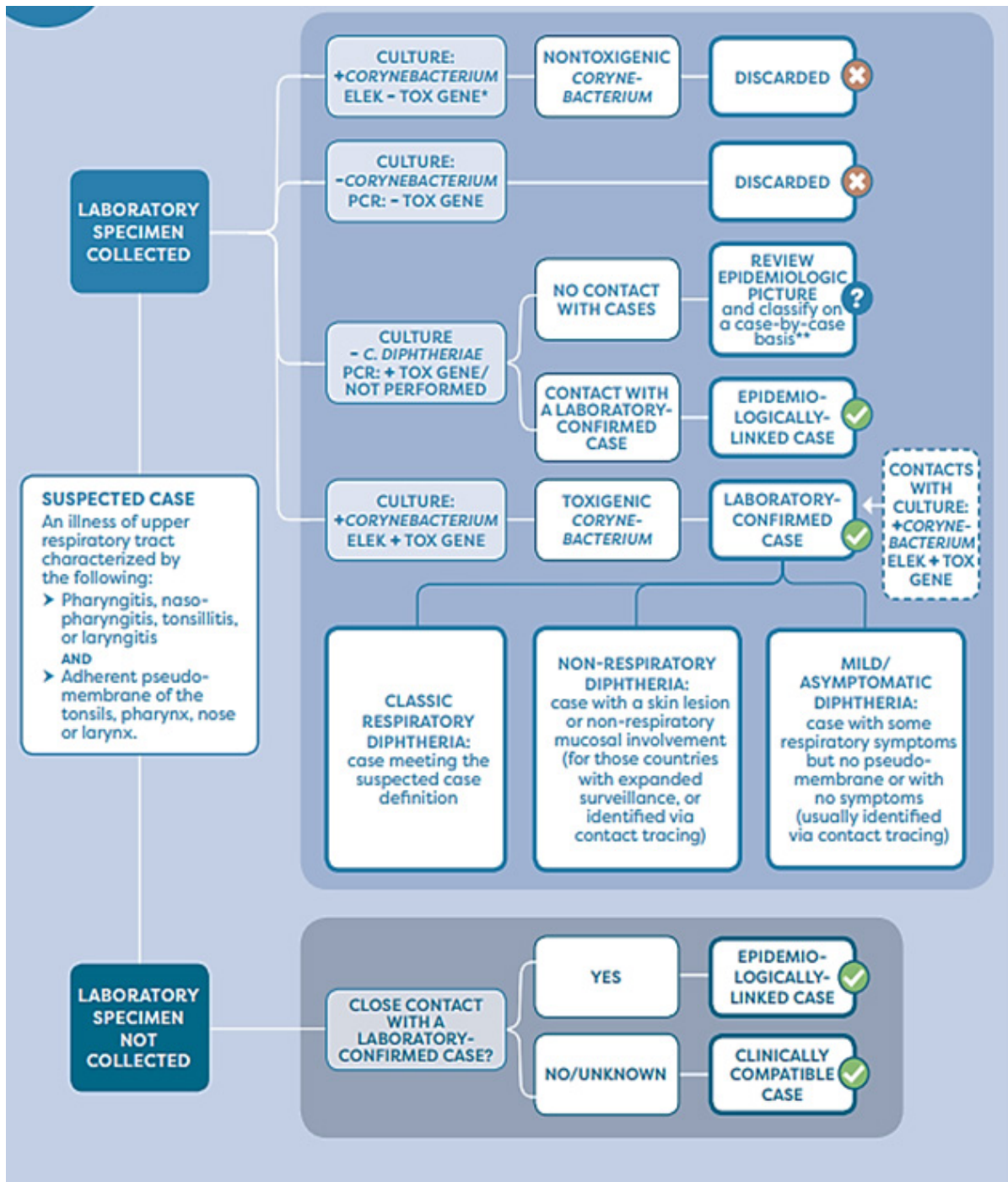


Fig. 5. Diphtheria notification and investigation form

[Logo the country and Name of institution]



Diphtheria Notification and Investigation Form

Case number		District	
State/Province		Neighborhood/Landmarks	
Municipality		Telephone	
Informant			
Service			

I. CASE IDENTIFICATION

First and last name			
Address			
Telephone		Father's name	
Mother's name		Date of birth	
Sex	<input type="checkbox"/> Male <input type="checkbox"/> Female	Day	Month Year
If date of birth unavailable, age		Months	Days

II. BACKGROUND

Date of symptom onset	Day	Month	Year	Consultation date	Day	Month	Year
Notification date	Day	Month	Year	Investigation date	Day	Month	Year
Case identified by:	<input type="checkbox"/> Spontaneous consultation (passive)			<input type="checkbox"/> Institutional search		<input type="checkbox"/> Community search	
Contact with confirmed case	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk	Attendance at school, kindergarten, or day care	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk
Number of diphtheria vaccine doses	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> ≥ 3	Date of last dose	Day	Month Year
Type of vaccine:	<input type="checkbox"/> DTP <input type="checkbox"/> Pentavalent <input type="checkbox"/> Other _____			Vaccination information obtained by:	<input type="checkbox"/> Vaccination card <input type="checkbox"/> Health services <input type="checkbox"/> Parents or another adult		

III. CLINICAL DATA, FOLLOW-UP AND TREATMENT

Signs and symptoms				Complications			
Fever (grade _____)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk	Neurological	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk
Tonsillitis	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk	Cardiac	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk
Pharyngitis	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk	Renal	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk
Laryngitis	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk	Tracheotomy	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk
Membranes (where _____)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk	Other complications	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk
Thoracic retraction	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk	Other symptoms and complications:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk
Hospitalization	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk	Bull-neck appearance	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk
Name of hospital	<input type="checkbox"/> Recovered <input type="checkbox"/> Transferred to _____ <input type="checkbox"/> Dead <input type="checkbox"/> Unknown			Admission date	Day	Month	Year
Final status				Registry/history #	Day	Month	Year
Antibiotics	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk	Date of discharge/death	Day	Month	Year
Duration of antibiotic therapy (days)				Type of antibiotics	Day	Month	Year
Antitoxin	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unk	Date of last antibiotic dose	Day	Month	Year
Dose of antitoxin				Date of antitoxin	Day	Month	Year
Other treatment:							

Example of Diphtheria notification and investigation form. In: Control of diphtheria, pertussis, tetanus, Haemophilus influenzae type B, and hepatitis B: field guide. Washington (DC): Pan American Health Organization, 2005. Annex 2 (Scientific and Technical Publication, No. 604/rep/05.1/pno.org/xml/handi/123456789-46726)

IV. SAMPLES AND LABORATORY ANALYSIS

	SAMPLE 1			SAMPLE 2			SAMPLE 3			SAMPLE 4		
Type of sample	<input type="checkbox"/> Nasopharyngeal <input type="checkbox"/> Membrane <input type="checkbox"/> Serum <input type="checkbox"/> Other:			<input type="checkbox"/> Nasopharyngeal <input type="checkbox"/> Membrane <input type="checkbox"/> Serum <input type="checkbox"/> Other:			<input type="checkbox"/> Nasopharyngeal <input type="checkbox"/> Membrane <input type="checkbox"/> Serum <input type="checkbox"/> Other:			<input type="checkbox"/> Nasopharyngeal <input type="checkbox"/> Membrane <input type="checkbox"/> Serum <input type="checkbox"/> Other:		
Identification #												
Date taken	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Date sent												
FOR LABORATORY USE												
Date received	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Laboratory name												
Identification # in laboratory												
Type of test												
Results	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Undetermined <input type="checkbox"/> Not processed			<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Undetermined <input type="checkbox"/> Not processed			<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Undetermined <input type="checkbox"/> Not processed			<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Undetermined <input type="checkbox"/> Not processed		
If <i>C. diphtheriae</i> was isolated, toxigenicity	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Undetermined <input type="checkbox"/> Not processed			<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Undetermined <input type="checkbox"/> Not processed			<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Undetermined <input type="checkbox"/> Not processed			<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Undetermined <input type="checkbox"/> Not processed		
Result dates	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year

V. CLASSIFICATION

Final classification	<input type="checkbox"/> Laboratory confirmation <input type="checkbox"/> Confirmed by epidemiological association <input type="checkbox"/> Clinically compatible confirmed case <input type="checkbox"/> Discarded, final diagnosis	Date classified	Day	Month	Year
Classified by (Name)					

Investigator		Telephone	
Institution			
Signature		Date	

Observations:

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Example of Diphtheria notification and investigation form. In: Control of diphtheria, pertussis, tetanus, Haemophilus influenzae type B, and hepatitis B: field guide. Washington (DC): Pan American Health Organization, 2005. Annex 2 (Scientific and Technical Publication, No. 604, <http://iris.paho.org/xmldata/12345678946726>)

2.2 LABORATORY DIAGNOSIS OF DIPHTHERIA

Diagnosis of diphtheria is confirmed by culture of the organism from the specimen and by demonstrating toxin production using an immunoprecipitation reaction (the modified Elek test).

- Examine clinical specimens by primary culture on blood tellurite medium followed by selective culture on cystinase medium (Tinsdale). Use screening and biochemical tests to identify the species. The confirmatory test for diphtheria is based upon the phenotypic detection of the toxin (Elek test).
- Confirmation of *Corynebacterium* should not be based on direct microscopy of smears from suspected lesions using traditional staining methods such as Gram, Albert, Neisser or Loeffler stains.
- Specimens could be negative if the patient was treated with antibiotics before specimen collection, if the specimen is of poor quality or if there was a delay in testing due to transportation delays. Consider this when assigning a final classification.
- Species identification can be further confirmed by microbiological tests such as API Coryne or VITEK system. The essential biochemical tests for the identification of *C. diphtheriae* are the catalase test (+); the reduction of nitrates (+) *biovar belfanti* (negative nitrate); the production of acid from glucose, maltose and ribose. Depending on the biovar, variable reactions can be observed for glycogen/starch. *C. diphtheriae* hydrolysis of urea is negative (urease -).
- PCR can be done directly on swab material to detect the presence of the A and B subunits of the diphtheria toxin gene (tox). However, in some cases the presence of tox does not confirm production of toxin; positive PCR results should therefore always be confirmed with the Elek test if there is an isolate. PCR is only available in some reference laboratories and should not replace bacterial culture as the primary and gold standard diagnostic test. However, in some situations (for example, specimens taken post-antibiotics, poor specimen quality or delayed testing due to transportation delays), PCR can be positive and culture negative. These cases should be reviewed to determine their classification.
- The UK Health Security Agency is a WHO collaborating centre and is available to all regions for confirmation and toxigenicity testing.
- Antibiotic susceptibility testing of suspected colonies can be done as an ancillary test to inform programmes on antibiotic treatment of cases and contacts.
- Diagnosis of *C. diphtheriae* is highly dependent on:
 - collecting the appropriate patient samples upon symptom presentation
 - transporting patient samples to the microbiology laboratory within 2–8 hours
 - patient samples can have small numbers of viable *C. diphtheriae*
 - culturing and antimicrobial susceptibility testing (AST) within 3 days
 - resistant *C. diphtheriae* strains are emerging
 - perform toxin detection per day
 - Elek or tox gene detection by PCR.

Specimen collection and storage

Two samples should be collected from every suspected case at first contact with the case, namely: a pharyngeal swab and a nasal swab. For the pharyngeal swab, use a dacron, nylon, polyester or flocced tipped applicator. The sample should be obtained under direct visualization, preferably from the edge of or directly beneath the pseudomembrane. For the nasal swab, a sample should be collected from the nares using a dacron, nylon, polyester, or flocced tipped applicator. Specimens should ideally be taken prior to starting antibiotics. However, take samples even if antibiotics have already been started. To ensure that as many patients as possible have a swab collected before

treatment, give clinicians adequate supplies and education about sample collection. Ensure that there is a way for samples to be stored and transported to avoid delays that can happen when public health officials must travel to collect a specimen. The swabs should be labelled appropriately with a unique identifier and the source of the specimen. Place specimens in appropriate transport media (Amies transport medium or Stuart medium) or place dry swabs in silica gel sachets. Transport these to the laboratory promptly at room temperature. If there are delays in transport, samples should be kept at 2–8 °C. If possible, a sample of the pseudomembrane should also be collected and placed in saline (not formalin). Ideally, all samples should be sent to the laboratory within 24 hours of collection and arrive at the laboratory within 2 days of collection, as delays may compromise the ability to isolate the bacteria. A culture collected from a wound should be handled the same as nasal and throat swabs.

- **Procedure for the collection of throat swabs from people with suspected diphtheria**
 - The health care providers must don appropriate PPEs before collecting the patient sample.
 - The pharynx should be clearly visible and well illuminated.
 - Depress the tongue with a tongue-depressor and swab the throat without touching the tongue or inside the cheeks.
 - Rub vigorously over any membrane, white spots or inflamed areas; slight pressure with a rotating motion must be applied to the swab.
 - If any membrane is present, lift the edge and swab beneath it to reach the deeply located organisms.
 - Place the swab in an Amies or Stuart transport medium and dispatch immediately to the laboratory for culture.
- **Procedure for the collection of nasal swabs from contacts of people with suspected diphtheria**
 - Through one nostril, insert the swab into the nose beyond the anterior nares.
 - Gently introduce the swab along the floor of the nasal cavity, under the middle turbinate, until the pharyngeal wall is reached. Care should be taken as the swab shaft thickness might cause discomfort to the patient.
 - Force must not be used to overcome any obstruction.
 - Place the swab in an Amies or Stuart transport medium and dispatch immediately to the laboratory for culture.
- **Procedure for the collection of swabs from skin lesions**
 - Lesions should be cleaned with sterile normal saline and crusted material removed.
 - Press the swab firmly into the lesion.
 - Place the swab in an Amies or Stuart transport medium.
 - Transport the swab immediately to the laboratory for culture.

Transportation of specimens

Ideally, all specimens should be sent to diphtheria reference laboratories within 24–48 hours of collection, as delays could compromise the ability to isolate the bacteria. Specimens should be accompanied with a specimen-submission form developed in each country. Information on the form should include information on the name, address, working hours (especially during Fridays and weekends) and contact numbers of the reference laboratories. Countries also must have efficient transportation and delivery systems in place for the transfer of laboratory samples from the field. Countries without testing facilities should collaborate with reference laboratories.

Fig. 6. Specimen collection and transport

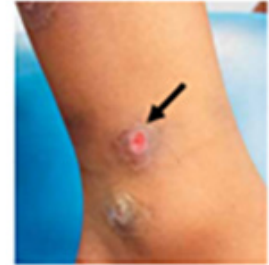
Diphtheria: Specimen Collection and Transport

• Collection of oropharynx or nasopharynx or wound

- **At onset of symptoms**
 - Before antimicrobial or antitoxin therapy
- **If a pseudomembrane is present**
 - Collect a swab from beneath the membrane
 - Place in semi-solid transport (Amies/Stuart)
 - Collect a piece of tissue if possible
- Place in a sterile plastic container.

• Transfer immediately to the laboratory

- Keep at 4-8°C if there is a delay in transport
 - A small number of *Corynebacterium* can be present in the patient sample
 - Transport within 2-8 hours from collection
 - For extended transit times, use silica gel packs



Isolation of *C. diphtheriae* by culture

The swabs, once placed in the appropriate transport medium and received at the laboratory, should be promptly inoculated onto 5% sheep or horse blood agar and tellurite-containing media (1). Diagnosis of diphtheria is confirmed by culture of the organism from the specimen and demonstration of toxin production. Species identification can be further confirmed by microbiological tests, for example the API Coryne or VITEK system.

- Confirmation of *Corynebacterium* should not be based on direct microscopy of smears from suspected lesions using traditional staining methods (for example, Gram stain, Albert, Neisser stains or Loeffler stain).
- A negative culture result is possible if the specimens are obtained from a patient who was pretreated with antibiotics prior to the collection of a specimen, or if a poor-quality specimen was collected or there was a delay in testing due to transportation issues. This should be considered when assigning a final classification. The final case classification flow chart is attached (Annex 1).

Toxigenicity testing and biotyping

After *C. diphtheriae* has been isolated, biotyping should be performed to determine the biovar (*intermedius*, *gravis*, *mitis* and *belfanti*), and toxigenicity testing should be conducted to determine whether the organisms produce the diphtheria toxin. The modified Elek immunoprecipitation test is used for the detection of toxin; this standard assay takes 24–48 hours. A positive culture with toxin-producing *C. diphtheriae* confirms the etiologic diagnosis.

Toxigenic *Corynebacterium* antimicrobial sensitivity testing (AST)

- **Management and treatment of any suspected diphtheria case:** all *C. diphtheriae* isolates (irrespective of toxin production), all *C. diphtheriae* isolates (cases and carriers) and all clinically significant strains of *C. ulcerans* and *C. pseudotuberculosis*.
- **The Clinical and Laboratory Standards Institute (CLSI) M45 2015:** no disk diffusion guidelines and broth microdilution (MIC).
- **The European Committee on Antimicrobial Susceptibility Testing (EUCAST):** disk diffusion guidelines available and broth microdilution (MIC).
- **EUCAST:** sensitivity testing should be performed on Mueller-Hinton agar + 5% defibrinated horse blood and 20 mg/L β-NAD (MH-F broth) and incubated at 35± 1°C in the air with 4-6% CO₂

Antimicrobial class	Antimicrobial agent	Disc content (ug)	Zone diameter (mm) and breakpoint (EUCAST)	MIC value and breakpoint (CLSI)	MIC value and breakpoint (CLSI)
Penicillins	Penicillin	-	-	-	S≤0.12 I=0.25-2 R≥4
Macrolides	Erythromycin	-	-	-	S≤0.5 I=1 R≥2
Lincosamides	Clindamycin	2	R <20 S ≥20	S≤0.5 R>0.5	S≤0.5 I=1-2 R≥4
Ansamycins	Rifampicin	5	R <25 S ≥30	S≤0.06 R>0.5	S≤1 I=2 R≥4
Oxazolidinones	Linezolid	10	R <25 S ≥25	S≤2 R>2	S≤2
Tetracyclines	Tetracycline	30	R <25 S ≥25	S≤2 R>2	S≤4 I=8 R≥16

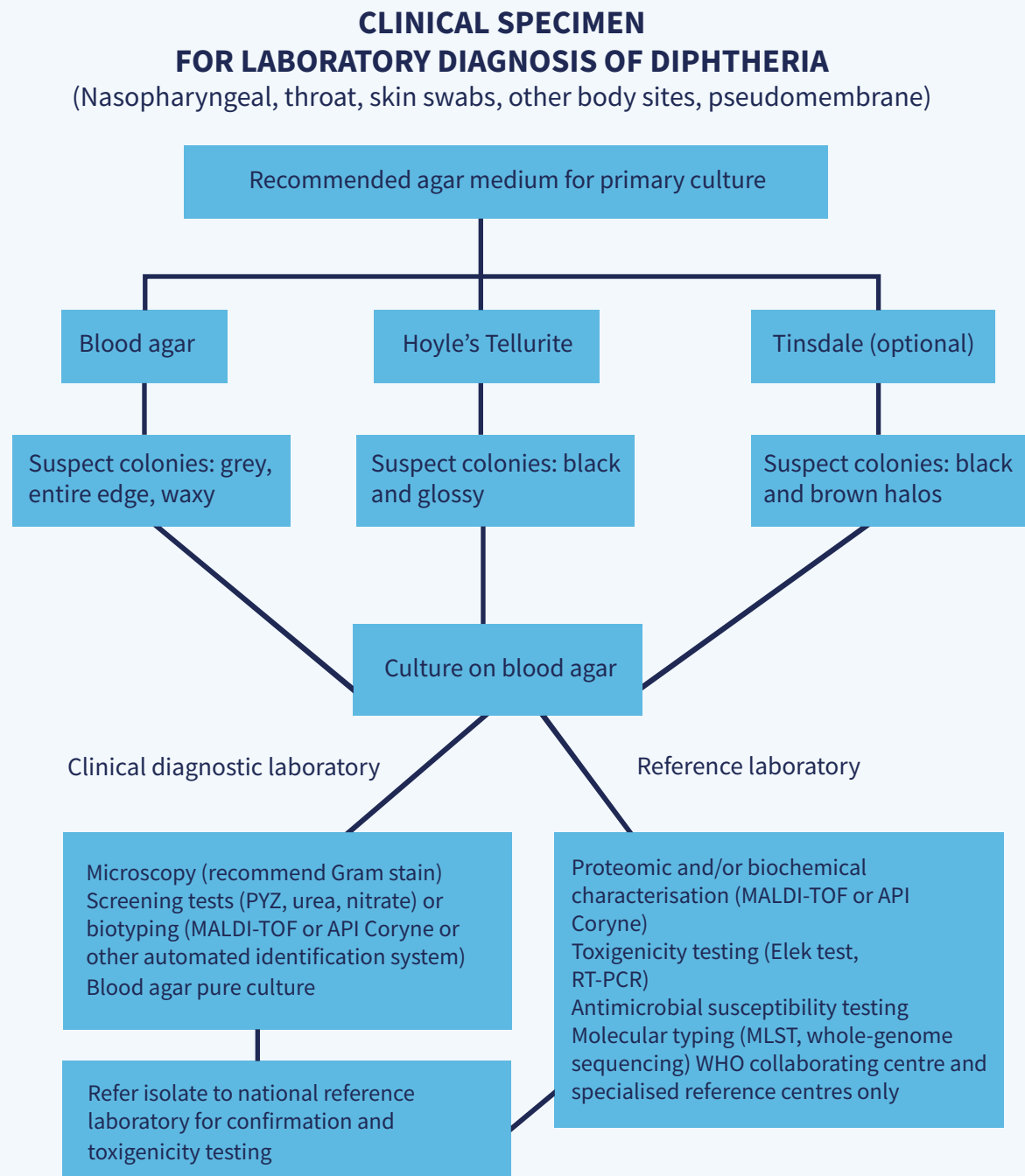
- **Increasing multidrug-resistant *Corynebacterium* is a challenge in many countries:** strains resistant to chloramphenicol, erythromycin, clindamycin and trimethoprim-sulfamethoxazole have been reported
- **Therefore, AST is highly recommended, particularly if clinically, macrolides are to be used in lieu of penicillin.**

Polymerase chain reaction testing

Polymerase chain reaction (PCR) can be performed directly on specimens or on isolates to detect the presence of the diphtheria toxin gene. However, the presence of diphtheria toxin gene does not confirm the production of toxin; for this reason, toxin production in PCR-positive isolates should be confirmed by the Elek test. PCR is only available in some reference laboratories but is not a substitute for bacterial culture as the primary diagnostic test. In some situations (for example, specimens taken after the use of antibiotics, poor specimen quality or delayed testing due to transportation delays) the culture may be negative; however, a positive PCR result could support the diagnosis and can be used to initiate public health activities. PCR is usually considered complementary to culture and Elek testing; in a very large outbreak, PCR could be used as the standalone confirmatory test as long as toxigenic diphtheria has been confirmed by culture and Elek testing in at least five cases. However, culture and Elek testing are still critical in large outbreaks and should be undertaken if new suspected cases are identified in a new area with no epidemiological link to the current outbreak. Additionally, for outbreaks lasting for an extended period, at least five samples should be tested by culture and Elek every month among suspected cases with no epidemiological linkage to a PCR-confirmed case. This helps to balance the limited resources and field challenges existing in

low-resource settings that are most likely to experience a diphtheria outbreak, while also ensuring that a toxigenic diphtheria outbreak is still ongoing. Elek and PCR tests are not readily available in many clinical microbiology laboratories, so these isolates should be sent to a reference laboratory proficient in performing the tests. For the latest guidance on laboratory diagnosis, please refer to the WHO laboratory manual for the diagnosis of diphtheria and other related infections.

Fig. 7. Recommended procedures and order to follow for the laboratory diagnosis of diphtheria and species identification for toxigenic *Corynebacterium*



2.3 CASE MANAGEMENT AND TREATMENT OF DIPHTHERIA

Clinical case management steps

Management of all suspect or confirmed diphtheria cases requires the following steps.

1. **Isolation.** Respiratory droplet isolation of patients with respiratory diphtheria is required and contact precautions are required for cutaneous diphtheria. Diphtheria is highly communicable and cases should be immediately isolated upon suspicion or confirmation to prevent spread of infection. Isolation units should be dedicated wards with patients isolated until two cultures 24 hours apart are negative, after completion of antibiotics treatment. All patients should be encouraged to wear masks and triaged to establish disease severity using the airway, breathing, circulation, disability, exposure (ABCDE) systematic approach. Samples from the infected mucosae or infected wound should be sent for laboratory confirmation. Patients with extensive pseudomembranes should be advised to gargle 1% hydrogen peroxide to slough off the membrane whilst awaiting laboratory confirmation and treatment. If facilities are not available for droplet isolation, place screens between patients to limit potential transmission and limit contact between the case and other patients in the health facility.
2. **Collection of nasal and pharyngeal swabs for culture.** Swabs should be taken as soon as possible after diphtheria is suspected, and treatment should not be delayed while waiting for laboratory results.
3. **Diphtheria antitoxin (DAT).** The mainstay of treatment is DAT. Disease course and outcome depend on how early from disease onset the antitoxin treatment is started; after about 3 days from onset, the risk of complications and fatal outcome increases with each day that DAT administration is delayed. If diphtheria is strongly suspected, treatment with DAT should be given immediately without waiting for laboratory results, preferably intravenously in serious cases and intramuscularly otherwise. The dose of DAT given varies depending on site and extent, time since onset and severity of infection.
4. **Antibiotic treatment.** Antibiotics eliminate bacteria and toxin production, prevent further transmission and limit carriage that can persist even after clinical recovery. Treatment should be continued for 2 weeks. Choice of antibiotics should depend on antibiogram. Treatment should be given parenterally until the patient can swallow with ease.
5. **Immunization as needed during convalescence.** Protective immunity does not always develop after recovery from the disease. Therefore, individuals recovering from diphtheria should complete the age-appropriate recommended course of diphtheria toxoid vaccination during convalescence. Further information on case management can be accessed at <https://openwho.org/courses/diphtheriaclinical-management>.
 - Type:
 - **pentavalent (for 6 weeks to 6 years old)**
 - **tetanus-diphtheria (Td) (for 7 years old and above).**
 - Number of doses:
 - **only one dose if documentary evidence of having completed a primary vaccination schedule is available;**
 - **three doses—at least 4 weeks interval between each dose.**

Operational diphtheria case management steps

- *Place patient immediately in isolation room (or area) and apply standard, droplet and contact precautions when caring for the patient.*
- *Administer DAT as soon as possible. Don't wait for culture confirmation to start treatment (it takes 8–10 hours to grow).*
- *Administer antibiotics (penicillin, erythromycin, azithromycin or clindamycin) as soon as possible. Ensure to request the AST on specimen. Do not wait for AST!! Commence treatment.*
- *Monitor closely and provide supportive therapy for severe complications (for example, airway management, cardiac, neurologic and renal failure).*
- *Vaccinate with an age-appropriate diphtheria toxoid-containing vaccine.*

Hospital admission

Suspected or confirmed diphtheria cases and those with severe symptoms will require admission to secondary or tertiary health care facilities capable of dealing with the respiratory and systemic complications, as well as isolation and DAT administration. All cases in the initial phase of admission (48 hours) require review every 2 to 4 hours and close observation, particularly in young children. For inpatients with extensive pseudomembranes, an anaesthesiology or ear, nose and throat consultation is recommended because of the possible need for tracheostomy and intubation. Patients with severe respiratory diphtheria require careful monitoring (ideally in a high- or intensive-care setting) for potentially life-threatening complications from local disease (for example, 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.

If family or patient refuses admission, below are the arguments to educate them.

- Contagious disease
 - Respiratory diphtheria is a contagious disease.
 - Admission will allow for isolation and treatment to stop the outbreak.
 - After 48 hours of antibiotics, patient will be less contagious.
- Treatment saves lives.
 - Untreated diphtheria can lead to suffocation and death.
 - Antitoxin is life-saving but can only be given in hospital.
 - Most antibiotics need to be taken for 14 days.
 - Close contacts also take antibiotics for 7 days.
- If patient still refuses, then take the actions below.
 - Send home with antibiotics, soap and medical masks.
 - Advise to restrict contact with others for initial 48 hours of antibiotics.
 - If symptoms worsen (lethargy, noisy breathing, among other things), then return for medical care immediately.

Infection prevention and control

Immediately place patients with symptoms of upper respiratory tract infection in a separate area until examined. In addition to standard precautions, droplet precautions are required for patients with respiratory diphtheria; contact precautions are required for cutaneous diphtheria. Suspected cases should also be admitted to a treatment facility with isolation capacity; a single room is preferable. If this is not possible, then cohort patients in confined areas, keeping suspected and confirmed cases separate. Keep the isolation area segregated from other patient care areas. Maintain 1 metre between patients when possible and keep patient-care areas well ventilated. Avoid patient movement or transport out of the isolation area. If movement is necessary outside of the isolation area, have the patient use a medical or surgical mask. Clean and disinfect frequently touched surfaces using dedicated materials. Assign dedicated cleaners for isolation rooms and equip them with appropriate personal protective equipment (PPE). Ensure the availability of protocols for room cleaning and disinfection (both routine and terminal), including solution preparation and PPE wearing. Avoid using any out-of-stock hygiene products or PPE. For patients confirmed to have diphtheria, continue isolation until elimination of the organism is demonstrated by negative cultures of two samples obtained at least 24 hours apart after completion of antibiotic therapy. In the absence of such follow-up cultures, patients should be isolated until they have completed the recommended antibiotic therapy.

During a large outbreak, space for isolation may be limited. If separate rooms are not available for isolation, screens should be placed between patients to limit potential transmission. Logistical constraints may also limit the feasible duration of isolation. The disease is usually not contagious 48 hours after antibiotics are instituted. Thus, when longer isolation is not feasible, patients can be moved out of isolation to a ward with barrier nursing after completing 48 hours of antibiotics therapy while droplet precautions are maintained. Patients who are well and not hospitalized should be advised to restrict contact with others until completion of antibiotic therapy.

Fig. 8. Ways to implement droplet and contact precautions

WAYS TO IMPLEMENT DROPLET AND CONTACT PRECAUTIONS

For family members:

- A family member, such as mother, can stay with her sick child in the treatment facility, if desired.
- The family member should also be taught to practise hand hygiene.
- The family member should be provided with a medical mask to wear when within one metre of the patient, and also a disposable gown, eye protection and gloves when in close contact.
- Take this as an opportunity to give prophylactic antibiotics to the family member.

For health-care workers:

- Practise proper hand hygiene
- Wear a medical or surgical mask when within one metre of the patient or when entering room.
- Wear gown, gloves, eye protection and medical or surgical mask if he or she will be performing a close examination of the patient and may be exposed to respiratory secretions.
- Remove personal protective equipment in contaminated areas and then leave room. • Use disposable or dedicated patient equipment when possible. If not possible, then clean and disinfect between uses, if sharing among patients.
- Refrain from touching eyes, nose or mouth with contaminated gloved or ungloved hands after patient's care or before hand hygiene.
- Avoid contaminating surfaces not involved with direct patient care, such as doorknobs, light switches and mobile phones.

Antibiotics

Antibiotics are used in the management of respiratory diphtheria with three major benefits: they kill the organism and thus prevents further toxin from being formed, slow the spread of local infection and reduce transmission. All diagnostic specimens should be collected before antibiotic treatment is started. However, should antibiotics already have been started, specimens should still be collected. Antibiotics should be started immediately without waiting for AST. Antibiotics are not a substitute for DAT, but they kill the organism. The appropriate antibiotic depends on the outbreak or local sensitivities, and there is a risk of penicillin resistance in the current outbreak. Treatment with antibiotics is weight based and should be continued for 2 weeks, even when patients are discharged from health facilities.

Table 3. Types of antibiotics and dosage according to disease severity

Disease severity	Antibiotic/ROA	Dosage (Treat for 14 days)
Less ill and able to swallow	Oral phenoxymethylpenicillin V	All persons 50 mg/kg/day, administer in divided dose 10–15 mg/kg/6hrly
	Oral erythromycin	All persons: 40–50 mg/kg/day (maximum, 2 g/day). Administer in divided dose, 10–15 mg/kg every 6 hours, maximum 500 mg per dose.
	Oral azithromycin	Children: 10–12 mg/kg once daily (max. 500 mg/day). Adults: 500 mg once daily.
	Oral clindamycin	Adults: 150–300 mg 6hrly Children: 25 mg/kg/day 6hrly
Severely sick	Procaine benzyl penicillin (penicillin G): administer intramuscular (IM)	All persons: 50 mg/kg once daily (maximum 1.2 g a day)
	Aqueous benzyl penicillin (penicillin G): administer IM or slow intravenous (IV)	All persons: 100 000 units/kg/day administer in divided dose of 25 000 IU/kg every 6 hours. Maximum dose is 4 million international units (MIU) or 2.4 g per day
	IV erythromycin	All persons: 40–50 mg/kg/day (maximum, 2 g/day). Administer in divided dose, 10–15 mg/kg every 6 hours, maximum 500 mg per dose
	Clindamycin” IM/IV	Adults: 600–1 200 mg in 2–4 divided doses Children: 15–25 mg/kg in 3–4 divided doses

Diphtheria antitoxin (DAT)

DAT is hyperimmune serum produced in horses. As antitoxin only neutralizes circulating toxin unbound to tissues, prompt administration of DAT is critical. Delayed administration increases the risk of late complications such as myocarditis and polyneuropathies. If diphtheria is suspected by clinicians, treatment with DAT should be given immediately without waiting for laboratory results. The entire therapeutic dose should be administered as a single dose. The amount of antitoxin recommended varies between 20 000 and 100 000 units, with larger amounts recommended for persons with extensive local lesions and longer intervals since onset. If there are no shortages, all confirmed patients should be given DAT; however, if supplies are low, then severe cases should be prioritized. DAT is generally not indicated in cases of cutaneous diphtheria without systemic manifestations. However, in cases where the ulcer is very large (> 2cm) and membranous, the risk of systemic absorption of toxin and subsequent systemic complications is increased, and DAT may be considered. Although data are limited, DAT administration to clinically suspect patients who are pregnant or breastfeeding should be considered and may be life-saving. Possible adverse reactions following administration of DAT are hypersensitivity reactions, febrile reaction and serum sickness. Ensure to check glycaemic levels in children >5 years hourly. If no allergic reactions are observed, the infusion rate could be increased progressively, over the stated period.

Anaphylaxis is a major medical emergency and the recognition and management of anaphylaxis can be found in the Immunization Safety Surveillance Guidelines for Immunization Programme Managers on Surveillance of Adverse Events following Immunization. Sensitization testing has been widely used in the past during diphtheria outbreaks and is recommended by some national authorities as well as manufacturers. It is recommended not to wait for bacteriological confirmation as any delay can diminish efficacy.

New WHO recommendations for the clinical management of diphtheria (2 February 2024)

- 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].

Source: *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.

Table 4. Recommended paediatric and adult DAT doses

Diphtheria clinic presentation	DAT dose (units)	Route
Nasal	10 000–20 000	Intramuscular
Nasopharyngeal	40 000–60 000	Intramuscular
Tonsillar	15 000–25 000	Intramuscular or intravenous
Pharyngeal/laryngeal Laryngeal or pharyngeal of 2-day duration	20 000–40 000	Intramuscular or intravenous
Combined/delayed diagnosis	40 000–60 000	Intravenous
Extensive disease of 3 or more days duration of any patient with diffuse swelling of the neck (respiratory distress, haemodynamic instability)	80 000–100 000	Intravenous
Skin lesions only (rare case where treatment is indicated above)	20 000–40 000	Intramuscular or intravenous

The recommended DAT dose depends on the site, extent and duration of disease, varying from 20 000 to 100 000 units in a single IV or IM dose, and should be given immediately after nasal and throat swabs have been taken.

Adverse reaction to DAT	Management of adverse reaction to DAT
<ul style="list-style-type: none"> • Anaphylaxis • Angioedema or other facial oedema • Cough • Oxygen desaturation • Wheeze • Generalized rash • Localized rash • Itching • Agitation/restlessness • Nausea or vomiting 	<ul style="list-style-type: none"> • Adrenaline • Hydrocortisone • Promethazine • Salbutamol nebulization • Oxygen • IV fluid • Ondansetron <p>If anaphylaxis occurs give IV epinephrine 0.2–0.5 mL of 1:1 000 solution</p>

Administering DAT

- **Each 10 mL ampoule contains 10 000 IU of DAT**
- Set up an acute care ward or high-dependency unit (HDU) to administer DAT.
- Premedicate patients with weight-based steroids or antihistamine.
- Take a serum sample before administering DAT.
- Give entire dose of DAT slowly 2–4 hours in 250–500 mL of normal saline (NS).
- Observe patient for adverse events (AE).
- Transfer patient to general ward if no AE and observe for up to 6 hours.
- Discharge patient by day 2 if no reaction and signs of improvement.
- Pregnant women should not receive DAT.

TIPS

- If availability is limited, then use lower-dose range and prioritize patients with severe disease.
- The same doses are recommended for children and adults.
- Do not repeat dosing. DAT is given as a single dose.
- May be administered IV (preferred in severe cases) or IM (mild to moderate cases).

Global supply of DAT

- WHO and global partners are taking daily assessment of DAT supply in order maintain quality and availability to all persons infected.
- However, there are at present (October 2023) outbreaks in 16 countries around the world, the largest of which is reported in India.
- If supply becomes exhausted, implications for treatment will need to be addressed using ethical principles.

Discussion points in relation to respiratory diphtheria and DAT

- Principle of utility: early DAT will probably save the most lives. Most severe cases have the highest mortality and without intensive care facilities, they will likely die immediately with or without DAT.
- Principle of equity: the entire population is vulnerable, should get preference.
- Life cycle: prioritization for children but setting specific age is not recommended.
- Lottery system: ensures equity and fairness if all children are able to access care in timely fashion. This is not the case here, they are too vulnerable.

Fair process for decision-making

- When several ethical considerations can be considered, it is essential to convene a transparent decision-making process to ensure a fair process before the crisis occurs.
- Broad representation should be inclusive of:
 - stakeholders (international and national)
 - local health ministry officials
 - representatives of the community.
- Decisions should be supported by relevant reasoning.
- Decisions can be revisable based on new evidence or reasoning.

Management of complications

Complications could present either early or late in the disease. Most early complications present within a week of onset of symptoms and include respiratory obstruction and acute respiratory distress. In the early phase, airway obstruction occurs due to oedema and pseudomembrane coating in the trachea and bronchi, causing cyanosis or suffocation of the infected person. Acute kidney injuries and cardiac abnormalities can lead to cardiac failure. Patients should be managed by a specialist in the appropriate environment. Airway management is crucial for patients with impending respiratory difficulty or the presence of laryngeal membranes. Interventions to prevent the risk of sudden asphyxia involve tracheotomy or mechanical removal of tracheobronchial pseudomembranes and/or intubation, ventilator and possibly extracorporeal membrane oxygenation (ECMO) where available. Patients should also be monitored continuously for development of cardiac complications.

Late complications usually manifest within 2 weeks to months of symptom onset and should be managed in appropriate settings. They include chronic cardiac and kidney disease, gait abnormalities, blood disorders and in some cases reactivation of latent tuberculosis.

- Two weeks after the initial pharyngeal phase, some patients may develop myocarditis (congestive heart failure, conduction abnormalities, and arrhythmias).
- In 2–6 weeks some experience debilitating neurologic dysfunction (neuropathy of cranial and peripheral nerves, and/or motor weakness/paralysis).
- Renal failure also occurs.

Airway obstruction and myocarditis are the main causes of death.

Follow-up care and contact tracing

Patients can be discharged after 48 hours of antibiotics treatment and advised to continue antibiotics up to 14 days. Ideally, patients are said to be negative if two samples for culture are tested negative 24 hours apart.

All contacts should be clinically assessed and kept under surveillance for a week. Antibiotics are recommended to be administered as prophylaxis and they include:

1. IM benzathine children 600 IU and adults 1200 IU single dose
2. oral erythromycin: children 40 mg/kg 6hrly and adults 1g/day, for 7 days
3. oral azithromycin 10–20 mg/kg once daily Children and 500 mg once daily for adults for 7 days.

However, these depend on susceptibility to the bacterium. Assess diphtheria toxoid vaccination status of exposed close contacts. If contacts are not fully vaccinated, recommend vaccination according to the WHO strategy.

2.4 PREVENTION OF DIPHTHERIA

WHO position on diphtheria vaccine

All children worldwide should be immunized against diphtheria. Recent diphtheria outbreaks in several countries reflect inadequate vaccination coverage and have demonstrated the importance of sustaining high levels of coverage in childhood immunization programmes. Every country should seek to achieve timely vaccination with a complete primary series plus booster doses. Those who are unimmunized are at risk regardless of the setting.

Primary vaccination for infants

As diphtheria toxoid is almost exclusively available in fixed combinations with other antigens, immunization programmes need to harmonize immunization schedules between diphtheria, tetanus and pertussis. For vaccination of infants, DTP-containing vaccine often includes other antigens scheduled at the same time, such as haemophilus influenzae type b (Hib), inactivated polio vaccine (IPV) and hepatitis B, in order to reduce the number of injections. A primary series of three doses of diphtheria toxoid-containing vaccine is recommended, with the first dose administered as early as 6 weeks of age. Subsequent doses should be given with an interval of at least 4 weeks between doses. The third dose of the primary series should be completed by 6 months of age if possible. If either the start or the completion of the primary series has been delayed, the missing doses should be given at the earliest opportunity with an interval of at least 4 weeks between doses. The need for early infant vaccination with DTP-containing vaccine is principally to ensure rapid protection against pertussis, because severe disease and death from pertussis is almost entirely limited to the first weeks and months of life. The three-dose primary series is the foundation for building lifelong immunity to diphtheria. In view of the historical low coverage in many countries, providing the primary series to persons who missed these doses in infancy is important. At any age those who are unvaccinated or incompletely vaccinated against diphtheria should receive the doses necessary to complete their vaccination.

Booster doses

Immunization programmes should ensure that three booster doses of diphtheria toxoid-containing vaccine are provided during childhood and adolescence. This series will provide protection throughout adolescence and adulthood. The diphtheria booster doses should be given in combination with tetanus toxoid using the same schedule, that is, at 12–23 months of age, 4–7 years of age and 9–15 years of age, using age-appropriate vaccine formulations. Given the increasing life expectancy worldwide, it remains to be determined whether a booster dose later in life may be necessary to ensure life-long protection. (63) National vaccination schedules can be adjusted within the age limits specified above to enable programmes to tailor their schedules based on local epidemiology, the timing of vaccination doses and other scheduled interventions, and any other programmatic issues. With an increasing proportion of children attending school worldwide, immunization programmes targeting school-age children are increasingly important. This is particularly relevant for the booster doses of diphtheria toxoid-containing vaccine. A second booster dose could be provided around the age of primary school entry and a third booster dose on completion of primary school or start of secondary school. Screening of vaccination status at school entry can also provide an effective opportunity to catch up on any missed vaccinations and reduce the risk of vaccine-preventable disease outbreaks in schools. A school-based immunization approach may be linked to other important health interventions for children and adolescents.

Catch-up schedule in children aged ≥ 1 year, adolescents and adults

Opportunities should be taken to provide or complete the three-dose diphtheria toxoid-containing vaccine series for those who were not vaccinated, or incompletely vaccinated, during infancy. For previously unimmunized children aged 1–7 years, the recommended primary schedule is three doses with a minimum interval of 4 weeks between the first and the second dose, and an interval of at least 6 months between the second and third dose, using DTP-containing vaccine. Using tetanus-diphtheria (Td) or tetanus, diphtheria, and pertussis (Tdap) combination vaccine, the recommended schedule for primary immunization of older children (>7 years), adolescents and adults is three doses with a minimum interval of 4 weeks between the first and the second dose, and an interval of at least 6 months between the second and third dose. Two subsequent booster doses using Td or Tdap combination vaccines are needed with an interval of at least 1 year between doses (see *Tetanus vaccines: WHO position paper*).⁽⁶⁴⁾ As responses to booster vaccination can still be elicited after intervals of 25–30 years, it is not necessary to repeat a primary vaccination series when booster doses have been delayed. To further promote immunity against diphtheria, the use of Td rather than tetanus toxoid (TT) is recommended during pregnancy to protect against maternal and neonatal tetanus in the context of prenatal care, and when tetanus prophylaxis is needed following injuries. Opportunities for catch-up vaccination could include the delivery of diphtheria toxoid-containing vaccine with other vaccinations such as human papillomavirus (HPV) vaccination for adolescents, or during routine vaccination on entry into military services or other institutions with similar requirements.

Special risk groups

Diphtheria toxoid-containing vaccines can be used in immunocompromised persons including HIV-infected individuals, though the immune response may be inferior to that in fully immunocompetent persons. All HIV-infected children should be vaccinated against diphtheria following the vaccine recommendations for the general population. A need for additional booster doses for HIV-infected persons or those with other congenital or acquired immunodeficiency has not been established. Vaccination can be given during pregnancy and can serve to boost immunity and increase the duration of protection in those who had not received the full set of recommended booster doses.

Vaccine co-administration

Concomitant administration of the first three doses of diphtheria toxoid-containing vaccine together with other childhood vaccines does not interfere with the response to any of these other antigens following either primary or booster vaccination. All vaccines that are consistent with the child's prior immunization history can be administered during the same visit. In particular, diphtheria toxoid-containing vaccine can be co-administered with Bacille Calmette-Guérin (BCG), HPV, IPV, oral polio vaccine (OPV), pneumococcal conjugate vaccine (PCV), rotavirus, measles, mumps and rubella vaccine and meningococcal conjugate vaccines. cross-reacting material (CRM) conjugate vaccines (such as Hib, pneumococcal and meningococcal vaccines) can be administered with or before, but not after, diphtheria toxoid-containing vaccine in the routine vaccination programme. When two vaccines are given during the same visit, they should be injected in different limbs. When three vaccines are given, two can be injected in the same limb and the third should be injected in the other limb. Injections in the same limb should be at least 2.5 cm apart so that local reactions can be differentiated. There are effective recommended methods to mitigate pain at the time of vaccination. ⁽⁶⁵⁾

Health care workers

In endemic settings and outbreaks, health care workers may be at greater risk of diphtheria than the general population. Therefore, special attention should be paid to immunizing health care workers who may have occupational exposure to *C. diphtheriae*. All health care workers should be up to date with immunization as recommended in their national immunization schedules.

Travellers

Travellers are generally not at special risk of diphtheria, unless they travel to an endemic country or outbreak setting. They should follow the vaccine recommendations for the general population and ensure that they are up to date with their diphtheria vaccinations before travelling.

Surveillance

Efficient national surveillance and reporting systems, with district-level data analysis, are essential in all countries. Countries should report all available data on diphtheria cases, including data from their integrated disease surveillance and response databases. Cases of diphtheria caused by *C. diphtheriae* (and *C. ulcerans*, where laboratory capacity is available) should be reported for countries with established capability for laboratory confirmation. Epidemiological surveillance ensuring early detection of diphtheria outbreaks should be in place in all countries. All countries should have access to laboratory facilities for reliable identification of toxigenic *C. diphtheriae*. Laboratory capacity should be strengthened where necessary.

Research

Immunity gaps may occur in older age groups due to waning immunity, but available data are insufficient to warrant global recommendations on diphtheria vaccination in these groups. Further studies, including serosurveys, are required to generate information on the duration of protection and the possible need for booster doses in older age groups. The impact of maternal Td or Tdap vaccination on infant immune responses to conjugate vaccines containing diphtheria toxoid or CRM has not been adequately studied.

Table 5. Vaccine presentations appropriate for the prevention of diphtheria

Type	Vaccine description	Route
DT	Diphtheria-tetanus (higher potency of diphtheria vaccine).	Children up to 6 years of age
Td	Diphtheria-tetanus (lower potency of diphtheria vaccine).	From 4 years of age under all circumstances,
Tdap	Diphtheria (reduced)-tetanus-pertussis (acellular)	Not indicated for children below the age of 4 years (ADACEL)
DTaP	Diphtheria-tetanus-pertussis (acellular)	Primary vaccination series, and booster as indicated by national schedule and licensed for use in children aged 6 weeks to 7 years
DTwP	Diphtheria-tetanus-pertussis (whole cell)	Primary vaccination series and booster as indicated by national schedule and licensed for use in children aged 6 weeks to 7 years
DTwP-Hib* vaccine	Diphtheria-tetanus-pertussis (whole cell)-haemophilus influenzae type b (conjugate vaccine)	Primary vaccination series and booster as indicated by national schedule and licensed for use in children aged 6 weeks to 7 years
DTwP-Hep B	Diphtheria-tetanus-pertussis(whole cell) and Hepatitis B	Primary vaccination series and booster as indicated by national schedule and licensed for use in children aged 6 weeks to 7 years
DTwP-Hep B-Hib*	Diphtheria-tetanus-pertussis (whole cell), Hepatitis B and Haemophilus influenzae type b	Primary vaccination series and booster as indicated by national schedule and licensed for use in children aged 6 weeks to 7 years
DTaP-HepB- Hib*-IPV	Diphtheria-tetanus-pertussis (acellular)-hepatitis B-haemophilus influenzae type b-polio (inactivated)	Primary vaccination series, and booster as indicated by national schedule and licensed for use in children aged 6 weeks to 7 years

* Hib – Not recommended for children > 5 years old. Note: for up-to-date product information on the different diphtheria toxoids that are prequalified by WHO, see: <https://extranet.who.int/pqweb/vaccines/list-prequalified-vaccines>. For up-to-date information on UNICEF Supply Division vaccine prices, see: <https://supply.unicef.org/>. Source: WHO Prequalification of Medical Products, Prequalified Vaccines. 2018.

2.5 PREPAREDNESS FOR DIPHTHERIA OUTBREAKS

Objectives of preparedness for diphtheria outbreaks

The main objectives of preparedness for diphtheria outbreaks:

- know the main areas of risk and take steps to minimize the risk or detect any problems as early as possible;
- ensure good preparatory outbreak response coordination prior to the outbreak for timely and effective response;
- rapidly detect and assess diphtheria-related events in countries; and
- have an understanding of existing DAT supplies, including stockpiles for ensuring rapid and easy access in case of outbreaks.

Guiding tools for response to diphtheria outbreaks

The purpose of standard operating procedures (SOPs) is to carry out operations correctly and always in the same manner. SOPs should be available at the place where the work is undertaken. The terminology of SOPs does not always have to be applied, and instead they may be designated as protocols, instructions or simply registration forms.

Guiding tools should address the following and could be specific for diphtheria or generic for communicable diseases and VPDs:

- SOPs for epidemiological analytical methods
- terms of reference for an outbreak coordination committee
- SOPs for sample collection, laboratory procedures and quality assurance
- SOPs for DAT management
- SOPs for safe injection practices
- SOPs for infection control in hospitals
- SOPs for effective communication and public awareness.

Detailed mapping and mobilization of resources

An advance detailed mapping and plan for mobilization of the necessary resources, including finances for the outbreak response, would optimize and better allocate the use of resources in vulnerable areas. Mapping of resources includes:

- antibiotics and medicine supplies necessary for cases and contacts;
- DAT supplies and requirements;
- diphtheria vaccines (age appropriate) that would allow adequate supplies of vaccine for outbreak response;
- a regular gap analysis of required stock;
- trained human resources (doctors, nurses, public health staff and laboratory staff);
- financial resources;
- tools, including case investigation forms, cases and contact line-list forms and laboratory requesting forms;
- information, education and communications materials (leaflets and brochures); and
- referral channels to higher-level health centres and hospitals.

Roles and responsibilities at different administrative levels during outbreaks

As part of effective preparedness and response activities for diphtheria outbreaks, the roles and responsibilities of health officials and providers at the national and subnational levels during an outbreak must be clearly outlined. Below are general necessary functions that should be in place during an outbreak situation but can be adapted to local context.

National level:

- conduct risk assessments and situational analyses to recognize the events and outbreaks in a timely manner;
- notify authorities and the public of the outbreak and coordinate outbreak control measures within the entire country, including with WHO and other partners;
- organize laboratory confirmation of specimens;
- convene a diphtheria outbreak coordination committee and delineate responsibilities;
- forecast for DAT, assess existing DAT stockpiles (as available at the national, regional or global levels) including regulatory approvals with regulatory mechanisms;
- determine the requirements for vaccines, antibiotics and medicines;
- coordinate with all partners to improve the immediate supply of DAT, as and when needed; and
- supervise and monitor field investigations.

District/regional/provincial level:

- support health facilities with case investigations;
- supervise and monitor surveillance, and conduct active case searches and contact tracing with health facilities to enhance surveillance;
- develop micro planning of outbreak investigations, plan appropriate interventions and management based on local epidemiology of the outbreaks;
- perform surveillance and conduct a periodic review of data;
- define the communications strategy needed to increase community awareness on the outbreak and the appropriate response, including vaccination strategies;
- disseminate weekly summaries of diphtheria outbreak surveillance data to relevant government authorities and health facilities during the outbreak;
- appropriately manage contacts, including outbreak response immunization;
- determine the needs of supply and logistics to support the outbreak; and
- communicate with appropriate higher authorities and increase public awareness to prevent further spread.

Health-facility level:

- detect, investigate, notify and report all suspected cases of diphtheria;
- collect specimens for laboratory confirmation;
- intensify surveillance by active case searches and record reviews;
- conduct appropriate management of cases and contacts; and
- refer to higher-level health centres and hospitals for cases that need hospitalization.

Laboratory support

For rapid and efficient laboratory support, the following laboratory preparatory procedures should be identified:

- ensure adequate laboratory capacity in the country and affected areas, including availability of quality laboratory reagents and quality-control systems at the national and subnational levels;
- ensure effective and efficient systems are in place for the transportation of laboratory samples, as required;
- identify national or subnational reference laboratories that can test the specimens; and
- collaborate with reference laboratories (for countries that do not have diphtheria laboratory capacity).

Surveillance

Surveillance for diphtheria should occur at the national, subnational and facility levels. Because diphtheria has become relatively rare, surveillance should be case based. All facilities identifying cases are required to report those cases. Even in countries with aggregate reporting, all outbreaks should be investigated immediately and case-based data should be collected. Laboratory testing of all suspected cases should ideally be conducted for case confirmation.

Training for health care workers

In order to prepare efficient and well-trained staff members – for early detection, including detection of the index case, and for the necessary management and control of outbreaks – it is necessary to conduct training for health care workers in outbreak-prone areas. The components of training may include information on the disease, the standard case definition used in countries, contacts, specimen collection, transportation, laboratory diagnosis and case-control management, including vaccination strategies. The participants should include clinicians from private clinics and laboratories. If resources permit, training community health workers could be beneficial. Ensure all health facilities are provided and aligned with the standard guidelines on case management and public health response. WHO has developed material that can be accessed for diphtheria-related training.

Monitoring and supervision

Periodic monitoring and supervision should be carried out in order to review preparedness, which includes periodic public health risk assessments. Setting specific standards during the implementation of the procedures may help foster qualitative and quantitative measurement of preparedness.

2.6 RESPONSE TO DIPHTHERIA OUTBREAKS

Objectives of response to diphtheria outbreaks

The main objectives of the response to diphtheria outbreaks:

- prevent and minimize the further spread of diphtheria cases;
- prevent complications and deaths by early diagnosis and proper management and treatment;
- assist public health workers in undertaking risk assessment;
- identify high-risk areas and implement appropriate public health control measures, including outbreak response immunization; and
- raise awareness in the community about diphtheria and its prevention.

Risk assessment

A risk assessment should be conducted at the beginning of an outbreak in order to help determine the level of risk to public health and guide the response activities. Prior to conducting the risk assessment, the outbreak coordination committee should ensure that relevant experience and expertise is available within the group to conduct the risk assessment. The risk assessment should utilize multiple sources of information to develop a clear understanding of the hazard, the exposure and the context. Information sources may include aggregate and case-based epidemiological data, vaccination coverage data, census data and other demographic, socioeconomic and geographic information, and information on health system capacity and function. When conducting a risk assessment for diphtheria, specific information that may be utilized to determine the burden of the disease and the degree of endemicity could include information on cases, as well as various other indicators such as national and subnational immunization coverage data and contributing causes, including hesitancy groups, mobile and ethnic populations, booster doses according to national schedules, dropout rates with diphtheria, pertussis and tetanus (DTP1) and DTP3, socioeconomic and living conditions (overcrowding), high-risk areas identified in micro-plans and access to health services.

After collecting and assessing this information, the next step would be to categorize areas of high and low risk in terms of vulnerability and to optimize planning so that resources and appropriate responses are directed towards the vulnerable areas. However, structured risk assessments can be conducted as routine periodic activity to inform and help target preparedness measures. This could be a joint effort while conducting EPI reviews and VPD surveillance assessments in countries with high-risk areas, such as increased disease incidence, low immunization coverage and migrating populations.

Notification of an outbreak

Once a diphtheria outbreak is confirmed, health-centre staff should immediately notify the next higher administration level, for example, the district or province, using the quickest available means of communication. The immediate notification report should include information on the number of cases and deaths by age group, vaccination status and date of onset (first day of sore throat), hospitalization and treatment (use of antibiotics and DAT), geographical location of the outbreak, and the activities planned to investigate and manage the outbreak. If cases are reported along border areas, health officials in the adjoining areas should be notified and efforts should be made to share information.

Detailed case investigation

Obtain information from each case (name, address, age, sex, vaccination status, date of last vaccination, date of onset, symptoms, date of specimen collection, treatment and outcome), which should be added to the case investigation form and compiled into a case line list. All the close contacts should be identified and also compiled into a contact line-list form. The data should be rapidly analysed as reliable information that can guide appropriate actions.

Contact management

The management of close contacts of a confirmed case of diphtheria includes three main components: contact follow up, prophylaxis with appropriate antibiotic and vaccination for the unvaccinated or partially vaccinated.

- Monitor close contacts for signs and symptoms for 10 days from the date of the last contact with a suspected case. At a minimum, close contacts are considered to be household members and others with a history of direct contact with a case. These may include caretakers, relatives, sexual contacts, fellow students and friends who regularly visit the home. Medical staff exposed to the case's oral or respiratory secretions or exposed to their wound should also be monitored. Ideally, surveillance staff should communicate daily with contacts to monitor for new symptoms, but the extent of monitoring is determined by public health resources. Take one nasal swab and one pharyngeal swab from all close contacts before starting antibiotic prophylaxis.
- Prophylactic antibiotics (penicillin or erythromycin) are indicated for close contacts for 7 days. If the culture is positive for toxigenic *Corynebacterium spp.*, then the contact should be treated as a case with an antibiotic course for 2 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.
- If the culture is positive for non-toxigenic *Corynebacterium spp.*, the contact should complete the course of antibiotics and be retested, though this is not classified as a laboratory-confirmed case.
- If the result is negative for *Corynebacterium spp.*, antibiotics and monitoring can be stopped.
- DAT is not recommended as post-exposure prophylaxis among contacts, as evidence of its benefit is limited. Assess diphtheria vaccination status of close contacts.
- Unvaccinated contacts should receive a full course of diphtheria toxoid-containing vaccine. Under-vaccinated contacts should receive the doses needed to complete their vaccination series.

Identification of contacts

The close contacts include:

- household members (all persons who slept in the same house/tent during the last 5 nights before onset of the case);
- any persons with a history of direct contact with the case; and
- health care workers exposed to oral or respiratory secretions or wound of a case-patient;
- at-risk contacts. For this eligible 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 the likely level of risk and need for prophylaxis.

Examples of such contacts include:

- friends, relatives, and caregivers who regularly visit the home;
- school/preschool class contacts;
- those who share the same room at work; and
- other health care workers who have had contact with the case.

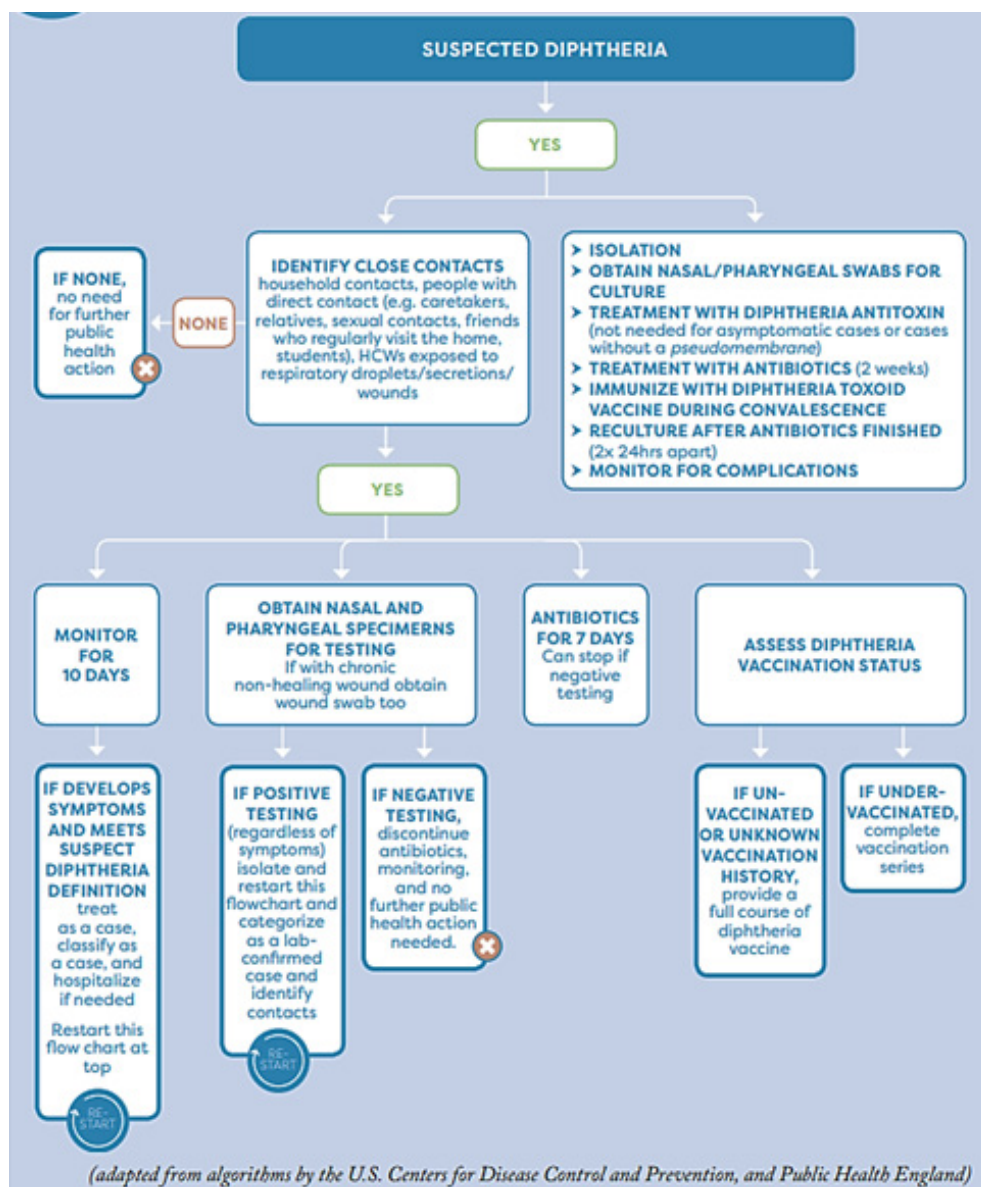
During identification of contacts, asymptomatic carriers and mild respiratory cases without pseudomembranes or non-respiratory manifestations of disease could be identified. Asymptomatic carriers, rather than people with overt disease, are usually the major source of transmission during community outbreaks. They should be identified and counted as laboratory-confirmed cases. They should be treated as outlined in Section 5 (Management and treatment of diphtheria) but do not require hospitalization.

Laboratory investigation of close contacts and eligible at-risk contacts

Two specimens for culture must be obtained from all close contacts and eligible at-risk contacts, one nasal swab and one pharyngeal swab before starting antibiotic prophylaxis.

- If the culture is positive for toxigenic *C. diphtheriae*, then the contact should be treated as a case and a new investigation of contacts should be undertaken, and proper case management should be implemented. These are classified as laboratory-confirmed cases.
- If the result is negative for *C. diphtheriae*, these contacts can stop antibiotics and monitoring.
- If the culture is positive for non-toxicogenic *C. diphtheria*, these contacts should complete the course of antibiotics and be retested, although this will not be counted as a case as it is non-toxicogenic.

Fig. 8 Diphtheria case management and contact management



Intensification of surveillance

During an outbreak, surveillance should be intensified to ascertain the size and the geographical extent of the outbreak. The following steps should be taken to intensify surveillance to actively seek additional cases:

- institute case-based reporting of all cases from all reporting sites;
- institute weekly reporting, regardless of frequency of reporting prior to the outbreak;
- conduct regular visits to schools, hospitals and private clinics to find additional cases; and
- if time and resources permit, additional case finding should be conducted in communities and health facilities in affected areas including:
 - active case searches for cases in the communities, with health care workers usually going door to door asking about suspected diphtheria cases; and
 - retrospective record searches in hospitals and clinics, including private facilities to review registers and records for additional case findings.

Communication for health

Before and during an outbreak, populations should understand the risks and how to protect themselves. Strategic communication, which addresses community concerns and gaps in knowledge, is a key intervention for protecting health. Using a Communication for Health (C4H) approach and ensuring the regular flow of accurate information as it becomes available can empower people to make healthy choices for themselves, their families and communities. Credibility and trust in institutions, messengers and the information they deliver are developed over time. A foundation must be built during “peacetime”; and built upon in crisis.

Recommended activities include:

- risk communications and community engagement activities, led by the ministry of health and in collaboration with partners, who are evidence-based, grounded in listening, respond to concerns, rumours, mis/disinformation and meet the needs of affected communities;
- engage with communities through multiple, trusted online and offline channels with messages and formats that are targeted and people-centred;
- leverage existing networks to mobilize supportive, trusted voices to encourage health protective behaviours such as hand hygiene and cough etiquette, to reach at-risk populations such as school children and health care workers;
- measure, evaluate and learn from C4H activities to maximize outcomes and impact.

Reactive vaccination

In the event of an outbreak, selective vaccination campaigns targeting at-risk populations, including health care workers and other outbreak responders, should be considered. In an outbreak setting with poorly vaccinated populations at high risk, the capacity to carry out a high-quality mass vaccination campaign should be rapidly evaluated. Vaccination strategies should be based on the epidemiology of the disease – for instance, age groups or special populations – targeting the affected and high-risk areas. Countries should plan preparation and implementation periods, number of rounds, budgets and the possibility of integration with other health interventions. Several vaccination strategies can be employed, such as door-to-door vaccinations, fixed vaccination posts and in-school vaccinations.

- The timing of the intervention is important and should be carried out immediately after a decision has been made. The timing of the intervention plays a key role in the number of cases and deaths that may potentially be prevented.
- The target age group depends on the susceptibility profile of the population, and the key factors to be considered are routine vaccination coverage in each birth cohort, the absolute number of cases in age-specific groups and previous supplemental immunization activities (SIAs). Once the age group targeted for vaccination is determined, all people in that age group should be vaccinated regardless of their previous vaccination status.
- The target area for vaccination response should include both outbreak-affected areas and adjacent high-risk areas. Immunization teams should pay particular attention to ensure that groups and areas with a high likelihood of not being reached, such as those with known low coverage, migrating populations and those residing in urban slums are vaccinated. During outbreaks in border areas, efforts should include cross-border sharing of information and, if possible, synchronization of vaccination activities.

Reinforcement of routine immunization

A diphtheria outbreak provides an opportunity to identify immunization programme weaknesses and correct them. The following steps should be taken to reinforce routine immunization:

- revisit and strengthen the affected district and health-facility micro-plans;
- analyse DTP1 coverage data and dropout rate (compare DTP1 with DTP3) to identify issues with access and utilization of routine immunization services and design activities in response;
- locate health centres conducting fixed immunization sessions that may need additional resources (vaccinators, vaccines or cold chain logistics);
- organize corrective measures such as additional outreach services for mobile camps and communities with a high proportion of unreached children;
- track and vaccinate missed children using the defaulter tracking monitoring system;
- conduct rapid coverage assessments for routine immunization in the affected and high-risk areas;
- implement catch-up vaccination strategies for missed children, such as routine immunization intensification, selective SIAs and other activities; and
- find opportunities to further strengthen routine immunization, such as the World Immunization Week and the periodic intensification of routine immunization.

III. Appendices

APPENDIX 1. OPERATIONAL PROTOCOL FOR CLINICAL MANAGEMENT OF DIPHTHERIA—ADPATED FROM THE 2017 COX’S BAZAR, BANGLADESH, DAT PROTOCOL

Antitoxin therapy (DAT): administer as soon as possible.

1. DAT is an equine serum product that is highly effective and the gold standard for treatment of diphtheria. (7)
2. DAT should be administered **immediately** to probable cases with respiratory diphtheria (sore throat, low grade fever and presence of adherent membrane on tonsils, pharynx or nose) based on clinical diagnosis. Do not wait for laboratory diagnosis.
(Probable Case 2. A person with an illness characterized by laryngitis or pharyngitis or tonsillitis, and an adherent membrane of the tonsils, pharynx and/or nose OR gross lymphadenopathy).
3. Diphtheria toxin that has already entered the host cells is unaffected by DAT. Therefore, to reduce complications and mortality, DAT should be administered as soon as possible after disease onset (see Appendix D)
4. DAT should be administered in a closely monitored setting with appropriate and available medical interventions as needed.
5. Pregnant women should not receive DAT.
6. The amount of antitoxin recommended varies; larger amounts are recommended for persons with extensive pseudomembrane, neck swelling, systemic signs and a longer interval since onset. The dose is the same for children and adults. Do not repeat dosing. **When in limited availability, use the lower dose range.**

How to deliver DAT

Dose. The amount of antitoxin recommended varies; larger amounts are recommended for persons with extensive local lesions and a longer interval since onset. The dose is the same for children and adults. Do not repeat dosing. When in limited availability, use the lower dose.

Diphtheria clinic presentation	DAT dose (units)	Route
Nasal	10 000–20 000	Intramuscular
Nasopharyngeal	40 000–60 000	Intramuscular
Tonsillar	15 000–25 000	Intramuscular or intravenous
Pharyngeal/laryngeal Laryngeal or pharyngeal of 2-day duration	20 000–40 000	Intramuscular or intravenous
Combined/delayed diagnosis	40 000–60 000	Intravenous
Extensive disease 3 or more days of duration of any patient with diffuse swelling of the neck (respiratory distress or haemodynamic instability)	80 000–10 0000	Intravenous
Skin lesions only (rare case where treatment is indicated above)	20 000–40 0000	Intramuscular or intravenous

Route. The IV route is the preferred route of administration of DAT, especially in severe cases. The antitoxin dose should be mixed in 250–500 mL of normal saline and administered slowly over 2–4 hours, closely monitoring for anaphylaxis. The antitoxin may be given IM in mild or moderate cases.

Temperature. Antitoxin should be warmed to 32–34 °C (90–95 °F) before injection.

Environment. Ensure that appropriate monitoring and medical interventions are available for adult and paediatric patients in case serious allergic reaction ensues.

- Monitoring devices: pulse oximeter, blood pressure (BP) cuff and thermometer.
- Emergency medicines: adrenaline (1:1000), salbutamol, antihistamine, prednisolone, crystalloid fluid, oxygen supply and delivery devices.
- Emergency equipment: bag valve mask, IV giving devices, airway management.

Procedure

1. Health care worker uses contact and droplet precautions: gloves, long-sleeved gown, surgical mask and eye protection.
2. Monitor patient's vital signs: BP, heart rate (HR), respiratory rate (RR), saturation of peripheral oxygen (SpO₂) and mental status before and after administration.
3. Perform sensitization testing.

Monitor for adverse events. If noted, then stop administration immediately.

Adverse event	Clinical description
Anaphylaxis (rapid onset)	Onset usually within minutes. <ul style="list-style-type: none"> • Skin: pruritus, flushing, urticaria and angioedema. • Respiratory: hoarse voice and stridor, wheeze, dyspnoea and cyanosis. * • Cardiac: rapid, weak pulse, hypotension and arrhythmias. Anaphylaxis is a major medical emergency, call for help.
Febrile reaction (within 20–60 minutes)	When fever occurs, it is characterized by a chilly sensation, slight dyspnoea and a rapid rise in temperature. Most febrile reactions are mild. Treat with antipyretics alone (that is, paracetamol); severe reactions may require other measures (tepid water baths, among other things) to reduce the temperature.
Serum sickness (usually 7–10 days after initial exposure, range 5–25 days)	Symptoms are fever, maculopapular skin rashes or urticaria in milder forms (90% of instances); arthritis, arthralgia and lymphadenopathy are also possible in more severe forms. Rarely, angioedema, glomerulonephritis, Guillain-Barre syndrome, peripheral neuritis or myocarditis can occur. Mild cases of serum sickness frequently resolve spontaneously over a few days to 2 weeks. Medications that may be helpful include antihistamines, non-steroidal anti-inflammatory drugs and corticosteroids.

Treatment of anaphylaxis**If anaphylaxis occurs, STOP infusion.**

1. Call for help.
2. Assess the airways, breathing and circulation. Start emergency treatments—if the child is not breathing, check pulse. If there is no pulse, start basic life support and give five rescue breaths with a bag-valve mask and 100% oxygen.
3. Give adrenaline (1:1000, 1 mg/mL) IM immediately:
 - 0.15 mL of 1:1000 to children < 6 years, repeat every 5 minutes as necessary
 - 0.3 mL of 1:1000 to children 6–12 years, repeat every 5 minutes as necessary
 - 0.5mL of 1:1000 epinephrine to adolescents and adults, repeat every 5 minutes, as necessary.
4. Ensure stabilization of airway, breathing and circulation.
 - Get IV/ intraosseous infusion (IO) access, give 100% oxygen, give crystalloid fluid (20 mL/kg IV) rapidly for shock and nebulized salbutamol for wheezing.
5. Also give antihistamine and steroids (that is, prednisolone 1 mg/kg).

Antibiotic treatment for probable and confirmed cases: antibiotics should be administered as soon as possible.

1. For patients who cannot swallow or are critically ill, use IV or IM preparations.
2. For severely ill patients unable to take oral therapy, use IV/IM formulation at the onset. Once the patient improves clinically, step down to oral antimicrobials.
3. For less sick patients, oral therapy can be used at the onset.
4. Check for penicillin allergy (risk of anaphylaxis from penicillin is very rare).

Disease severity	Antibiotic/ROA	Dosage (Treat for 14 days)
Less ill and able to swallow	Oral phenoxymethylpenicillin V	All persons 50 mg/kg/day, administer in divided dose 10–15 mg/kg/6hrly
	Oral erythromycin	All persons: 40–50 mg/kg/day (maximum, 2 gm/day). Administer in divided dose, 10–15 mg/kg every 6 hour, maximum 500 mg per dose.
	Oral azithromycin	Children: 10–12 mg/kg once daily (max. 500 mg/day). Adults: 500 mg once daily.
	Oral Clindamycin	Adults: 150–300 mg 6hrly. Children: 25 mg/kg/day 6hrly.
Severely sick	Procaine benzyl penicillin (penicillin G): administer IM	All persons: 50 mg/kg once daily (maximum 1.2 grams a day)
	Aqueous benzyl penicillin (penicillin G): administer IM or slow IV	All persons: 100 000 units/kg/day administer in divided dose of 25 000 IU/kg every 6 hours. Maximum dose is 4 MIU or 2.4 grams per day
	IV erythromycin	All persons: 40–50 mg/kg/day (maximum, 2 gm/day). Administer in divided dose, 10–15 mg/kg every 6 hour, maximum 500 mg per dose.
	Clindamycin IM/IV	Adults: 600–1200 mg in 2–4 divided doses. Children: 15–25 mg/kg in 3–4 divided doses.

Supportive therapy for patients with complications

Monitor the patient closely

1. The patient's condition, especially respiratory status, should be assessed often, at least every 2–4 hours, for any signs of respiratory distress from the development of airway obstruction or aspiration. This includes vital signs and pulse oximetry.
2. Also monitor cardiac function with ECG for conduction abnormalities and arrhythmias (if possible).

If patient shows any sign of inspiratory stridor, fast respiratory rate, chest in-drawing, restlessness, lethargy or cyanosis, then call for help and proceed with airway management.

Oxygen therapy can mask airway obstruction, use with caution

1. Avoid using oxygen routinely. Signs of respiratory distress (such as fast respiratory rate, severe lower chest wall in-drawing and restlessness) are signs of requiring airway support; proceed to secure airway. Desaturation in isolated upper airway obstruction is a sensitive sign for impending airway compromise and deterioration. If there is desaturation (SpO₂ < 90%), this is a sign that the airway is obstructing and you need to act to secure the airway. Use oxygen while you are in the process of securing the airway.

2. Administer oxygen if there is incipient airway obstruction and securing airway is deemed necessary and soon to be performed or if SpO₂ < 90%.
Avoid pharyngeal irritating interventions such as routine use of nasogastric tubes and nasopharyngeal catheters. Even placement of a nasal cannula may disturb child and precipitate obstruction of the airway.

If signs of airway compromise, proceed to secure airway (see Appendix D). Securing airway is a life-saving intervention. Call for help immediately.

1. Securing the airway is a life-saving intervention. Consult a senior doctor with extensive experience in difficult airway management immediately. This includes an anaesthetist, intensivist, surgeon (preferably, an ears, nose and throat (ENT) surgeon). Tracheostomy in infants carries significant risks, so it should be done with great caution by skilled surgeons.
2. If there are signs of incipient (impending) complete airway obstruction (signs of respiratory distress such as inspiratory stridor, fast respiratory rate, restlessness, chest wall in-drawing, accessory muscle use and desaturation), then secure airway immediately. If skilled personnel are available, take patient to operating theatre. A graded approach is recommended, with an orotracheal approach preferred (when possible); always use a difficult airway algorithm. If the airway is not secured with an orotracheal approach, then proceed to tracheostomy (if experienced surgeon is available) or needle cricothyroidotomy (as a temporizing emergency procedure until tracheostomy can be performed by emergency procedure).
3. If the patient develops complete airway obstruction (cyanosis, SpO₂ < 90–94, lethargy), then perform an emergent tracheostomy (if experienced surgeon is available) or needle cricothyroidotomy (temporizing emergency procedure). Under such circumstances, orotracheal intubation may not be possible and may dislodge the membrane and fail to relieve the obstruction, and should only be performed by skilled personnel. Once attempted, be prepared also to perform emergent airway procedure.
4. Administration of nebulized adrenaline is used in many causes of upper airway obstruction as a temporizing measure. Though specific data on its efficacy in acute respiratory diphtheria is not available, consider its use for upper airway obstruction. As a trial, administer nebulized adrenaline (2 mL of 1:1000 solution). Can be repeated hourly if effective.

Manage shock

1. A child with all signs of shock (delayed capillary refill (CR) > 3 seconds + weak and fast pulse + cold extremities or frank hypotension) needs careful resuscitation. Because shock can be due to sepsis or cardiac failure, it is imperative to look for signs of cardiac failure. In addition, also check if the child has severe malnutrition. If there are no signs of cardiac failure and/or fluid overload (absence of crackles, hepatomegaly and oedema), then give gentle fluid bolus. If the suspect shock is due to heart failure, then use inotropes (such as dopamine or adrenaline) and do not administer fluids. Refer to the WHO Integrated Management of Childhood Illness (IMCI) handbook for sick children.

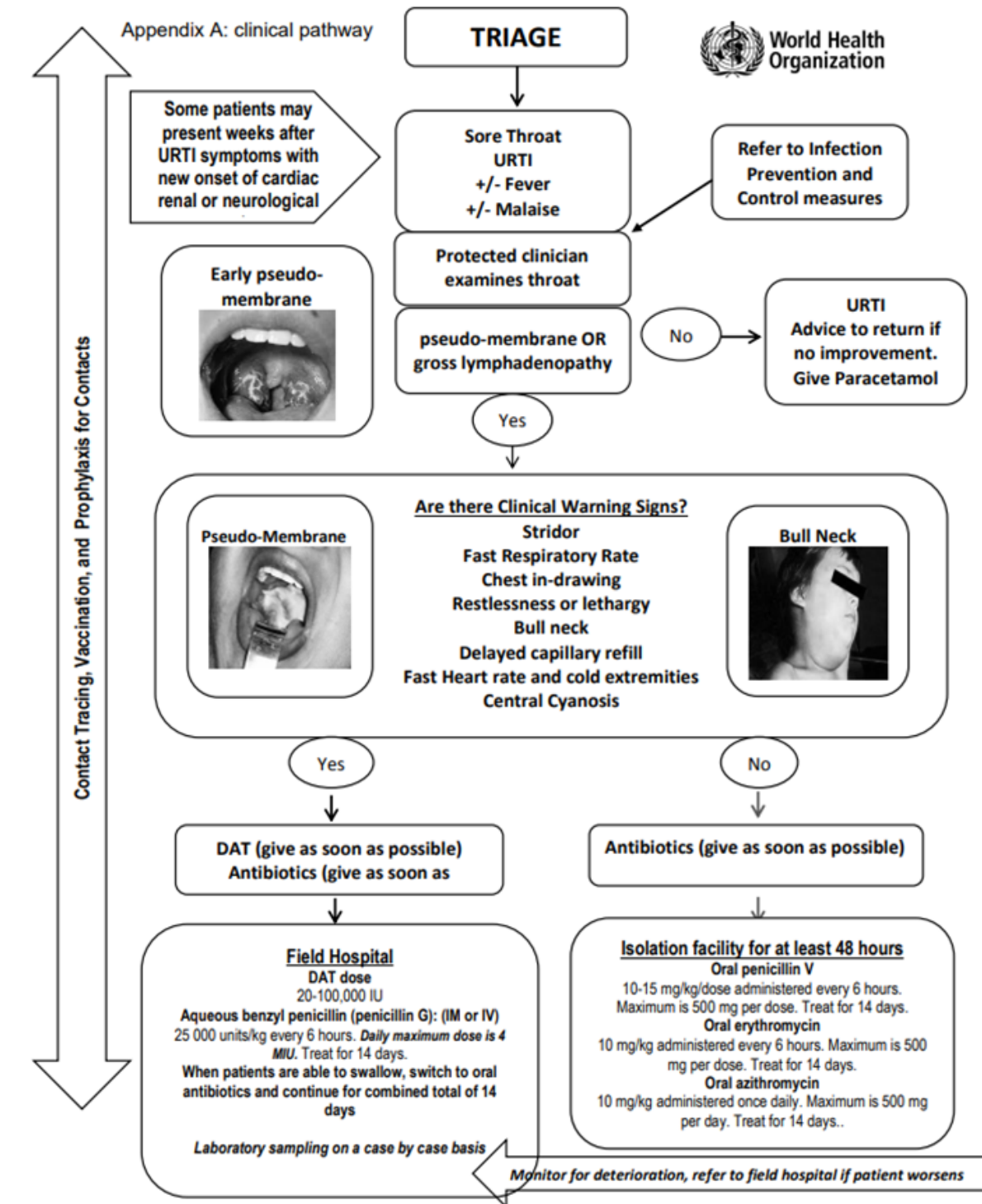
Other supportive treatments

1. If the patient has fever (>38 °C) or pain that appears to be causing distress, give paracetamol.
2. Encourage the child to eat and drink. If the child has difficulty in swallowing, nasogastric feeding may be required. The nasogastric tube should be placed with extreme caution by an experienced clinician or, where available, an anaesthetist.
3. Avoid frequent examinations and invasive procedures when possible or disturbing the child unnecessarily.

Myocarditis (which may occur 2–7 weeks after the onset of illness) can present with a weak, irregular pulse and evidence of heart failure. Treat with supportive therapies according to national standards.

Neurologic paralysis (may occur 1 to 3 months after the onset of the disease) and can lead to difficulty with swallowing (paralysis of the soft palate), vision (ocular motor paralysis), breathing (paralysis of respiratory muscles) and ambulation (limb paralysis). Treat with supportive therapies according to national standards.

APPENDIX 2: TRIAGE AND CLINICAL PATHWAY



APPENDIX 3: SUGGESTED KEY PERFORMANCE INDICATORS (KPI)

Diphtheria prevention and control management should be evaluated at least yearly to ensure that the country is able to meet expected objectives accurately. To assess the effectiveness of the overall diphtheria outbreak response, these are complemented by key performance indicators (KPIs), which measure the output or outcome level.

The KPIs will be agreed upon on a case-by-case basis. They are typically reported weekly during outbreak and can be adjusted based on the evolution of the emergency. Below are suggested performance indicators.

N	Indicator	Target	How to calculate (Numerator/denominator)	Comments
1	Percentage of all suspected diphtheria cases that have had an investigation initiated within 48 hours of notification	≥ 80%	Number of suspected cases of diphtheria for which an investigation has been initiated within 48 hours of notification/ number of suspected diphtheria cases x 100	Timeliness of investigation
2	Percentage of suspected diphtheria cases with two specimens collected (pharyngeal swab and nasal swab)	≥ 80%	Number of suspected cases of diphtheria with two specimens collected/number of suspected diphtheria cases x 100	Specimen collection. During outbreak investigations where epidemiological linkage increases, epidemiologically linked cases should be removed from the denominator.
3	Percentage of suspected diphtheria cases with specimens taken before antibiotic administration	≥ 80%	Number of suspected cases of diphtheria with a specimen collected before antibiotics/ number of suspected diphtheria cases with a specimen collected x 100	Timeliness of sample collection
4	Percentage of specimens tested for toxigenicity by Elek testing	≥ 80%	Number of specimens tested for toxigenicity by Elek testing/ number of specimens received x 100	Toxigenicity testing rate. Indicator only applies to public laboratories
5	Percentage of specimens received at the laboratory within 2 days of collection	≥ 80%	Number of specimens received within 2 days of collection by laboratory/number of specimens x 100	Timeliness of specimen transport. Indicator only applies to public laboratories
6	Percentage of specimens tested by culture with results reported within 3 days of receipt of specimen	≥ 80%	Number of specimens tested by culture with results reported within 3 days of specimen receipt/number of specimens tested by culture x 100	Timeliness of reporting laboratory results.

7	Percentage of antibiotic susceptibility testing of specimens with suspected colonies performed		Number of specimens tested for antibiotic susceptibility testing/number of specimens received x 100	Antibiotic susceptibility testing of suspected colonies can be done as an ancillary test to inform programmes on antibiotic treatment of cases and contacts.
8	Percentage of diphtheria cases (1) confirmed by culture and caused by toxigenic <i>Corynebacterium</i> species OR (2) based on clinical diagnosis with evidence of toxin production (including the presence of adherent membrane on tonsils, pharynx, and/or nose, or gross lymphadenopathy) that received DAT in hospital settings	≥ 80%	Number of laboratory-confirmed and clinical diphtheria cases with evidence of toxin production that received DAT/number of reported diphtheria cases caused by toxigenic <i>Corynebacterium</i> species x 100	Effective use of DAT. <i>DAT should be administered immediately to probable cases with respiratory diphtheria (sore throat, low grade fever and presence of adherent membrane on tonsils, pharynx or nose) based on clinical diagnosis. Do not wait for laboratory diagnosis.</i>
9	Percentage of close contacts of diphtheria cases with two specimens collected (pharyngeal swab and nasal swab) taken before antibiotic administration	≥ 80%	Number of close contacts of diphtheria cases with two specimens collected/number of close contacts x 100	This is part of the contact tracing. Priority should be given to contacts becoming suspected cases with the onset of signs or symptoms.
10	Percentage of close contacts of diphtheria cases that received antibiotics prophylaxis for 7 days	≥ 85%	Number of close contacts of diphtheria cases that received antibiotics prophylaxis for 7 days/number of close contacts x 100	Post-exposure antibiotics prophylaxis of close contacts of diphtheria cases
11	Percentage of close contacts of diphtheria cases that completed at least three doses of diphtheria-containing vaccines	≥ 85%	Number of close contacts of diphtheria cases that completed at least three doses of diphtheria-containing vaccines/number of close contacts x 100	Provide a full course of diphtheria vaccine to all unvaccinated or unknown vaccination history
12	Case fatality ratio	≤ 5 –10%	Number of diphtheria-related deaths reported/number of diphtheria cases reported x 100	Provide a full course of diphtheria vaccine to all unvaccinated or unknown vaccination history

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