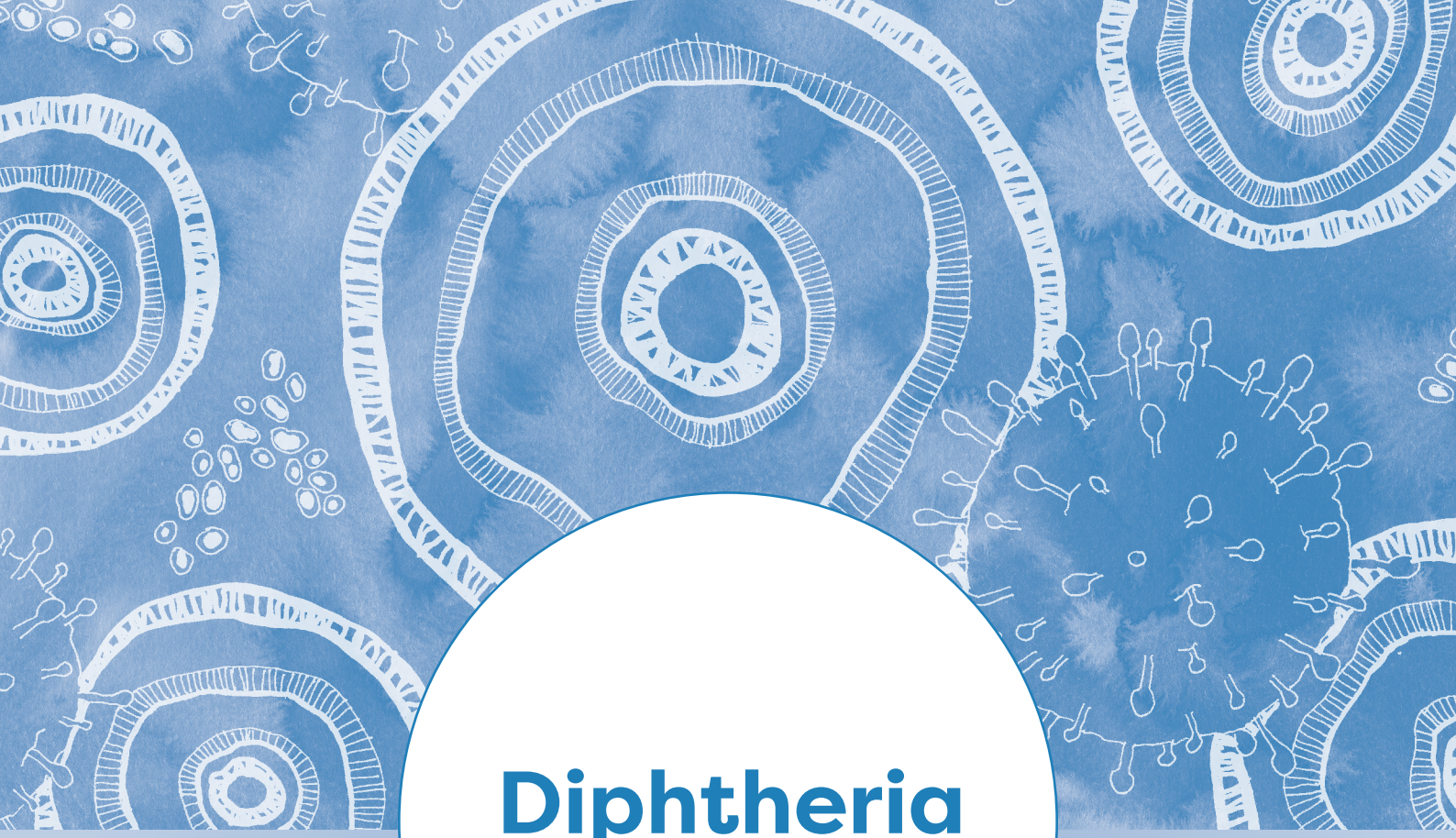


Diphtheria

Vaccine-Preventable Diseases

Surveillance Standards

World Health Organization

DISEASE AND VACCINE CHARACTERISTICS

Diphtheria is caused by *Corynebacterium* species, mostly by toxin-producing *Corynebacterium diphtheriae* and rarely by toxin-producing strains of *C. ulcerans* and *C. pseudotuberculosis*. The most common type of diphtheria is classic respiratory diphtheria, whereby the exotoxin produced characteristically causes the formation of a pseudomembrane in the upper respiratory tract and damages other organs, usually the myocardium and peripheral nerves. Acute respiratory obstruction, acute systemic toxicity, myocarditis and neurologic complications are the usual causes of death. The infection can also affect the skin (cutaneous diphtheria). More rarely, it can affect mucous membranes at other non-respiratory sites, such as genitalia and conjunctiva.

C. diphtheriae is transmitted from person to person by intimate respiratory and direct contact; in contrast, *C. ulcerans* and *C. pseudotuberculosis* are zoonotic infections, not transmitted person-to-person. The incubation period of *C. diphtheriae* is two to five days (range 1– 10 days). A person is infectious as long as virulent bacteria are present in respiratory secretions, usually two weeks without antibiotics, and seldom more than six weeks. In rare cases, chronic carriers may shed organisms for six months or more. Skin lesions are often chronic and infectious for longer periods. Effective antibiotic therapy (penicillin or erythromycin) promptly terminates shedding in about one or two days.

Case fatality ratios up to 10% have been reported in diphtheria outbreaks, and are higher in settings where diphtheria antitoxin (DAT) is unavailable *(1)*. In the past decade, there have been 4,000–8,000 diphtheria cases reported annually worldwide *(2)*. Global diphtheria cases reported to WHO are likely an underestimation of the real burden of disease due to under-reporting, exclusion of non-respiratory diphtheria cases and exclusion of cases caused by the other potentially toxigenic species.

Diphtheria toxoid, the vaccine to prevent diphtheria, should be given to infants as a primary series of three doses, followed by three appropriately spaced booster doses to ensure long-term protection *(3)*.

BOX 1

Focus of surveillance on respiratory disease caused by toxigenic Corynebacterium species

The surveillance standards in this document focus primarily on classic respiratory diphtheria. This is because respiratory tract disease constitutes the majority of clinical diphtheria disease, is the most severe form of clinical diphtheria and is more amenable to detection by surveillance systems *(4)*. These surveillance standards focus on toxigenic Corynebacterium species (spp.) because non-toxigenic *Corynebacterium spp.* causes less severe disease and is not vaccine-preventable, as diphtheria toxin is the antigen for all diphtheria vaccine formulations.

Cutaneous and other mucosal disease are clinically significant and can transmit the bacteria, particularly in tropical and underdeveloped settings. However, non-respiratory presentations are less common, making up approximately 2% of all diphtheria cases. Finding these cases would require screening many patients with non-specific case definitions.

Asymptomatic cases and mild respiratory cases are usually identified through contact tracing. Additionally, countries may choose to conduct expanded diphtheria surveillance to include other anatomical sites (cutaneous, mucosal) when they have a high-quality respiratory diphtheria surveillance system in place.

RATIONALE AND OBJECTIVES OF SURVEILLANCE

The objectives of diphtheria surveillance are to:

- monitor disease burden and define transmission patterns
- identify outbreaks to trigger investigation and prevent further cases
- determine appropriate vaccine policy in the country, such as the need to introduce booster doses or change the vaccine formulation.

TYPES OF SURVEILLANCE RECOMMENDED

Surveillance for diphtheria should be national and facility-based. Because diphtheria has become relatively rare, surveillance should be case-based. All 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.

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.

FINAL CASE CLASSIFICATION

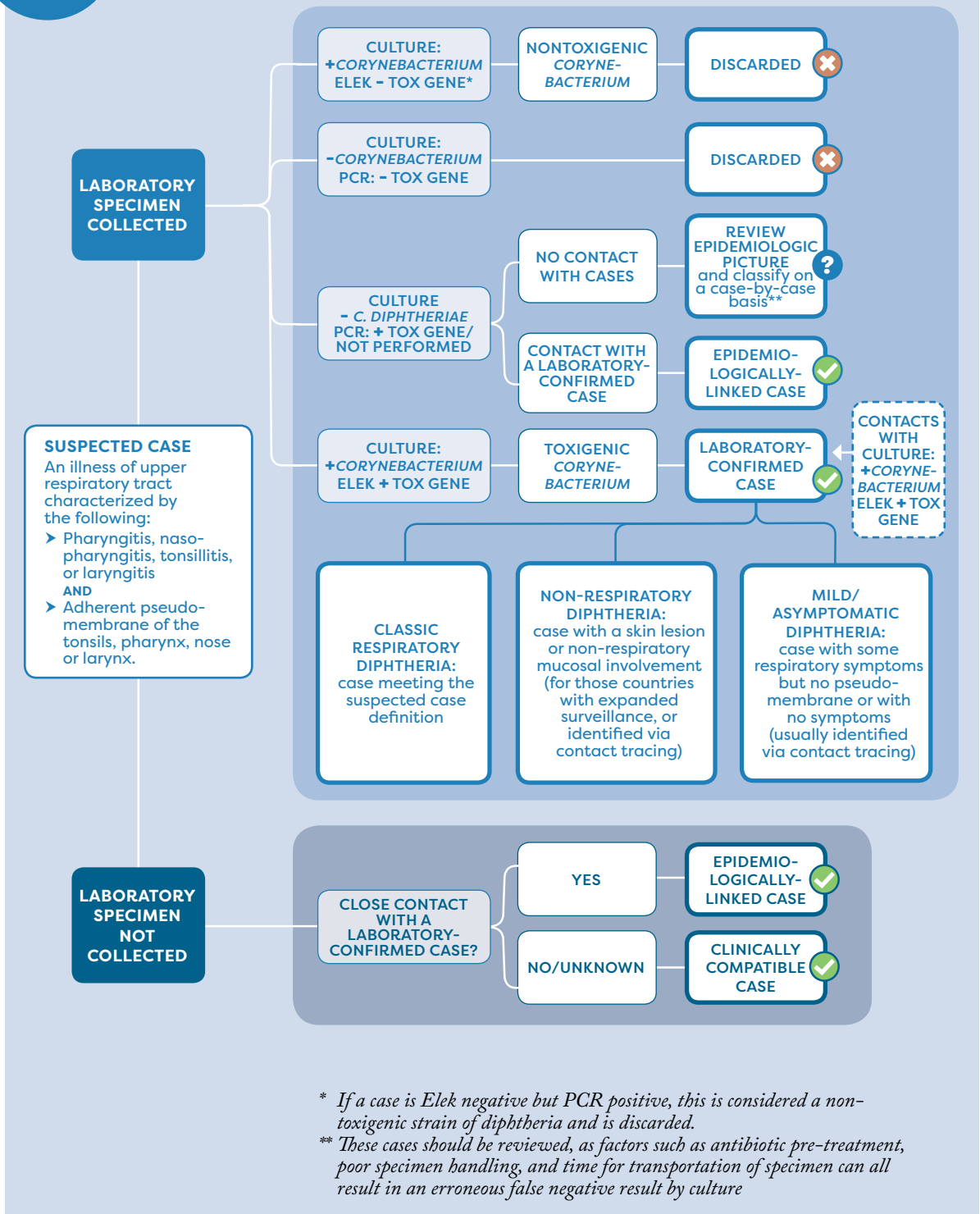
- **Laboratory-confirmed case.** A laboratory-confirmed case is a person with *Corynebacterium spp.* isolated by culture and positive for toxin production, regardless of symptoms. Toxigenicity must be confirmed by the phenotypic Elek test in all instances. Polymerase chain reaction (PCR) can complement 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 *Corynebacterium spp.* is isolated by culture and tests positive for toxin production.
- **Epidemiologically linked 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 onset of sore throat.
- **Clinically compatible 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.
- **Discarded case.** A discarded case is a suspected case that meets either of these criteria:
  - *Corynebacterium spp.* but negative Elek test (non-toxigenic *Corynebacterium)*

    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, as their treatment and public health response is the same as other laboratory-confirmed cases.

See Figure 1 for a summary of the final case classification process.

FIGURE 1

Final Case Classification



* *If a case is Elek negative but PCR positive, this is considered a non-toxigenic strain of diphtheria and is discarded.*

** *These cases should be reviewed, as factors such as antibiotic pre-treatment, poor specimen handling, and time for transportation of specimen can all result in an erroneous false negative result by culture*

CASE INVESTIGATION

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. Public health 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 pseudomembrane) prior to antibiotic treatment. Cases should then be treated promptly without waiting for laboratory confirmation (see Figure 2).

SPECIMEN COLLECTION

Two samples should be collected from every suspected case at first contact with the case: a pharyngeal swab and a nasal swab. For the pharyngeal swab, use a cotton-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 cotton-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 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 two 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.

LABORATORY TESTING

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 stain.
- 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 (+); the production of acid from glucose, maltose and glycogen/starch; and hydrolysis of urea (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 (see Figure 1).
- Public Health England 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.

DATA COLLECTION, REPORTING AND USE

Note that information on contacts and cases should be recorded separately. Contacts should not be counted as cases unless they are laboratory-confirmed or have symptoms consistent with diphtheria.

RECOMMENDED DATA ELEMENTS

- Demographic Information
  - Name (if confidentiality is a concern the name can be omitted so long as a unique identifier exists)
  - Unique case identifier
  - Date of birth (or age if date of birth is not available)
  - Sex
  - Place of residence (city, district, and province)
- Reporting Information
  - Date of notification to Public Health
  - Date of investigation
- Clinical Information
  - Date of onset (first day with sore throat)
  - Signs and Symptoms
    - Pharyngitis
    - Nasopharyngitis
    - Tonsillitis
    - Laryngitis
    - Adherent pseudomembrane. If so describe location (pharynx, nasal, tonsils, etc.)
    - Fever
    - Systemic disease (heart, brain, etc.)
    - Cutaneous lesions
    - Other non-respiratory involvement. If yes, where?
  - Hospitalization status
    - Date of hospital admission
  - Outcome (patient survived, died, or unknown)
    - Date of death
  - Treatment type
    - Antibiotic
      - Type, none, or unknown
      - Date of first dose
    - Antitoxin
      - Yes, no, unknown
      - Date of antitoxin
- Laboratory methods and results
  - Specimen(s) collected?
  - Date of specimen collection

- Specimen(s) collected before antibiotic provision?
- Types of specimens collected: nasal, throat, wound, pseudomembrane, other (specify)
- Date specimen(s) received in laboratory
- Culture
  - Positive
    - *Corynebacterium diphtheriae*
    - *Corynebacterium ulcerans*
    - *Corynebacterium pseudotuberculosis*
  - Negative
    - Unknown/indeterminate
- Elek test: positive, negative, not done, unknown/indeterminate
- PCR: positive, negative, not done, unknown/indeterminate (differentiate if PCR targets *C. diphtheriae* or tox)
  - Specimen not processed (if obtained)

- Vaccination status
  - Number vaccine doses received prior to onset of illness (by recall if documentation is not available)
  - Type of diphtheria vaccine received (DT, DT(a) P, Td, Tdap, DTap or other combinations) and dates of vaccine doses
- Epidemiologic Data
  - Is person a contact of laboratory-confirmed case? (write down case ID)
  - Close contact with anyone who traveled in the week before onset of illness? If yes, where did they travel?
  - Contact with animals; ingestion of unpasteurized dairy products
  - Travel within 10 days of illness onset? If yes, where?
- Case Classification
  - Final classification of the case: laboratory confirmed, epidemiologically linked and clinically compatible cases; discarded
  - Sub-classification: classic respiratory, mild/asymptomatic, cutaneous

REPORTING REQUIREMENTS AND RECOMMENDATIONS

Designated reporting sites at all levels should report suspected, laboratory-confirmed, epidemiologically linked and clinically compatible cases at a specified frequency, such as weekly or monthly, even if there are zero cases (often referred to as "zero reporting"). International Health Regulations (IHR) do not require reporting of diphtheria cases. Diphtheria is included on the WHO/UNICEF Joint Reporting Form (JRF) that should be completed annually.

RECOMMENDED DATA ANALYSES

Total diphtheria cases are the sum of laboratory-confirmed, epidemiologically linked and clinically compatible cases.

- Number of cases by final classification by month, year, and geographical area
- Incidence rates by month, year, and geographical area
- Number of cases by sex and age groups (suggested age groupings: < 1, 1–4, 5– 9, 10–14, 15–19, 20–29, 30–39, 40–49, 50–64, ≥ 65)
  - An additional analysis should look at cases by year of birth to look for a cohort effect over time.
  - In some areas, there might be too few cases to do a quality data analysis; therefore cases from multiple years might have to be evaluated together to understand the epidemiologic picture.
- Age-specific and second administrative unit-specific incidence rates by month and year
- Cases by number of doses received, laboratory results, treatment type. Immunization status should be categorized by number of doses, where possible, because designation of partial or full vaccination status cannot be compared easily across countries implementing different vaccination schedules.
- Time since last diphtheria vaccine dose
- Case fatality ratio
- Percentage of cases who receive DAT
- Percentage of cases by species type of Corynebacterium
- Percentage of cases by subclassification (classic respiratory, mild/asymptomatic, cutaneous)

USING DATA FOR DECISION-MAKING

- Use descriptions of cases (for example, by age or second-administrative level) to guide changes in vaccination policies and strategies, and inform corrective actions.
- Monitor case fatality ratio and, if high, determine cause (poor case management, lack of antibiotics/antitoxin, patients not seeking treatment in time, etc.) so that corrective action can be taken.
- Determine age-specific incidence rate, geographical area and season of diphtheria cases to understand risk groups and risk periods.
- Monitor incidence rate in relation to vaccination status to assess impact of control efforts, identify vaccine failures, and collect evidence in order to modify vaccination policies and strategies, including the need and timing of booster doses.
- Detect outbreaks and implement control measures, including the need for outbreak response with vaccination and the need and age range for catch-up vaccination.
- Investigate outbreaks to understand epidemiology, determine why outbreaks have occurred (such as failure to vaccinate, vaccine failure, accumulation of susceptibles, waning immunity, new toxigenic strain) and ensure proper case management.
- The percentage of cases with laboratory testing should be high (> 80%); if not, there is a need to strengthen laboratory specimen collection and confirmation.

Surveillance data on diphtheria cases should be used in conjunction with immunization coverage data and, if available, serosurvey data by geographical area to identify areas of poor programme performance.

SURVEILLANCE PERFORMANCE INDICATORS

Surveillance should be evaluated at least yearly to ensure that the country is able to meet the objectives of surveillance accurately. Below are suggested surveillance performance indicators.

TABLE 1

Recommended surveillance performance indicators

SURVEILLANCE ATTRIBUTE	INDICATOR	TARGET	HOW TO CALCULATE (NUMERATOR / DENOMINATOR)	COMMENTS
COMPLETENESS OF REPORTING	Percentage of designated sites reporting diphtheria data, even in the absence of cases (zero reporting)	≥ 80%	Total number of reports received / total number of reporting sites x 100 (for given time period)	
TIMELINESS OF REPORTING	Percentage of surveillance units reporting to the national level on time, even in the absence of cases	≥ 80%	# of surveillance units in the country reporting by the deadline / # of surveillance units in the country x 100	At each level reports should be received on or before the requested date.

SURVEILLANCE ATTRIBUTE	INDICATOR	TARGET	HOW TO CALCULATE (NUMERATOR / DENOMINATOR)	COMMENTS
ADEQUACY OF INVESTIGATION	Percentage of all suspected diphtheria cases that have had an adequate investigation	≥ 80%	# of suspected cases of diphtheria for which an adequate investigation was done / # of suspected diphtheria cases x 100	*Note 1:* Adequate investigations include completing a case investigation form, collecting a nasal and pharyngeal specimen, line listing of close contacts. *Note 2:* For any case, if any of the above are not conducted, the investigation will be considered inadequate.
TIMELINESS OF INVESTIGATION	Percentage of all suspected diphtheria cases that have had an investigation initiated within 48 hours of notification	≥ 80%	# of suspected cases of diphtheria for which an investigation initiated within 48 hours of notification / # of suspected diphtheria cases x 100	
SPECIMEN COLLECTION	Percentage of suspected diphtheria cases with two specimens collected (pharyngeal swab and a nasal swab)	≥ 80%	# of suspected cases of diphtheria with 2 specimens collected / # of suspected diphtheria cases x 100	During outbreak investigations where epidemiological linkage increases, epidemiologically linked cases should be removed from the denominator.
TIMELINESS OF SPECIMEN COLLECTION	Percentage of suspected diphtheria cases with specimens taken before antibiotic administration	≥ 80%	# of suspected cases of diphtheria with a specimen collected before antibiotics / # of suspected diphtheria cases with a specimen collected x 100	
TOXIGENICITY TESTING RATE	Percentage of specimens tested for toxigenicity by Elek testing	≥ 80%	# specimens tested for toxigenicity by Elek testing / # of specimens received x 100	Indicator only applies to public laboratories.
TIMELINESS OF SPECIMEN TRANSPORT	Percentage of specimens received at the laboratory within 2 days of collection	≥ 80%	# of specimens received within 2 days of collection by laboratory / # of specimens x 100	Indicator only applies to public laboratories.
TIMELINESS OF REPORTING LABORATORY RESULTS	Percentage of specimens tested by culture with results reported within 3 days of receipt of specimen	≥ 80%	# of specimens tested by culture with results reported within 3 days of specimen receipt / # of specimens tested by culture x 100	

CLINICAL CASE MANAGEMENT

Management of all suspect diphtheria cases requires the following steps (see Figure 2):

1. **Isolation.** Respiratory droplet isolation of patients with respiratory diphtheria is required; contact precautions are required for cutaneous diphtheria. Maintain isolation until elimination of the organism is demonstrated by negative cultures of two samples obtained at least 24 hours apart after completion of antimicrobial therapy. If facilities are not available for droplet isolation, screens should be placed 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. **DAT.** The mainstay of treatment is DAT. Disease course and outcome depend on how early from disease onset that antitoxin treatment is started; after about three days from onset, the risk of complications and fatal outcome increases with each day DAT administration is delayed. If diphtheria is strongly suspected, treatment with DAT should be given immediately without waiting for laboratory results, 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 (penicillin or erythromycin) eliminate the bacteria and toxin production, prevent further transmission and limit carriage that can persist even after clinical recovery. Treatment should be continued for two weeks. 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/diphtheria-clinical-management.

CONTACT TRACING AND MANAGEMENT

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 seven days. If the culture is positive for toxigenic *Corynebacterium spp.*, then the contact should be treated as a case with an antibiotic course for two weeks (DAT is not needed for asymptomatic cases or cases without a pseudomembrane). Do a new investigation of contacts and implement proper case management, including isolation. This contact would now be classified as a laboratory-confirmed case.
- 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.

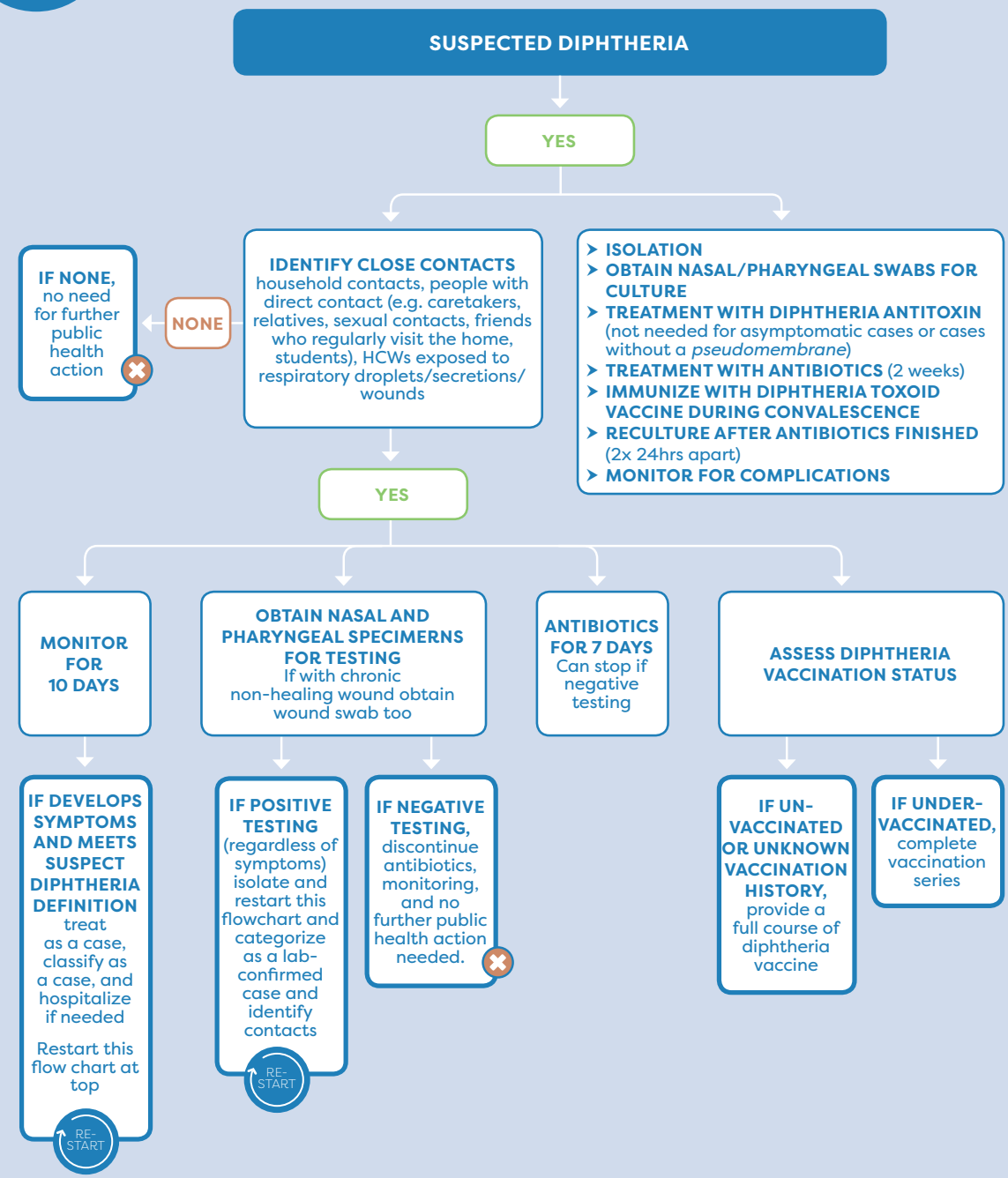
- If the result is negative for *Corynebacterium spp.*, antibiotics and monitoring can be stopped.

Diphtheria antitoxin 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 *(1)*. See Figure 2.

FIGURE 2

Case management and contact tracing



(adapted from algorithms by the U.S. Centers for Disease Control and Prevention, and Public Health England)

SURVEILLANCE, INVESTIGATION AND RESPONSE IN OUTBREAK SETTINGS

DEFINITION OF AN 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, you can identify additional cases using clinical diagnosis based on typical pseudomembraneous pharyngitis without laboratory confirmation. However, laboratory investigation of suspected cases is strongly recommended. Do not delay treatment pending laboratory confirmation. Depending on the size of the outbreak a country can choose to not test all suspected cases, to avoid overwhelming the laboratory. In this situation, the definition of an epidemiologically linked case can be extended to include linkage to another epidemiologically linked case, rather than to a laboratory-confirmed case. This chain should only continue for approximately two to three incubation periods (about three weeks), at which point any new cases identified should be tested to confirm the outbreak continues to be toxigenic diphtheria. Once five cases are confirmed to be toxigenic diphtheria, epidemiological linking to other epidemiologically linked cases can continue. The process of reconfirming diphtheria among new cases should continue every two to three incubation periods. Cases should be line listed. Modifications may need to be made to the case investigation form to capture new risk factors.

Of note, whilst 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 have been confirmed by culture and Elek testing in at least five cases. However, culture and Elek testing is still critical in large outbreaks; culture and Elek testing should be undertaken if new suspected cases are identified in a new area with no epidemiologic link to the current outbreak. Additionally, for outbreaks lasting for an extended period, at least 5 samples should be tested by culture and Elek every month among suspected cases with no epidemiologic link to a PCR-confirmed case. This helps to balance the limited resources and field challenges existing in low resource settings which are most likely to experience a diphtheria outbreak while also ensuring that a toxigenic diphtheria outbreak is still ongoing.

Investigations of contacts might reveal asymptomatic cases, mild respiratory cases without pseudomembranes, or non-respiratory manifestations of disease. These should be identified and counted as laboratory-confirmed or epidemiologically linked cases. They should be treated as outlined in the **Clinical case management** section above.

In very large outbreaks, case-based surveillance and contact tracing may no longer be feasible, and aggregate surveillance may be done instead. Countries should make this decision based on epidemiology and resources. However, case-based surveillance is always preferable because contact tracing and post-exposure prophylaxis can be a life-saving prevention strategy.

PUBLIC HEALTH RESPONSE

The principal response to outbreaks is intensified diphtheria vaccination through a combined approach of selective or non-selective vaccination efforts and strengthening of routine services.

OUTBREAK RESPONSE IN A HIGHLY VACCINATED POPULATION

In case of a first diphtheria case or a small cluster of cases in a highly vaccinated population, contacts of a diphtheria case should be monitored for development of disease, have specimens collected, treated with antibiotics and vaccinated as described above. Contacts who test positive should be monitored until two subsequent cultures after treatment are negative.

OUTBREAK RESPONSE IN POORLY VACCINATED POPULATION

Follow the same steps as you would for an outbreak response in a highly vaccinated population, but consider the urgent initiation of a larger mass-immunization campaign. Vaccination strategy should be based on the epidemiology of the disease targeting the affected areas, and might need to include adult vaccination. Several vaccination strategies can be employed, such as door-to-door vaccination, fixed vaccination posts and in-school vaccination.

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