Committee: Infectious Disease

Title: Revision to the Case Definition for National Diphtheria Surveillance

☒ Check this box if this position statement is an update to an existing standardized surveillance case definition.

I. Statement of the Problem

Diphtheria is caused by toxin-producing *Corynebacterium diphtheriae*. This disease primarily manifests as respiratory infections that may result in death, but it may also present as mild infections in non-respiratory sites, such as the skin. While respiratory diphtheria is now extremely rare, non-respiratory infections caused by toxin-producing bacteria have recently been detected. Non-respiratory disease caused by toxin-producing *C. diphtheriae* may act as a source of transmission and can lead to new respiratory and non-respiratory diphtheria disease; both respiratory and non-respiratory disease caused by toxin-producing bacteria require public health follow-up. The current diphtheria surveillance case definition (position statement '09-ID-05) includes only respiratory disease, and does not clearly distinguish between disease caused by toxin-producing or non-toxin-producing bacteria. The proposed position statement provides modifications to the diphtheria surveillance case definition which better reflect the epidemiology of diphtheria in the U.S, in order to focus efforts on identifying disease caused by toxin-producing bacteria and appropriately guide public health interventions.

II. Background and Justification

Diphtheria is a rare, vaccine-preventable, bacterial disease caused by toxin-producing strains of *C. diphtheriae*. Important sites of infection include the respiratory mucosa and skin. Other non-respiratory sites of infection, such as the conjunctiva, ear, and genital mucosa, may also be affected, although rarely. The hallmark of respiratory diphtheria is the presence of a tough, grayish-white pseudomembrane over the tonsils, the pharynx, or larynx. Before treatment was available, the case-fatality rate for respiratory diphtheria was approximately 50%; with treatment and vaccination more widely available, the case-fatality rate has remained approximately 10%. Cutaneous diphtheria is usually mild, typically consisting of non-distinctive sores or shallow ulcers that are often slow to heal. Historically, humans have been considered the only reservoir of *C. diphtheriae*. The disease is transmitted from person to person by respiratory droplets or direct contact with respiratory secretions or discharges from skin lesions. While seldom developing into invasive or systemic disease, cutaneous diphtheria lesions may act as a reservoir. Further transmission may result in respiratory or non-respiratory infections in other susceptible persons. Infections with non-toxigenic *Corynebacterium* causes less severe disease and are not vaccine-preventable, as the diphtheria toxoid is the antigen for all diphtheria vaccine formulations.

Widespread use of vaccines containing diphtheria toxoid beginning in the 1920s and the introduction of universal childhood immunization in the late 1940s have contributed to diphtheria being well controlled in the U.S. Incidence of diphtheria has declined from >100 cases per 100,000 population (an average 125,000 cases per year) in the 1920s, to less than 0.01 case per 100,000 population annually (0-2 cases per year) in the 2000s. While there has been near elimination of respiratory diphtheria, sporadic cases of toxigenic diphtheria continue to occur and have included non-respiratory site infections.

Diphtheria has been a notifiable condition since 1920. The current case definition only includes respiratory diphtheria cases and does not distinguish between disease caused by toxin and non-toxin producing bacteria. In the time since the case definition was published, respiratory diphtheria has become extremely rare, while non-respiratory infections caused by toxin-producing bacteria have been identified. These non-respiratory infections are most commonly cutaneous. Non-respiratory disease caused by toxin-producing bacteria is typically not severe but transmission to susceptible individuals may efficiently occur. Based on
the current epidemiology in the U.S., a modification to the case definition is necessary to better identify all diphtheria disease caused by toxin-producing *C. diphtheriae* so that transmission and additional disease can be prevented.

### III. Statement of the desired action(s) to be taken

CSTE recommends the following actions:

1. Utilize standard sources (e.g. reporting*) for case ascertainment for diphtheria. Surveillance for diphtheria should use the following recommended sources of data to the extent of coverage presented in Table III.

   [*Reporting: process of a healthcare provider or other entity submitting a report (case information) of a condition under public health surveillance to local or state public health. Note: notification is addressed in a Nationally Notifiable Conditions Recommendation Statement and is the process of a local or state public health authority submitting a report (case information) of a condition on the Nationally Notifiable Conditions List to CDC.*

<table>
<thead>
<tr>
<th>Source of data for case ascertainment</th>
<th>Population-wide</th>
<th>Sentinel sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician reporting</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Laboratory reporting</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Reporting by other entities (e.g., hospitals, veterinarians, pharmacies, poison centers), specify:</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Death certificates</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Hospital discharge or outpatient records</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Extracts from electronic medical records</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Telephone survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School-based survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, specify:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Utilize standardized criteria for case identification and classification (Sections VI and VII and Technical Supplement) for diphtheria.

3. Restrict reporting of respiratory diphtheria to cases of toxin-producing *C. diphtheriae*.

4. Initiate reporting of non-respiratory disease caused by toxin-producing *C. diphtheriae*.

5. Exclude histopathologic diagnosis as a confirmatory diagnostic method.

6. Please see accompanying NNC Recommendation Statement for additional Desired Actions to be Taken (page 7).

### IV. Goals of Surveillance

To rapidly identify any case of diphtheria caused by toxin-producing *C. diphtheriae* and to prevent transmission in the United States.
V. Methods for Surveillance: Surveillance for diphtheria should use the recommended sources of data and the extent of coverage listed in Table III.

Surveillance should be conducted using routine sources of data for vaccine-preventable diseases, including clinician reporting, laboratory reporting, reporting by other health care institutions (e.g., hospitals, veterinarians, pharmacies), death certificate cause of death information, and hospital/electronic medical records.

VI. Criteria for case ascertainment

A. Narrative: A description of suggested criteria for case ascertainment of a specific condition.

Report any illness to public health authorities that meets any of the following criteria:

1. Isolation of toxin-producing *C. diphtheriae* from any anatomical site

2. Acute upper respiratory illness in a person with an adherent membrane of the nose, pharynx, tonsils, or larynx, which is suspected by a health care provider to be possible diphtheria, and for which there is not a more likely diagnosis.

3. A person who is suspected by a health care provider to have a diagnosis of diphtheria and who is a contact of a laboratory-confirmed case of diphtheria.

4. Death certificate lists diphtheria as a cause of death or significant condition contributing to death.

Other recommended reporting procedures

- All cases of diphtheria should be reported.
- Reporting should be ongoing and routine.
- Reporting should be immediate.

B. Disease-specific data elements to be included in the initial report

**Epidemiological Risk Factors**

- Doses of diphtheria toxoid-containing vaccine received
- Year of last known tetanus-diphtheria booster vaccine received
- History of recent international travel to a country with endemic diphtheria
  - Dates
  - Countries visited
- Contact with person(s) who recently returned from a country with endemic or epidemic diphtheria
  - Dates
  - Countries
- Country of birth

VII. Case Definition for Case Classification

A. Narrative: Description of criteria to determine how a case should be classified.

**Clinical Criteria**

- Upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx OR
- Infection of a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa)
Laboratory Criteria

**Confirmatory laboratory evidence:**
Isolation of *C. diphtheriae* from any site AND Confirmation of toxin-production by Elek test or by another validated test capable of confirming toxin-production

**Presumptive laboratory evidence:** N/A

**Supportive laboratory evidence:**
Histopathologic diagnosis

Epidemiologic Linkage

Epidemiologic linkage requires direct contact with a laboratory-confirmed case of diphtheria.

Case Classifications

**Confirmed:**
- An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx and any of the following:
  - isolation of toxin-producing *Corynebacterium diphtheriae* from the nose or throat OR
  - epidemiologic linkage to a laboratory-confirmed case of diphtheria.

OR

- An infection at a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa) with
  - isolation of toxin-producing *C. diphtheriae* from that site

**Suspect:**
- In the absence of a more likely diagnosis, an upper respiratory tract illness with each of the following:
  - an adherent membrane of the nose, pharynx, tonsils, or larynx AND
  - absence of laboratory confirmation AND
  - lack of epidemiologic linkage to a laboratory-confirmed case of diphtheria.

OR

- Histopathologic diagnosis

Comments:
- Cases of laboratory-confirmed, non-toxin-producing *C. diphtheriae* (respiratory or non-respiratory) should not be reported by state or local health departments to CDC as diphtheria cases.
- Negative laboratory results may be sufficient to rule-out a diagnosis of diphtheria; however, clinicians should carefully consider all lab results in the context of the patient’s vaccination status, antimicrobial treatment, and other risk factors.
- PCR and MALDI-TOF diagnostics for *C. diphtheriae*, when used alone, do not confirm toxin production. These tests, when used, should always be combined with a test that confirms toxin production, such as the Elek test.

B. Criteria to distinguish a new case of this disease or condition from reports or notifications which should not be enumerated as a new case for surveillance

Individuals without evidence of clinical criteria as described by the diphtheria surveillance case definition but for whom toxin-producing *Corynebacterium diphtheriae* is confirmed via laboratory testing (isolation and toxigenicity testing by modified Elek test or other validated test capable of confirming toxin-production) should not be classified as cases. These individuals are considered carriers of the bacteria and are not reportable.
VIII. Period of Surveillance
Surveillance should be ongoing.

IX. Data sharing/release and print criteria
CSTE recommends the following case statuses be included in the CDC Print Criteria:

- ☒ Confirmed
- ☐ Probable
- ☐ Suspect
- ☐ Unknown

State/territorial health agencies will report Confirmed cases of diphtheria to CDC. Data will be released to the general public by CDC in the form of aggregated annual counts. More detailed data requests will be referred to the jurisdiction responsible for the diphtheria notification.

X. Revision History

<table>
<thead>
<tr>
<th>Position Statement ID</th>
<th>Section of Document</th>
<th>Revision Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>09-ID-05</td>
<td>I, II, III, VII A &amp; B</td>
<td>Add non-respiratory diphtheria infections</td>
</tr>
<tr>
<td>09-ID-05</td>
<td>I, II, III, VII A &amp; B</td>
<td>Add requirement for toxin-production</td>
</tr>
</tbody>
</table>

XI. References

XII. Coordination

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   18-ID-03

   6
Nationally Notifiable Conditions (NNC) Recommendation Statement

Position Statement Title: Revision to the Case Definition for National Diphtheria Surveillance

Disease/Condition: Diphtheria

☒ This statement updates a disease/condition already on the Nationally Notifiable Conditions List.
☒ No change to the CDC notification timeframe is recommended.
☒ No new subtypes or additional disease/condition categories are added to the accompanying position statement.

This NNC Recommendation Statement recommends the following:
1. Utilize standardized criteria for case identification and classification (based on Sections VI and VII and Technical Supplement of accompanying position statement) for diphtheria and add diphtheria to the Nationally Notifiable Condition List
   ☐ Immediately notifiable, extremely urgent (within 4 hours)
   ☒ Immediately notifiable, urgent (within 24 hours)
☐ Routinely notifiable
☐ No longer notifiable

2. CSTE recommends that all States and Territories enact laws (statute or rule/regulation as appropriate) to make this disease or condition reportable in their jurisdiction. Jurisdictions (e.g. States and Territories) conducting surveillance (according to these methods) should submit case notifications* to CDC.

3. Expectations for Message Mapping Guide (MMG) development for a newly notifiable condition: NNDSS is transitioning to HL7-based messages for case notifications; the specifications for these messages are presented in MMGs. When CSTE recommends that a new condition be made nationally notifiable, CDC must obtain OMB PRA approval prior to accepting case notifications for the new condition. Under anticipated timelines, notification using the Generic V2 MMG would support transmission of the basic demographic and epidemiologic information common to all cases and could begin with the new MMWR year following the CSTE annual conference. Input from CDC programs and CSTE would prioritize development of a disease-specific MMG for the new condition among other conditions waiting for MMGs.

4. CDC should publish data on diphtheria as appropriate (see Section IX of corresponding position statement).

5. CSTE recommends that all jurisdictions (e.g. States or Territories) with legal authority to conduct public health surveillance follow the recommended methods as outlined here and in the accompanying standardized surveillance position statement.

*Notification: process of a local or state public health authority submitting a report (case information) of a condition on the Nationally Notifiable Conditions List TO CDC.
Technical Supplement

Table VI. Table of criteria to determine whether a case should be reported to public health authorities.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Clinical Evidence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory illness with membrane on the tonsil(s), pharynx, larynx, or nose.</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of possible diphtheria by a healthcare provider</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Death certificate lists diphtheria as a cause of death or significant condition contributing to death</td>
<td>N</td>
<td>S</td>
</tr>
<tr>
<td>Absence of a more likely diagnosis</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Laboratory Evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolation of <em>C. diphtheriae</em> from any anatomical site</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Epidemiological Evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact with a laboratory-confirmed case of diphtheria</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
S = This criterion alone is SUFFICIENT to report a case.
N = All "N" criteria in the same column are NECESSARY to report a case.

Table VII. Classification Table: Criteria for defining a case of diphtheria.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Suspect</th>
<th>Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx.</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Infection of a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa)</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Absence of a more likely diagnosis</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Laboratory evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolation of <em>C. diphtheriae</em> from the nose or throat</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Isolation of <em>C. diphtheriae</em> from a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa)</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Confirmation of toxin-production by Elek test or other validated test capable of confirming toxin-production</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Histopathologic diagnosis</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Epidemiologic evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact with a laboratory-confirmed case of diphtheria</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Absence of epidemiologic linkage</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
S = This criterion alone is SUFFICIENT to classify a case.
N = All "N" criteria in the same column are NECESSARY to classify a case. A number following an "N" indicates that this criterion is only required for a specific disease/condition subtype (see below). If the absence of a criterion (i.e., criterion NOT present) is required for the case to meet the classification criteria, list the absence of criterion as a necessary component.