

Field Guide for Preparedness and Response to Diphtheria Outbreaks in the Western Pacific Region



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Abbreviations

CFR	case fatality rate
DAT	diphtheria antitoxin
DT	diphtheria-tetanus vaccine
DTP	diphtheria-tetanus-pertussis
DTP1	first dose of diphtheria-tetanus-pertussis-containing vaccine
DTP3	third dose of diphtheria-tetanus-pertussis-containing vaccine
ECG	electrocardiography
EPI	Expanded Programme on Immunization
IM	intramuscular
IV	intravenous
JRF	joint reporting form
PCR	polymerase chain reaction
SC	subcutaneous
SIA	supplementary immunization activity
SOP	standard operating procedure
Td	tetanus and low-dose diphtheria toxoid
Tdap	Td with acellular pertussis vaccine, adult formulation
UNICEF	United Nations Children's Fund
USCDC	United States Centers for Disease Control and Prevention
VPD	vaccine-preventable disease
WHO	World Health Organization

About this Guide

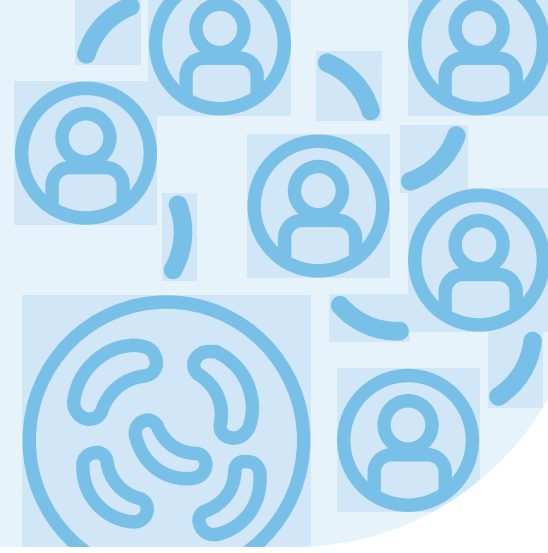
This *Field Guide for Preparedness and Response to Diphtheria Outbreaks in the Western Pacific Region* is a reference resource for Member States to develop national guidelines adapted to their local context.

Countries may also use this Guide to facilitate outbreak preparedness and public health responses to reduce morbidity and mortality due to diphtheria.

A vaccine-preventable disease outbreak necessitates coordination among the departments of disease control, laboratories and the Expanded Programme on Immunization. The level of coordination among various departments and users of this Guide at different levels will be the decision of ministries of health.

1

Background



Diphtheria is an acute communicable upper-respiratory illness caused by the *Corynebacterium* species, mostly by toxin-producing *Corynebacterium diphtheriae*, and rarely by toxin-producing strains of *C. ulcerans* and *C. pseudotuberculosis*. *C. ulcerans* and *C. pseudotuberculosis* are zoonotic infections and are not transmitted from person to person.

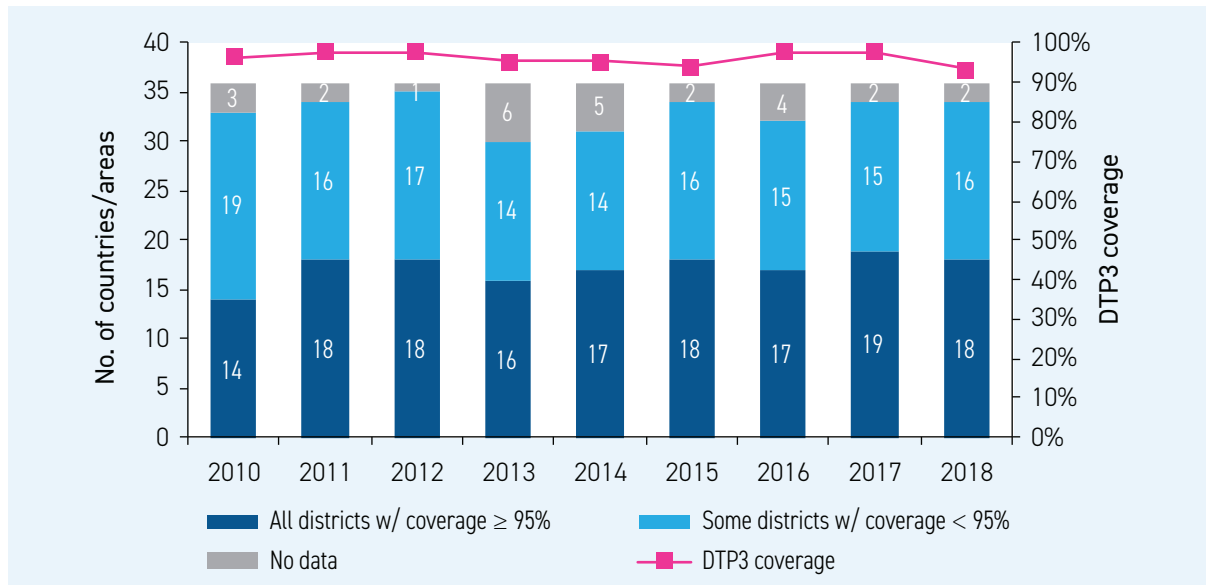
This *Field Guide for Preparedness and Response to Diphtheria Outbreaks in the Western Pacific Region* examines *C. diphtheriae* most commonly presented as a membranous pharyngitis, although other presentations such as cutaneous disease also occur. The organism produces a powerful exotoxin that causes necrosis of the respiratory mucosa and formation of a pseudomembrane that firmly adheres to the underlying mucosa. Expansion of the pseudomembrane may lead to respiratory obstruction. Absorption of diphtheria toxin can cause myocarditis, leading to heart failure and death. In the era before there was a diphtheria antitoxin (DAT), the case fatality rate (CFR) for diphtheria was as high as 50%, but it is currently estimated as 5-10% (1).

When the World Health Organization (WHO) Expanded Programme on Immunization (EPI) was launched in 1974, with diphtheria vaccine as one of the original six EPI antigens, the incidence of diphtheria worldwide dramatically decreased. The patterns of epidemiology have changed over time. A recent review of global diphtheria epidemiology, which included an analysis of cases and information about age, showed age distribution shifts and found that the majority of cases occur in adolescents and adults (2). An age shift in cases from children to adolescents and adults was observed from countries in the WHO Western Pacific Region such as the Lao People's Democratic Republic (3), the Philippines (2) and Viet Nam (4). People, especially children, who are not vaccinated or are partially vaccinated against diphtheria are most at risk of diphtheria. Adolescents and adults are also at risk, as immunity is known to wane in late childhood or adolescence if the last dose was given during the first year of life (5).

1.1 Immunization in the Western Pacific Region

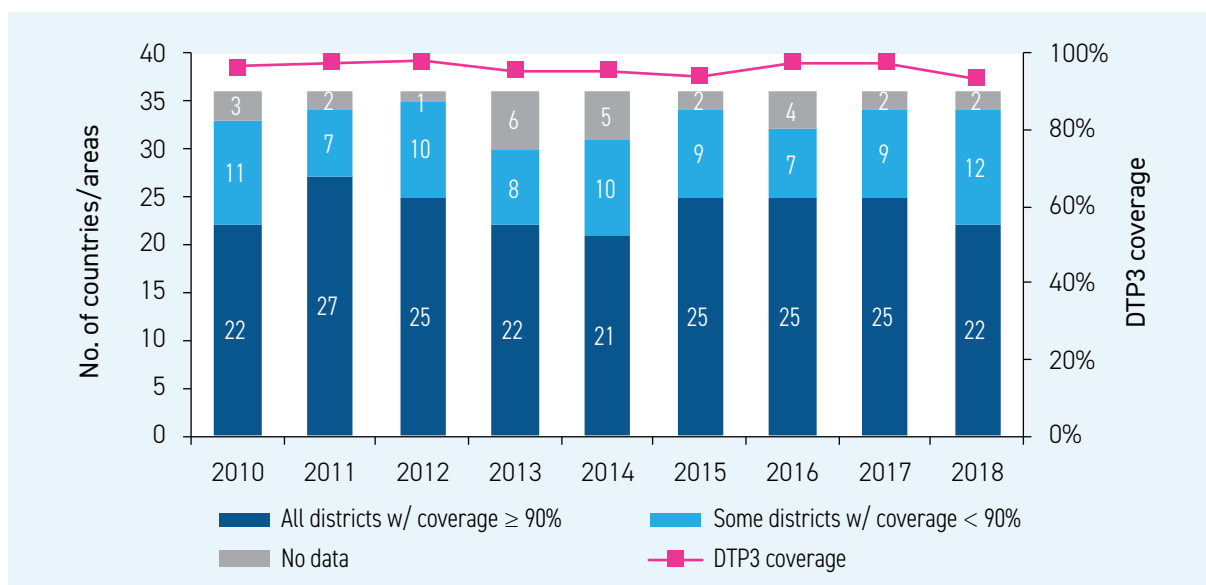
The *Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific* set regional vaccination coverage targets for 2020 to reduce morbidity and mortality from vaccine-preventable diseases (VPDs) including diphtheria. The proposed targets are: (i) reach $\geq 95\%$ national coverage for all vaccines used in national immunization programmes; and (ii) reach $\geq 90\%$ coverage in every district or equivalent administrative unit for all vaccines used in national immunization programmes (6). The achievements with a third dose of diphtheria-tetanus-pertussis-containing vaccines (DTP3) from 2010 to 2018 are illustrated in Figs. 1 and 2.

FIG. 1. Number of countries and areas in the Western Pacific Region reaching $\geq 95\%$ DTP3 national coverage and regional DTP3 coverage



Source: WHO Immunization Data Portal Diphtheria Tetanus Toxoid and Pertussis (DTP) vaccination coverage. 2018. (7)

FIG. 2. Number of countries and areas in the Western Pacific Region reaching $\geq 90\%$ DTP3 coverage in every district and regional DTP3 coverage



Source: WHO Immunization Data Portal Diphtheria Tetanus Toxoid and Pertussis (DTP) vaccination coverage. 2018. (7)

Immunization coverage in the Western Pacific Region has remained high with DTP3 coverage ranging from 93% to 98% from 2011 to 2018. However, the immunization coverage is uneven

across geographical areas, with a considerable proportion of unimmunized children, which is one of the risk factors for the occurrence of diphtheria outbreaks. In the Lao People's Democratic Republic, despite a steady increase, DTP3 coverage was only 84% in 2018. The Philippines experienced a stock-out of diphtheria-tetanus-pertussis (DTP) vaccine, resulting in DTP3 coverage of 55% in 2015, although the gaps were partially filled through a catch-up immunization targeting children up to 2 years old. In Papua New Guinea, DTP3 coverage has been consistently below 70% (Table 1).

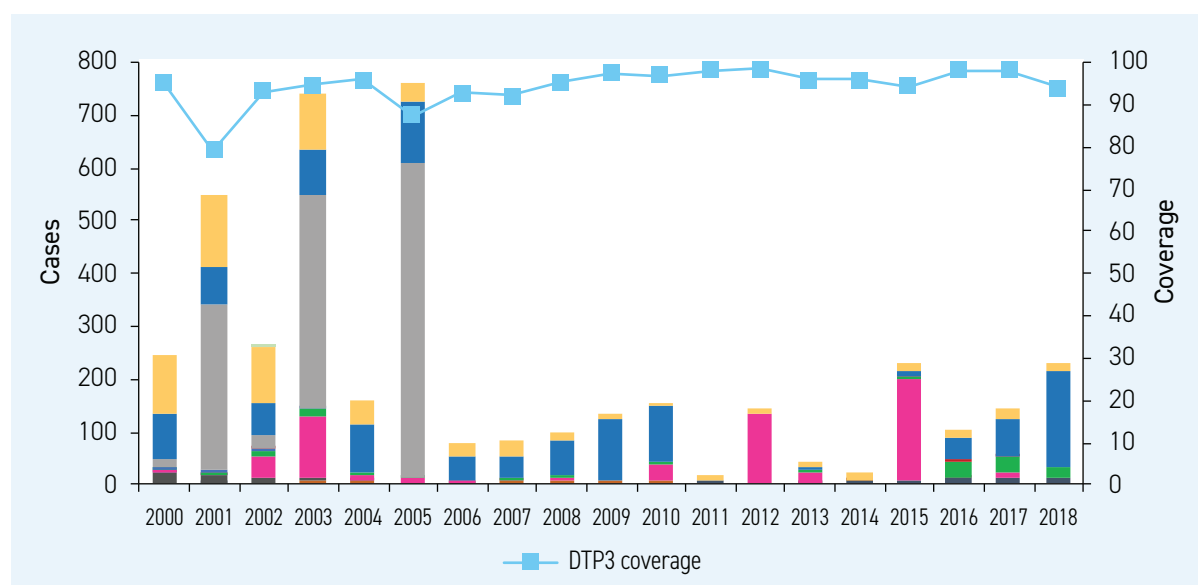
TABLE 1. Countries with reported DTP1 (1 dose), DTP3 (3 doses) coverage below 90%, Western Pacific Region, 2010–2018, by percentage

Country	2010		2011		2012		2013		2014		2015		2016		2017		2018	
	DTP1	DTP3	DTP1	DTP3	DTP1	DTP3	DTP1	DTP3	DTP1	DTP3	DTP1	DTP3	DTP1	DTP3	DTP1	DTP3	DTP1	DTP3
Lao People's Democratic Republic	81	74	83	78	87	79	89	87	94	88	93	89	85	82	89	85	86	84
Malaysia	95	95	96	100	95	100	97	97	93	97	95	99	88	95	93	99	95	100
Pacific island countries and areas	91	88	93	90	95	90	94	89	94	88	96	91	96	89	95	90	88	84
Philippines	81	79	92	88	91	88	93	89	78	72	64	55	87	91	89	88	66	65
Papua New Guinea	84	70	83	61	85	63	88	68	87	62	83	62	87	61	69	51	67	50
Viet Nam	93	93	97	95	99	97	83	59	95	95	98	97	96	96	98	94	79	75

Source: WHO Immunization Data Portal Diphtheria Tetanus Toxoid and Pertussis (DTP) vaccination coverage. 2018. (7)

1.2 Diphtheria in the Western Pacific Region

Information on diphtheria incidence is available through the WHO/United Nations Children's Fund (UNICEF) Joint Reporting Form (JRF) on immunization, with the annual number of cases reported from each country. Additional information is occasionally available from outbreak investigations. The number of cases reported from countries in the Region since 2000 are summarized below (Fig. 3, Table 2). There are countries such as Australia, China and Japan with few or no cases reported in recent years and with consistently high DTP3 coverage, suggesting the disease is under control. However, in countries such as the Lao People's Democratic Republic, Malaysia, the Philippines and Viet Nam, cases have been consistently reported over the years, with periodic outbreaks. In Papua New Guinea, no cases have been reported since 2005 despite low coverage.

FIG. 3. Number of cases of diphtheria and DTP3 coverage, Western Pacific Region, 2000–2018*


The colours in the graph represent countries indicated in Table 2.

* Includes all cases confirmed by laboratory testing or epidemiological linkage, plus those clinical cases that were reported without a laboratory specimen or epidemiological linkage.

Source: WHO Immunization Data Portal Diphtheria reported cases and incidence. 2018. (8)

TABLE 2. Number of cases* of diphtheria by countries, Western Pacific Region, 2000–2018

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
AUS	0	1	0	0	0	0		0	0	0	0	4	0	1	2	2	8	8	11
KHM	0	0	0	3	4	0	0	5	7	3	3	0	0	0	0	0	0	0	0
CHN	19	12	11	9	2	0	1	0	0	0	0	0	0	0		0	0	0	0
JPN	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LAO	3	2	40	116	11	9	2	2	2	0	34	0	130	20	0	194	3	10	0
MYS	1	4	7	11	3	3	0	2	4	0	3	0	0	4	2	4	31	32	18
MNG	4	6	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NEZ	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2	2	1	1	0
PNG	15	311	26	403	0	593	0	0	0	0	0	0	0	0	0	0	0	0	0
PHL	88	73	62	88	89	118	47	39	65	118	107	0	0	6	0	9	42	68	183
VNM	113	133	105	105	49	36	25	32	17	8	6	13	12	11	16	15	13	21	13
VUT	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Note: AUS = Australia, KHM = Cambodia, CHN = China, JPN = Japan, LAO = Lao People's Democratic Republic, MYS = Malaysia, MNG = Mongolia, NZL = New Zealand, PNG = Papua New Guinea, PHL = Philippines, VNM = Viet Nam, VUT = Vanuatu

* Includes all cases confirmed by laboratory testing or epidemiological linkage, plus those clinical cases that were reported without a laboratory specimen or epidemiological linkage.

Source: WHO Immunization Data Portal Diphtheria reported cases and incidence. 2018. (8)

1.3 Issues and challenges

Issues and challenges relate to the following areas.

I. Outbreak preparedness and response

Management and treatment

1. Lack of national guidelines to ensure prompt diagnosis and management including isolation, infection prevention and control, and treatment with DAT and antibiotics.
2. Lack of management of asymptomatic carriers who could be the source of transmission during outbreaks.
3. Lack of standard procedures for specimen collection, storage, transportation and laboratory diagnosis.

Prevention and control (diphtheria toxoid)

4. No standard practice for diphtheria toxoid vaccination during convalescence.
5. No clear guidance on choice of vaccines – diphtheria-tetanus (DT) vaccine, child type vs. tetanus and low-dose diphtheria toxoid (Td) vs. Td with acellular pertussis vaccine, adult formulation (Tdap) during outbreaks.

Preparedness

6. Lack of understanding the roles and responsibilities at various administrative levels (national and subnational) for outbreak response.
7. Lack of monitoring and supervision to review preparedness, including national DAT and vaccine stockpiles.
8. Lack of completeness and accuracy of JRF data, highlighting issues in surveillance and reporting quality.
9. Lack of quality outbreak investigation report and lessons learnt identified through outbreak reviews for better preparedness and response for future outbreaks.

Response

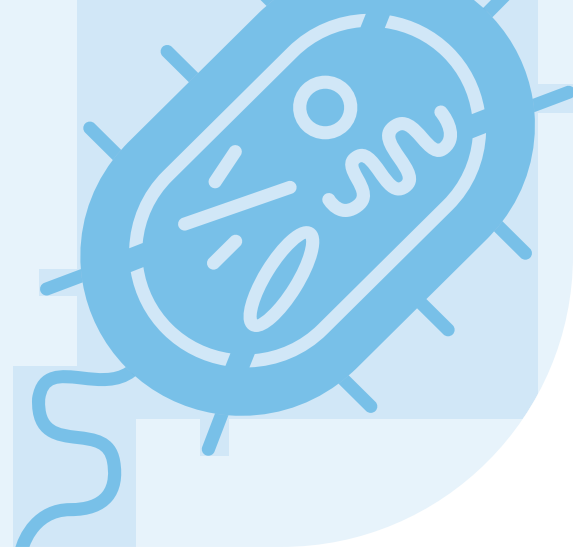
10. Failure to timely identify, report and investigate cases and outbreaks.
11. Failure to identify, monitor and treat close contacts, susceptible people and carriers.
12. Lack of appropriate outbreak response immunization strategies (timing, target age, target area).
13. Lack of timely risk communications and public awareness during outbreaks, including cross-border collaboration.

II. Immunization programme

14. Low routine immunization coverage due to stock-outs, insufficient outreach sessions, inadequate services for mobile and ethnically diverse populations, vaccine hesitancy, hard-to-reach areas, etc.
15. Lack of booster doses in the national immunization schedules.

2

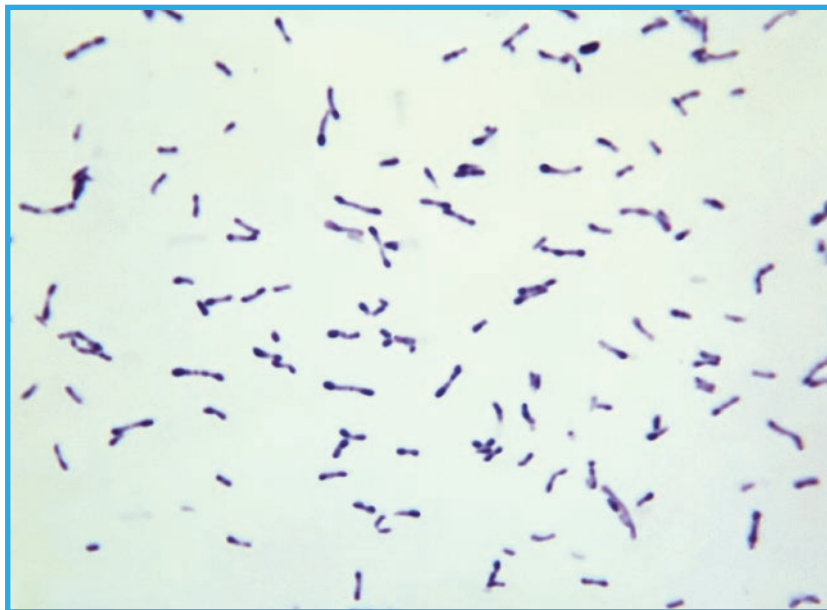
Disease



2.1 Infectious agent

Diphtheria is an acute communicable upper-respiratory illness mainly caused by the toxin-producing *Corynebacterium diphtheriae*, an aerobic gram-positive bacillus, usually with one end being wider, thus giving the often club-shaped appearance (Fig. 4).

FIG. 4. *Corynebacterium diphtheriae*



Source: CDC Public Health Image Library (9)

There are four biovars of *C. diphtheriae*: *intermedius*, *gravis*, *mitis* and *belfanti*. The disease affects the mucous membranes of the respiratory tract (respiratory diphtheria), the skin (cutaneous diphtheria) and rarely mucous membranes at other non-respiratory sites, such as genital and conjunctiva.

Human isolates of *C. diphtheriae* may be either toxigenic or nontoxigenic. Toxin production (toxigenic) occurs only when the bacillus is infected (lysogenized) by a specific virus (bacteriophage) carrying the genetic information for the toxin. Only toxigenic strains can cause severe disease (10). Nontoxigenic strains of *C. diphtheriae* generally may cause a mild sore

throat, but they infrequently can cause severe exudative sore throat (pharyngitis). Nontoxigenic strains may be invasive and cause endocarditis and arthritis (11).

2.2 Reservoir

Humans are the reservoir for *C. diphtheriae*. In outbreaks, high percentages of children are found to be transient carriers (10).

2.3 Mode of transmission

Transmission is most often person to person, usually through respiratory droplets, like from coughing or sneezing. Transmission may also occur from contact with skin lesions or articles soiled with discharges from lesions of an infected person (fomites).

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.

2.4 Temporal pattern

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

2.5 Incubation period

The incubation period for respiratory diphtheria is two to five days; however, disease can develop as long as 10 days after exposure (12).

2.6 Pathogenesis

The exotoxin produced by *C. diphtheriae* is by far the most important pathogenic factor associated with the organism. The toxin 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 heart, nerves and kidneys.

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

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 two or three 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. 5). Efforts to dislodge the pseudomembrane result in bleeding. Anterior cervical lymph nodes become markedly enlarged and tender. In patients with severe diseases, the lymph node swelling is associated with considerable inflammation and oedema of the surrounding soft tissues, giving rise to so called "bull-neck" appearance.

FIG. 5. Pseudomembrane



Source: Diphtheria. Hunter's Tropical Medicine and Emerging Infectious Diseases 10th Edition (13)

Laryngeal diphtheria

- Laryngeal diphtheria occurs in 25% of cases, and in 75% of these instances the pharynx is involved (5). 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 greater morbidity and mortality as a result of airway obstruction and the greater degree of toxin absorption from the extensive membrane.

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. 6). This form of diphtheria occurs rarely, most commonly as a result of nontoxigenic strains though cases of cutaneous diphtheria caused by toxin-producing *C. diphtheriae* have been reported (14). Cutaneous diphtheria is not reported in the JRF, but occasional information is available through published data (15).

FIG. 6. Cutaneous diphtheria



Source: CDC Public Health Image Library (16)

2.8 Complications

- 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 (17). 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 (5). They usually begin two to eight 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 it may require mechanical ventilation.
- Other complications of diphtheria include pneumonia, otitis media, renal failure, encephalitis, cerebral infarction and pulmonary embolism.

2.9 Period of communicability

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

2.10 Differential diagnosis

Respiratory diphtheria should be clinically differentiated from other causes of membranous pharyngitis or stridor (18,19).

TABLE 3. 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 (18) and WHO operational protocol for clinical management of diphtheria (19)

3

Definitions and case classifications



The following terms are sourced from *WHO Vaccine Preventable Diseases Surveillance Standards (20)*.

3.1 Suspected cases

Any person with illness of the upper-respiratory tract characterized by pharyngitis, nasopharyngitis, tonsillitis or laryngitis, and adherent pseudomembrane of the tonsils, pharynx, larynx and/or nose.

Note: Some countries can choose to expand the suspected case definition to include mild cases without a pseudomembrane and non-healing ulcers in a person with a travel history to countries with endemic disease or countries with diphtheria outbreaks.

3.2 Laboratory-confirmed cases

A laboratory-confirmed case is a person (regardless of symptoms) with *Corynebacterium spp.* isolated by culture and positive for toxin production.

3.3 Epidemiologically linked cases

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 onset of sore throat.

3.4 Clinically compatible cases

This type of case meets the definition of a suspected case and lacks both a confirmatory laboratory test result and epidemiological linkage to a laboratory-confirmed case.

3.5 Discarded cases

A discarded case is a suspected case that meets either of these criteria: i) *Corynebacterium spp.* but negative Elek test (nontoxigenic *Corynebacterium*); or ii) negative polymerase chain reaction (PCR) for the diphtheria toxin gene.

3.6 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 people should still be reported as laboratory-confirmed cases, as their treatment and public health response are the same as other laboratory-confirmed cases.

3.7 Outbreak

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

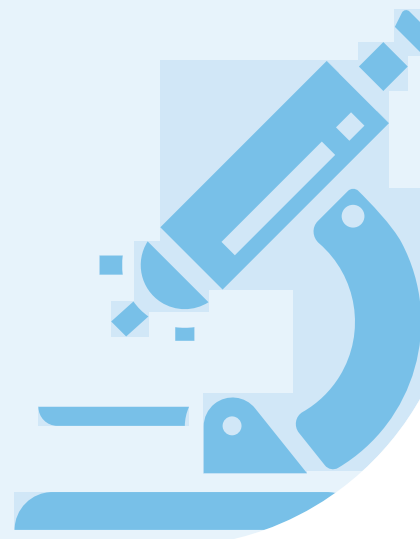
Changes to surveillance during an outbreak

During outbreaks, clinical diagnosis based on typical pseudomembranous pharyngitis without laboratory confirmation can be used to identify cases. Depending on the size of the outbreak, and so as not to overwhelm the laboratory, a country can choose not to test all suspected cases. In this situation, the definition of an epidemiologically linked case can be extended to linkage to another epidemiologically linked case, rather than to laboratory-confirmed cases. In this situation, the final case classification would need to be modified to include epidemiologically linking cases to other epidemiologically linked cases. This chain should only continue for approximately two to three incubation periods (for example, three weeks), at which point any new cases identified should be tested to confirm that the outbreak continues to be toxigenic diphtheria. Once five cases are confirmed to be toxigenic diphtheria, then epidemiological linking to other epidemiologically linked cases can continue; the process of reconfirming diphtheria among new cases should be continuing every two to three incubation periods. Cases should be "line listed", and modifications might need to be made to the case investigation form to capture new risk factors.

In very large outbreaks, case-based surveillance and contact tracing might not be feasible any longer and aggregate surveillance might be conducted. Countries should make this decision based on epidemiology and resources but contact tracing and post-exposure prophylaxis can be a life-saving prevention strategy.

4

Laboratory diagnosis



4.1 Specimen collection and storage

Two specimens – a pharyngeal/throat swab and a nasal swab – should be collected from every suspected case. Ideally, specimens should be taken prior to starting antibiotics; however, samples should still be taken even if antibiotics have already been started. The swabs should be labelled appropriately with a unique identifier and source of the specimen, and it should be placed in appropriate transport media (Amies or Stuart media in icepacks; or dry swabs in silica-gel sachets) and transported to the laboratory at 2–8 °C (1,19).

4.1.1 Procedure for the collection of throat swabs from people with suspected diphtheria

- 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.

4.1.2 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.
- 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.

4.1.3 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.

4.2 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 (19). 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.

4.3 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 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, Loeffler).
- 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).

4.4 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 (1). A positive culture with toxin-producing *C. diphtheriae* confirms the etiologic diagnosis.

4.5 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 these tests.

For the latest guidance on laboratory diagnosis, please refer to the *WHO laboratory manual for the diagnosis of diphtheria and other related infections* (21).



5 Management and treatment of diphtheria

5.1 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 two to four hours and close observation, particularly in young children (19). 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.

5.2 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, and 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 one metre between patients when possible and keep patient-care areas well ventilated. Avoid patient movement or transport out of isolation area. If movement is necessary out of isolation area, have patient use a medical or surgical mask (18).

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 (10,20). 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 (10). 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.

WAYS TO IMPLEMENT DROPLET AND CONTACT PRECAUTIONS (18)

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 in 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 (22).
- 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.

5.3 Antibiotics

Antibiotics are used in the management of respiratory diphtheria with three major benefits: it kills the organism and thus prevents further toxin from being formed, it slows the spread of local infection, and it reduces transmission. All diagnostic specimens should be collected before antibiotic treatment is started. However, should antibiotics already have been started, specimens should still be collected. The recommended antibiotics are erythromycin or penicillin. For the treatment of patients with respiratory diphtheria, recommended regimens are as follows (23):

- **Erythromycin** 500mg four times daily for 14 days; or
- **Procaine penicillin G** 300 000 units every 12 hours for patients \leq 10 kg and 600 000 units every 12 hours for patients $>$ 10 kg intramuscularly until the patient can take **oral penicillin V** 250 mg four times daily for a total treatment course of 14 days.

Elimination of the organism should be documented by two consecutive negative cultures obtained at least 24 hours apart, with the first specimen collected 24 hours after therapy is completed (10).

5.4 Diphtheria antitoxin (DAT)

DAT is hyperimmune serum produced in horses. As antitoxin only neutralizes circulating toxin un-bound to tissues, prompt administration of DAT is critical. Delayed administration increases the risk of late effects such as myocarditis and polyneuropathies.

If diphtheria is suspected by clinicians, treatment with DAT should be given immediately without waiting for laboratory results. DAT is generally not indicated in cases of cutaneous diphtheria without systemic manifestations. However, in cases where the ulcer is very large ($>$ 2cm²) and membranous, the risk of systemic absorption of toxin and subsequent systemic complications is increased, and DAT may be considered (17). Although data are limited, DAT administration to clinically suspect patients who are pregnant or breastfeeding may be considered as the therapy and may be life-saving.

Possible adverse reactions following administration of DAT are hypersensitivity reactions, febrile reaction and serum sickness. 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* (25). 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. Administer according to the Besredka method to assess possibility of allergy (26).

BESREDKA METHOD

- Inject 0.1 mL subcutaneously (SC) and wait 15 minutes.
- If there is no allergic reaction (no erythema at the injection site or a flat erythema of less than 0.5 cm in diameter), inject a further 0.25 mL subcutaneously.
- If there is no reaction after 15 minutes, inject the rest of the product intramuscularly (IM) or intravenously (IV) depending on the volume to be administered.
- If patient demonstrates sensitivity on testing after any injection, then cease injections and do not administer the remaining DAT dose. Use desensitization protocol from the United States Centers for Disease Control and Prevention (27).

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 (Table 4).

TABLE 4. Recommended paediatric and adult DAT dose

Diphtheria clinical presentation	DAT dose (units)
Pharyngeal or laryngeal disease of two days duration	20 000 – 40 000
Nasopharyngeal disease	40 000 – 60 000
Extensive disease of three or more days duration, or any patient with diffuse swelling of neck	80 000 – 100 000
Skin lesions only (rare case where treatment is indicated above)	20 000 – 40 000

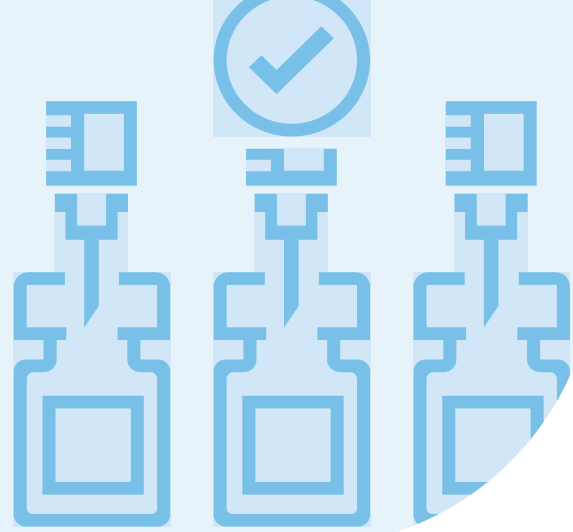
TIPS

- If limited availability, then use lower-dose range.
- The same doses are recommended for children and adults.
- Do not repeat dosing.
- May be administered IV (preferred in severe cases) or IM (mild to moderate cases).

Source: CDC. Use of Diphtheria Antitoxin (DAT) for Suspected Diphtheria Cases. (27)

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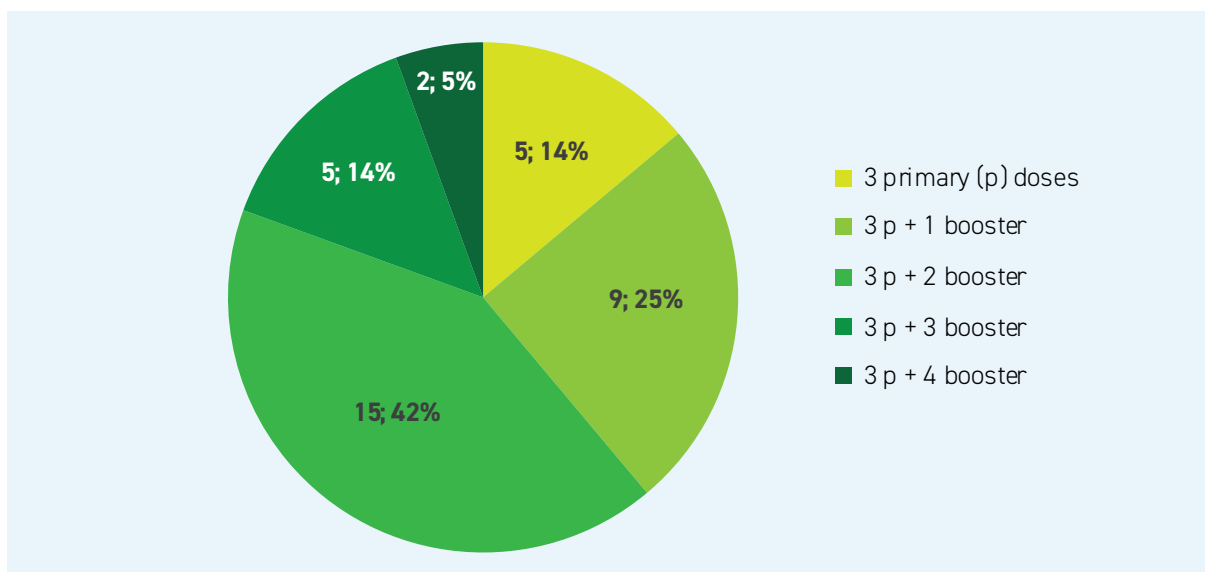
Prevention of diphtheria



6.1 Diphtheria vaccines

The WHO position paper on diphtheria vaccines, published in August 2017 (1), provides revised recommendations on the optimal number of doses and timing of diphtheria vaccinations, as well as guidance on the alignment of vaccination schedules for different antigens included in routine childhood immunization programmes, considering the widespread use of combination vaccines. The recommendation is a three-dose primary series and three booster doses of diphtheria toxoid-containing vaccine. The three-dose primary series 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 four weeks between doses, and the third dose of the primary series should be completed by 6 months of age, if possible. The three boosters should be given in combination with tetanus toxoid at 12–23 months of age, 4–7 years of age and 9–15 years of age, using age-appropriate vaccine formulations (1). The number of doses in the national immunization schedules varies for countries and areas in the Western Pacific Region, according to the 2018 JRF (Fig. 8). Countries and areas, with the age range of scheduled diphtheria toxoid vaccination, are listed as follows (Table 5).

FIG. 8. Number (and percentage) of countries and areas with various diphtheria vaccination schedules in the Western Pacific Region, 2018



Source : WHO Immunization Data Portal Vaccination Schedule for Diphtheria. 2018. (28)

TABLE 5. Countries and areas and range of age of last scheduled diphtheria toxoid dose

Vaccination schedule	Range of age of last scheduled diphtheria toxoid dose	Countries and areas
3 primary doses	≤ 6 months	Cambodia, Lao People's Democratic Republic, Philippines, Papua New Guinea, Solomon Islands
3 primary doses + 1 booster	1–6 years (booster)	Brunei Darussalam, China, Hong Kong SAR (China), New Caledonia, Niue, French Polynesia, Tuvalu, Viet Nam
3 primary doses + 2 boosters	4 –11 years (booster)	Australia, Cook Islands, Fiji, Guam, Japan, Kiribati, Federated States of Micronesia, Mongolia, Malaysia, New Zealand, Nauru, Samoa, Singapore, Tokelau, Vanuatu, Wallis and Futuna
3 primary doses + 3 boosters	6–25 years (booster)	American Samoa, Commonwealth of the Northern Mariana Islands, Palau, Republic of Korea, Tonga
3 primary doses + 4 boosters	6–25 years (booster)	Macao SAR (China), Marshall Islands

Note: SAR = Special Administrative Region

Source: WHO Immunization Data Portal Vaccination schedule for Diphtheria. 2018. (28)

Protective immunity does not always develop after recovery from diphtheria. Therefore, individuals recovering from diphtheria should complete the age-appropriate recommended course of diphtheria toxoid vaccination during convalescence (1). 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 induce herd immunity/community immunity and reduce the threat of an outbreak (1).

The available forms of vaccines appropriate for the prevention of diphtheria are presented in Table 6.

TABLE 6. Vaccine presentations appropriate for the prevention of diphtheria

Type	Vaccine description	Appropriate indications
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, such as school immunization programmes, antenatal care and supplementary vaccination campaigns
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*	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 toxoid 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. (29)

7 Preparedness for diphtheria outbreaks



7.1 Objectives of preparedness for diphtheria outbreaks

The main objectives of preparedness for diphtheria outbreaks are:

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

7.2 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 (30). 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 they 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 (24)
- SOPs for sample collection, laboratory procedures and quality assurance
- SOPs for DAT management (7)
- SOPs for safe injection practices
- SOPs for infection control in hospitals
- SOPs for effective communication and public awareness.

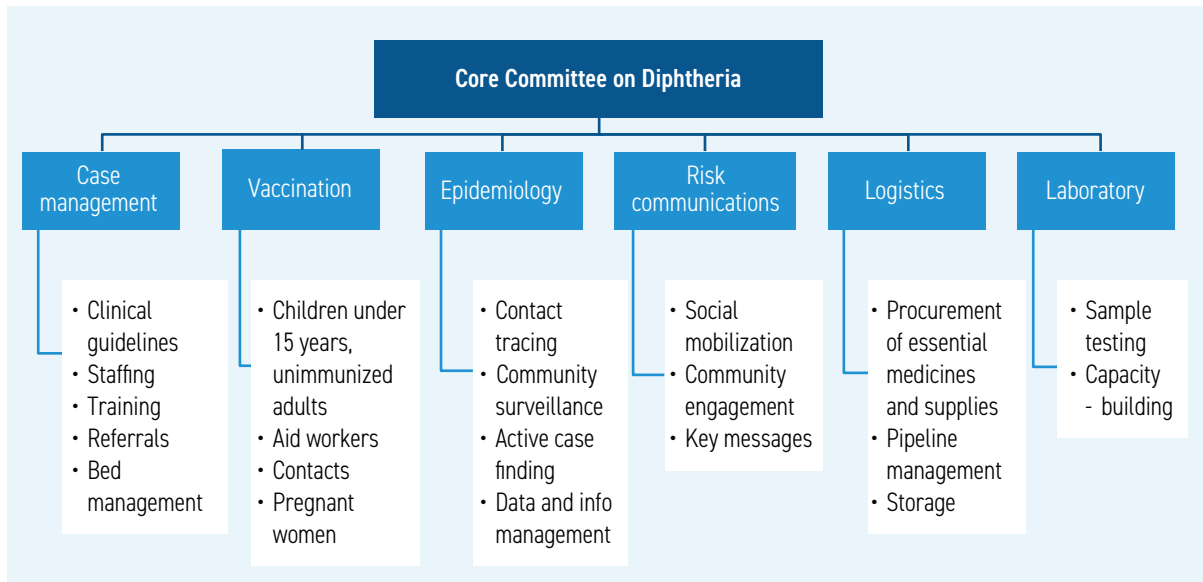
7.3 Detailed mapping and mobilization of resources

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

- 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, laboratory staff);
- financial resources;
- tools, including case investigation forms, cases and contact line-list forms, laboratory requesting forms;
- information, education and communications materials (leaflets, brochures); and
- referral channels to higher-level health centres and hospitals.

7.4 Outbreak coordination committee

During large diphtheria outbreaks in 2017, such as those in Bangladesh and Yemen, a diphtheria outbreak coordination committee comprised of the ministry of health and multi-agency partners was activated to respond to the outbreak. The outbreak coordination committee assumed leadership of the joint efforts to control the outbreaks and focus on providing technical support to the affected districts (31,32). Countries prone to diphtheria outbreaks or with limited resources should have similar mechanisms in place that could be linked with existing systems or committees for response to other communicable diseases. The coordination mechanism leverages and aligns the critical capacities of members within the response pillars outlined below (Fig. 9).

FIG. 9. Core Committee on Diphtheria in Bangladesh

Source: Bangladesh Ministry of Health and Family Welfare/WHO. Bangladesh Rohingya Crisis: Sector Response to the Diphtheria Outbreak. 2017. (31)

7.5 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 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 microplanning 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, record reviews;
- conduct appropriate management of cases and contacts; and
- refer to higher-level health centres and hospital for cases that need hospitalization.

7.6 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 system at the national and subnational levels;
- ensure effective and efficient systems are in place for the transportation of lab 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).

7.7 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.

7.8 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 with 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 (18).

7.9 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 enable qualitative and quantitative measurement of preparedness.

7.10 Diphtheria antitoxin (DAT) stockpiles

In the recent years, there has been a global decline in the production and supply of DAT from the manufacturers, due mainly to the increasing use of vaccines and declining incidence of the disease. Since the use of DAT is limited to the treatment of individual cases, demand is unpredictable. It is fair to say that demand overall has stabilized over approximately the last 10 years but remains strongly influenced by outbreaks. The number of DAT manufacturers has declined considerably, and most of the industry has stopped production. A few countries, such as Bulgaria, China, India, Indonesia and the Russian Federation still have manufacturing facilities. A few countries hold stockpiles; however, the stockpiles are small and most have either expired or have had the expiry dates extended through re-testing by an independent laboratory to confirm efficacy of the product. Other issues include quality control, standardization and production

under good manufacturing practices. There is no process for WHO prequalification for this type of product, so it is difficult to guarantee the quality. Most countries have no stockpile of DAT, and rely on donations from existing stockpiles in the event of an outbreak. However, the prolonged time required for accessing, shipping, procurement and regulatory mechanisms in countries may mean supplies arrive too late to save the lives of the patients. This continues to be a prominent issue with DAT supplies in countries in the Western Pacific Region experiencing cases or outbreaks.

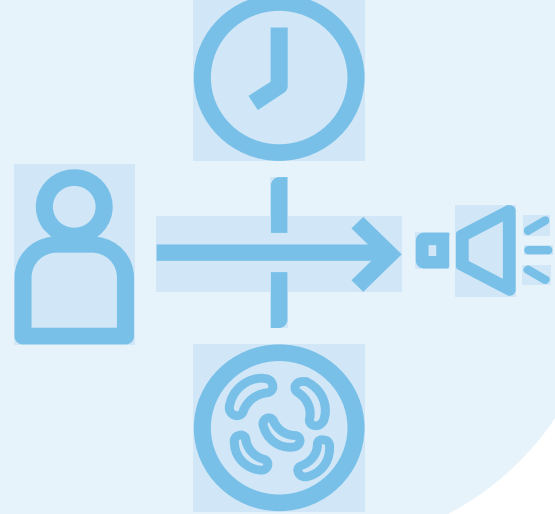
DAT is included in the *WHO Model List of Essential Medicines for Children (2017)* (33); however, countries must define their own essential medicines list/formulary for public sector purchasing. Depending on the country's regulation mechanism and the national regulatory authorities, it can be fully registered, fast tracked (in case of emergency), or the country can import it as an orphan drug (rare disease indication) or investigational new drug (for clinical trials).

During the WHO Strategic Advisory Group of Experts on Immunization (SAGE) discussion in October 2017, partners requested WHO to organize an ad hoc working group to improve the availability of DAT and to propose a mid- to long-term solution to explore the need for a DAT stockpile. An ad hoc working group for DAT has been formed, led by WHO with partners including the UNICEF Supply Division, USCDC, the European Commission, Médecins Sans Frontières (Doctors without Borders) and more. The specific objective of this working group is to ensure that any population experiencing cases or an outbreak of diphtheria has rapid and easy access to quality DAT. Assessing and addressing product quality has been to date the highest priority of the working group. The working group has also explored options for forecasting demand, strengthening procurement strategies, developing a sustainable mechanism for DAT stockpiles at the manufacturer site, centralized location (for example WHO headquarters) or at regional level, and a decision-making process for the release and allocation of DAT during emergencies.

The ad hoc working group should also explore new products and manufacturers for antitoxin fragment F (ab) 2 and monoclonal antibodies that can be safer, effective and affordable for any country in need. The potential size of such a stockpile needs careful consideration since treatment of diphtheria cases is also dependent on diagnostic capacity and the provision of health-care services.



Response to diphtheria outbreaks



8.1 Objectives of response to diphtheria outbreaks

The main objectives of the response to diphtheria outbreaks are:

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

8.2 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 (34). 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 DTP1 and DTP3, socioeconomic and living conditions (overcrowding), high-risk areas identified in micro-plans, and access to health services. After collecting and assessing these 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 these 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 the high-risk areas, such as increased disease incidence, low immunization coverage and migrating populations.

8.3 Notification of an outbreak

A single confirmed case should be managed as outlined in Section 5 (Management and treatment of diphtheria) of this Guide. Once a diphtheria outbreak is confirmed, health-centre staff should immediately notify the next-higher administration level, for example 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 the border areas, health officials in the adjoining areas should be notified and efforts should be made to share information.

8.4 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.

8.5 Identification of contacts

The close contacts include:

- household members (all persons who sleep in the same house/tent during the last five nights before onset of the case);
- any persons with history of direct contact with 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 (5). These 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 (20).

8.6 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 nontoxigenic *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 nontoxigenic.

8.7 Management of close contacts and eligible at-risk contacts

- Monitor close contacts and eligible at-risk contacts, through home visits or telephone contact for signs and symptoms of diphtheria for at least 10 days after the last contact with the index case or until the laboratory testing allows exclusion of the case.
- Educate contacts about the disease and advise them to seek medical care if they develop symptoms (fever, sore throat, malaise, development of pseudomembrane).
- Travel history should be requested as the close contact may be the source of the case's infection.

- Administer antibiotics for prophylaxis (23):
 - **benzathine penicillin** IM single dose:
 - for individuals aged < 6 years: administer 600 000 units;
 - for individuals ≥ 6 years: administer 1 200 000 units;

or
 - **oral erythromycin**:
 - 500 mg four times daily for 7 to 10 days.
- Exclude from school or work until 48 hours of prophylactic antibiotics have been completed (19).
- Diphtheria 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 (1).
- DAT is not recommended as post-exposure prophylaxis, as evidence is limited regarding its benefit and the risks of allergic reaction to horse serum.

During outbreaks in school settings, children who arrive at schools or learning centres with sore throat and fever should be discouraged from attending school and referred to the closest health centre for evaluation and treatment:

- check children for signs and symptoms before they enter the school or learning centre or, at least before the start of any learning activity;
- if diphtheria is suspected in a child, inform the child and parent/caregiver to seek medical care as soon as possible;
- complete referral to the closest health centre; and
- follow up on the referred child to ensure health services are sought and to monitor the outcome.

8.8 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:

- 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.

8.9 Communication for health

Before and during an outbreak, populations should understand risks and how they can 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 a 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, that 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.

8.10 Outbreak response immunization

In the event of an outbreak, selective vaccination campaigns targeting at-risk populations, including health-care workers and other outbreak responders, should be considered (17). 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 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 (20). The age-appropriate formulations can be found in Table 4.

- **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.

8.11 Reinforcement of routine immunization

A diphtheria outbreak provides an opportunity to identify immunization programme's 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, 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.

9

Learning lessons from diphtheria outbreaks



9.1 Evaluation of outbreak response

After the outbreak, the outbreak coordination committee should perform an evaluation of:

- the cause of the outbreak, such as accumulation of susceptible populations;
- the case fatality rate to assess and identify interventions that could have been carried out to prevent more deaths;
- management of the outbreak, including use of resources (DAT, antibiotics, vaccine, etc.);
- existing diphtheria surveillance and reporting in the country;
- preparedness for the diphtheria outbreak; and
- impact of the outbreak, on various parameters including economics and other health-delivery programmes.

9.2 Outbreak report

After the outbreak, a written report should be prepared analysing the outbreak and summarizing its response. It should provide useful information on the lessons learned throughout the outbreak for better preparedness for and response to future outbreaks. The outbreak report should consist of the following components:

- descriptive analysis of the outbreak (time, place and person), including cases and contacts line-list with, vaccination history, treatment history including DAT, hospitalization and outcomes;
- most-affected groups stratified by age, sex, geography and ethnicity;
- timeline of activities in outbreak detection, investigation and response;
- description on risk assessment conducted and evaluation measures implemented during the outbreak;
- contributing factors identified such as overcrowded locations, low routine immunization coverage and gaps in susceptibility;
- surveillance performance in routine and intensified activities during the outbreak;
- information on routine immunization and outbreak response immunization in the affected area; and
- impact on overall health-care system and financial costs of the outbreak.

Feedback is critical. The written findings, including a clear description of the epidemiological characteristics and recommendations, should be disseminated to all stakeholders and partners in order to prevent future outbreaks.

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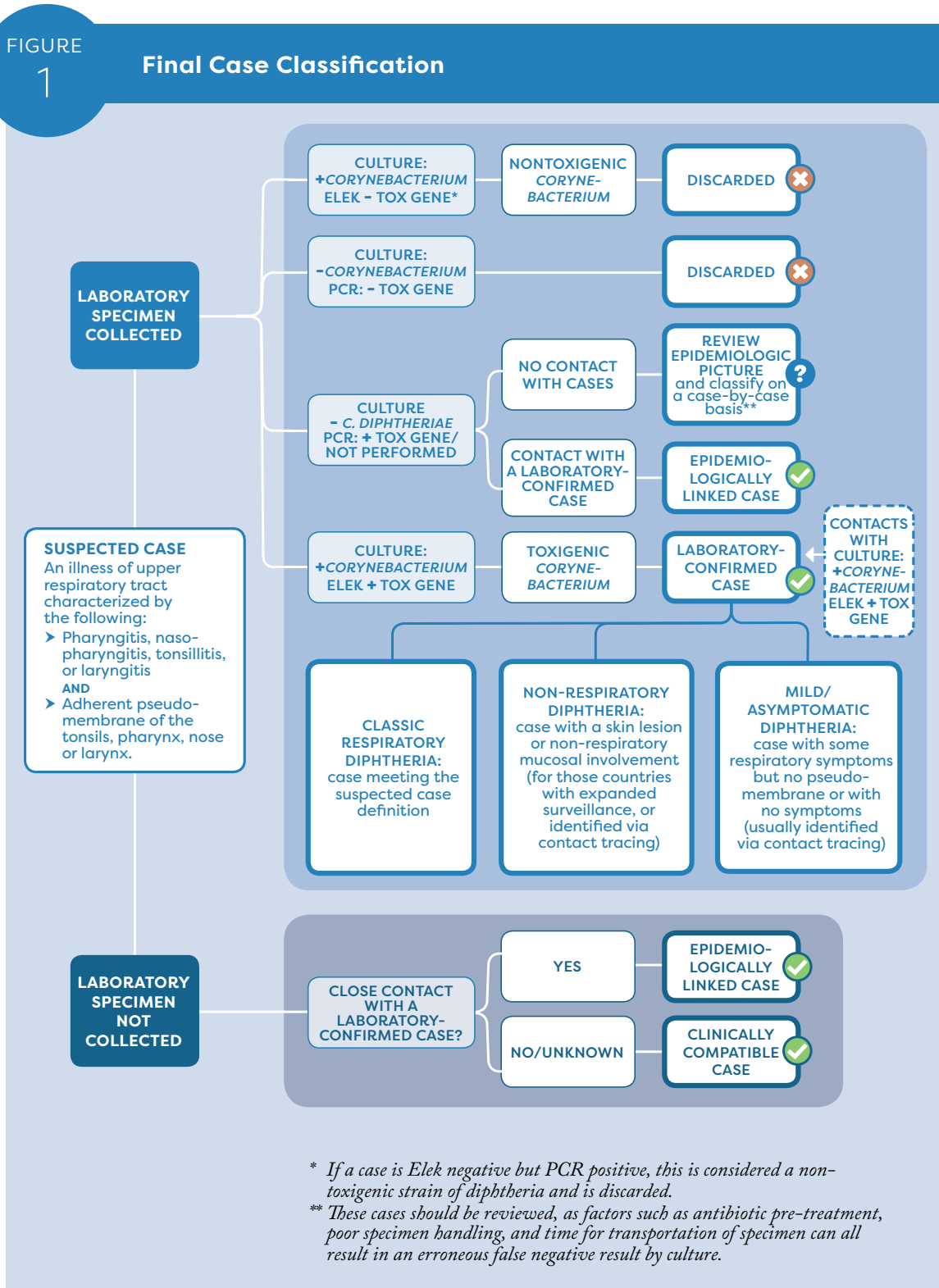
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Annexes

Annex 1. Final case classification

FIGURE 1

Final Case Classification

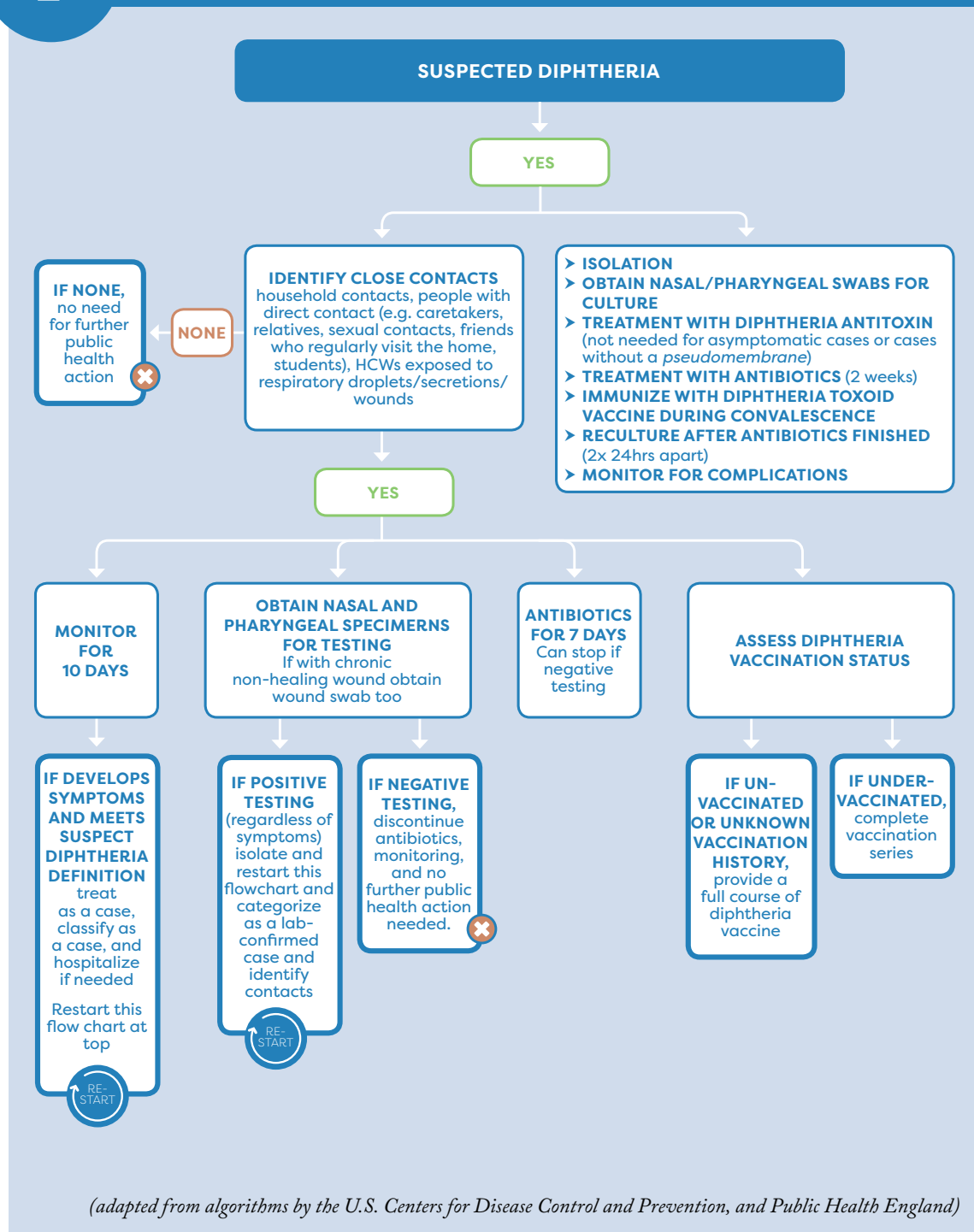


Source: WHO. Diphtheria: Vaccine preventable diseases surveillance standards, Surveillance standards for vaccine-preventable diseases, 2nd Edition. 2018. <https://www.who.int/publications/m/item/vaccine-preventable-diseases-surveillance-standards-diphtheria>

Annex 2. Case management and contact tracing

FIGURE
2

Case management and contact tracing



Source: WHO. Diphtheria: Vaccine preventable diseases surveillance standards, Surveillance standards for vaccine-preventable diseases, 2nd Edition. 2018. <https://www.who.int/publications/m/item/vaccine-preventable-diseases-surveillance-standards-diphtheria>

