Chapter 1: Diphtheria

Tejpratap S.P. Tiwari, M.D.

I. Disease Description

Diphtheria is an uncommon disease in the United States. It is caused by infection with toxigenic strains of gram-positive *Corynebacterium diphtheriae*. Important sites of infection are the respiratory mucosa (respiratory diphtheria) and the skin (cutaneous diphtheria). Rarely, extra-respiratory mucosal sites, e.g., the eye, ear, or genitals, may be affected. Humans are the only known reservoir of *C. diphtheriae*. The disease is transmitted from person to person by respiratory droplets or direct contact with respiratory secretions, discharges from skin lesions or, rarely, fomites.

The onset of respiratory diphtheria is insidious and begins after an incubation period of 2–5 days. Initial symptoms of illness include a sore throat, difficulty in swallowing, malaise, and low-grade fever. The hallmark of respiratory diphtheria is the presence of an exudate that organizes into a tough, grayish-white pseudomembrane over the tonsils, the pharynx, or larynx. The pseudomembrane is strongly adherent to the underlying tissue, and attempts to dislodge it usually result in bleeding. Accompanying inflammation of the cervical lymph nodes and surrounding soft-tissue swelling of the neck give rise to a "bull-neck" appearance and are signs of moderate to severe disease. The membrane may progressively extend into the larynx and trachea and cause airway obstruction, which, if left untreated, can be fatal. Absorption of diphtheria toxin from the site of infection can cause systemic complications, including damage to the myocardium, nervous system and kidneys. Untreated respiratory diphtheria usually lasts for one to 2 weeks, but complications can persist for months. The case-fatality rate is about 10%. Nontoxigenic strains of *C. diphtheriae* may cause a mild sore throat and, rarely, a membranous pharyngitis, but these strains can be invasive and cause bacteremia and endocarditis.[1] Isolation of nontoxigenic strains of *C. diphtheriae* from the throat does not necessarily indicate a pathogenic role in the illness. A small percentage of the population may carry nontoxigenic or toxigenic strains of *C. diphtheriae* without disease symptoms, but the frequency at which this occurs is unknown.

Cutaneous diphtheria, caused by either toxigenic or nontoxigenic strains of *C. diphtheriae*, is usually mild, typically consisting of nondistinctive sores or shallow ulcers, and rarely causes toxic complications (1%–2% of infections with toxigenic strains). Since 1980, cutaneous diphtheria has not been a nationally reportable disease.

Rarely, other *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*) may produce diphtheria toxin. Toxigenic *C. ulcerans* may cause classic respiratory diphtheria-like illness.[2, 3] Both species may cause disease in animals.

II. Background

Although diphtheria is now reported only infrequently in the United States, in the prevaccine era, the disease was one of the most common causes of illness and death among children. Since the introduction and widespread use of vaccines containing diphtheria toxoid (formalin-inactivated diphtheria toxin) beginning in the 1920s and 1930s and universal childhood immunization in the late 1940s, diphtheria has been well controlled in the United States. In the 1970s, diphtheria was endemic in the Southwest, the Northern Plains, and the Pacific Northwest. The last major outbreak was in Seattle, Washington, in the 1970s.[4] In recent years, some cases in the United States have been related to importation.[5–7] From 1980 to 2010, 55 cases of diphtheria were reported to CDC's National Notifiable Diseases Surveillance System. The majority of cases (77%) were among persons 15 years of age or older. Four of the five fatal cases occurred among unvaccinated children; the fifth fatal case was in a 75-year-old male returning to the United States from a country with endemic disease.[5, 6] Although few cases of respiratory diphtheria have been reported in the United States in the past 2 decades, enhanced surveillance in a previously endemic-disease area—a Northern Plains Indian community—has shown ongoing circulation of toxigenic *C. diphtheriae*.[8] Similarly, endemic circulation of toxigenic *C. diphtheriae* strains has also persisted in some communities in Canada.[9]

Diphtheria remains endemic in many parts of the developing world, including some countries of the Caribbean and Latin America, Eastern Europe, Southeast Asia, and Africa. In the 1990s, a large epidemic of diphtheria occurred in the former Soviet Union where diphtheria had previously been well controlled and this renewed interest in the factors associated with persistent circulation of toxigenic *C. diphtheriae*.[10, 11] During the past decade, many developing countries have achieved high childhood immunization coverage with DTP/DTaP vaccine resulting in significant reduction in diphtheria incidence.[12] However, sporadic cases and outbreaks still occur among population subgroups.[10–12] A feature of these outbreaks is that the majority of cases have occurred among adolescents and adults instead of children. Many of these adolescents and adults had not received routine childhood vaccination or booster doses of diphtheria toxoid. Rarely, outbreaks occur in well-vaccinated populations with intense exposure to toxigenic *C. diphtheriae*, but disease is usually mild and with fewer complications and no fatalities.[13]

III. Importance of Rapid Identification

Prompt recognition and reporting of the disease is important to ensure early, appropriate treatment with diphtheria antitoxin; to obtain necessary laboratory specimens before antibiotic or antitoxin treatment; to identify and evaluate contacts; and to provide necessary antimicrobial prophylaxis to prevent further spread. The outcome of diphtheria infection improves with early, appropriate treatment.

IV. Importance of Surveillance

About half of U.S. adults are estimated to have levels of diphtheria toxin antibodies below the lower limit of protection (0.01 IU/ml). This is because immunity to diphtheria wanes with time after vaccination, and many older adults may not have received either a primary vaccination series or a recommended tetanus-diphtheria toxoid (Td) booster every 10 years. In 1996, endemic transmission of *C. diphtheriae* was documented in a Northern Plains state.[8] Persons traveling to the United States from countries where diphtheria is endemic may import the disease. Therefore, continued awareness of diphtheria is needed and enhanced surveillance is particularly important in areas in which diphtheria was endemic in the 1970s.[8]

The source of infection for persons with diphtheria may be asymptomatic carriers (persons infected with *C. diphtheriae* bacteria in the nose and/or throat but who do not have disease symptoms). Carriers often augment the spread of the bacteria to other persons.

Surveillance, prompt investigation, and treatment of case-patients and close contacts help to halt the spread of disease. Information obtained through surveillance is used to characterize infected persons or areas so that additional intervention efforts can be focused to reduce disease incidence.

V. Disease Reduction Goals

Since 2003, no case of diphtheria was reported in the United States and the *Healthy People 2010* goal to eliminate indigenous diphtheria among persons younger than 35 years of age in the U.S. was achieved.[14]

VI. Case Definition

The following case definition for diphtheria was revised by the Council of State and Territorial Epidemiologists (CSTE) and published in 2010.[15]

Probable: In the absence of a more likely diagnosis, an upper respiratory tract illness with 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.

Confirmed: An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx; and any of the following: isolation of *Corynebacterium diphtheriae* from

the nose or throat; or histopathologic diagnosis of diphtheria; or epidemiologic linkage to a laboratory-confirmed case of diphtheria.

Comment: Cutaneous diphtheria should not be reported. Respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria. All diphtheria isolates, regardless of association with disease, should be sent to the Diphtheria Laboratory, National Center for Immunization and Respiratory Diseases (NCIRD), CDC.

Rarely, respiratory diphtheria-like illness may result from infection with toxigenic *C. ulcerans*. *C. pseudotuberculosis* may also produce a diphtheria toxin but usually causes infection in non-respiratory sites. All Isolates of *C. diphtheriae*, *C. ulcerans*, and *C. pseudotuberculosis* should also be forwarded to CDC.

An epidemiologically linked case is one in which the patient has had contact with one or more persons who have or had the disease, and transmission of the agent by the usual modes of transmission is plausible. A case may be considered epidemiologically linked to a laboratory-confirmed case if at least one case in the chain of transmission is laboratory confirmed.

VII. Laboratory Testing

Diagnostic tests used to confirm infection include isolation of *C. diphtheriae* by culture and toxigenicity testing. Although no other tests for diagnosing diphtheria are commercially available, CDC can perform a polymerase chain reaction (PCR) test on clinical specimens to confirm infection with a toxigenic strain. The PCR assay allows for detection of the regulatory gene for toxin production (dtxR) and the diphtheria toxin gene (tox).[16] PCR is particularly useful if nonviable *C. diphtheriae* organisms are present in clinical specimens that are obtained from a patient after antibiotic therapy has been initiated. The state health department should be contacted to report a suspected case and to arrange for laboratory testing.

Although, as performed by the CDC Diphtheria Laboratory, PCR provides supportive evidence for the diagnosis, data are not yet sufficient for PCR to be accepted as a criterion for laboratory confirmation. A case that is PCR positive without isolation of the organism or histopathologic diagnosis and without epidemiologic linkage to a laboratory-confirmed case should be classified as a probable case.

For additional information on laboratory testing for confirmation of diphtheria, see Chapter 22, "Laboratory Support for the Surveillance of Vaccine-Preventable Diseases."

Note: *Other pathogens can cause a membrane in the throat and over the tonsils, including Streptococcus spp., Epstein-Barr virus and cytomegalovirus (both of which cause infectious mononucleosis syndrome), Arcanobacter hemolyticum, Candida albicans, fusiform bacteria (can cause Vincent's angina), and some viruses. The patient's healthcare provider should be encouraged to perform appropriate laboratory tests to rule out these conditions and organisms.*

Isolation of C. diphtheriae *by culture*

Isolation of *C. diphtheriae* by culture is essential for confirming diphtheria. However, even if the patient's culture is negative, isolation of *C. diphtheriae* from close contacts may help confirm the diagnosis of the case. Clinical specimens for culture should be taken from the nose or nasopharynx, and throat from all persons with suspected cases and their close contacts. If possible, swabs also should be taken from beneath the membrane, or a piece of the membrane should be removed. Specimens for culture should be obtained as soon as diphtheria (involving any site) is suspected, even if treatment with antibiotics has already begun. For more information on collection of clinical specimens, see Appendix 1. The laboratory should be alerted to the suspicion of diphtheria because isolation of *C. diphtheriae* requires special culture media containing tellurite.

Toxigenicity testing and biotyping

After *C. diphtheriae* has been isolated, biotyping should be performed to determine the biotype (intermedius, belfanti, mitis, or gravis), and toxigenicity testing using the Elek test should be done to determine whether the organisms produce diphtheria toxin. Demonstration of toxin

production confirms a case as diphtheria. Note that PCR does not demonstrate production of diphtheria toxin but only detection of the diphtheria toxin gene. A positive PCR test in the absence of a positive culture does not meet the laboratory criteria for classifying a case as confirmed diphtheria. Elek and PCR tests are not readily available in many clinical microbiology laboratories; isolates should be sent to a reference laboratory proficient in performing the tests.

Polymerase chain reaction (PCR) testing

Isolation of *C. diphtheriae* may not always be possible because many patients will have received antibiotics before a diagnosis of diphtheria is considered. PCR allows for detection of the regulatory gene for toxin production (dtxR) and the diphtheria toxin gene (tox) on nonviable organisms. Additional clinical specimens for PCR testing at CDC should be collected when specimens are being collected for culture. Clinical specimens (nasal and throat swabs, pieces of membrane, biopsy tissue) can be transported to CDC with cold packs in a sterile empty container or in silica gel sachets. For detailed information on collection and shipping of specimens, and for arranging PCR testing, the state health department may contact the CDC Diphtheria Laboratory (404-639-1231).

Serologic testing

Measurement of the patient's serum antibodies to diphtheria toxin before administration of antitoxin may help in assessing the probability of the diagnosis of diphtheria. The state health department or CDC can provide information on laboratories that offer this test (few laboratories have the capability to accurately test antibody levels). If antibody levels are less than 0.01 IU/ml, immunity is likely to be absent, but a level of greater than 0.1 IU/ml is considered protective and diphtheria is unlikely to be the cause of the patient's illness. Diphtheria antibody levels between 0.01 IU/ml and 0.09 IU/ml indicate the presence of some or limited immunity.

Submission of C. diphtheriae *isolates*

All isolates of *C. diphtheriae*, whether toxigenic or nontoxigenic, regardless of association with disease, and from any anatomic site (respiratory, cutaneous, or other) should be sent to the CDC Diphtheria Laboratory, CDC, for reference testing. To arrange specimen shipping, the state health department should be contacted.

Submission of isolates of other Corynebacterium *species*

Infrequently, other diphtheria toxin-producing *Corynebacterium* species (e.g., *C. ulcerans* or *C. pseudotuberculosis*) may be isolated from patients. Such isolates should also be sent to the CDC laboratory (404-639-1231).

VIII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[17] These regulations and laws list the diseases that are to be reported, and describe those persons or groups who are responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Persons reporting these conditions should contact their state health department for state-specific reporting requirements.

Reporting to CDC

Suspected diphtheria cases should be reported promptly by telephone to the CDC Emergency Operations Center (770-488-7100) so that diphtheria antitoxin can be obtained for the patient. An FDA-licensed diphtheria antitoxin product is no longer available commercially in the United States. However, diphtheria antitoxin is available from CDC under an Investigational New Drug (IND) protocol[18] (See Section X, "Treatment," for contact information), additional epidemiologic and clinical data are needed as requirements under the IND.

The healthcare provider should notify the state health department promptly so that an epidemiologic investigation can be initiated. Reports of probable and confirmed cases should be forwarded by the state health department to the National Notifiable Disease Surveillance System (NNDSS) via the National Electronic Telecommunications System for Surveillance (NETSS)

or National Electronic Disease Surveillance System (NEDSS). Reporting should not be delayed because of incomplete information or lack of laboratory confirmation.

Respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria. Rarely, respiratory diphtheria-like illness may result from infection with other *Corynebacterium* species (e.g., *C. ulcerans*, *C. pseudotuberculosis*). Such cases should also be reported to CDC.

Cutaneous diphtheria is no longer notifiable, and these cases should not be reported to NNDSS.

Information to collect

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may also be collected at the direction of the state health department.

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
  - Length of time in United States
- Reporting Source
  - County
  - Earliest date reported
- Clinical
  - Hospitalizations: dates and duration of stay
  - Date of illness onset
  - Site of infection (e.g., nose, throat, larynx)
  - Symptoms (e.g., fever, sore throat)
  - Signs (e.g., neck edema, stridor, tachycardia)
  - Complications (e.g., myocarditis, neuritis)
  - Outcome (patient survived or died)
    - Date of death
    - Postmortem examination results
    - Death certificate diagnoses
- Treatment
  - Date of administration of antitoxin
  - Number of units of antitoxin given
  - Antibiotics given
  - Antibiotic dosage given
  - Duration of therapy
- Laboratory
  - Culture
  - Biotype and toxigenicity test
  - PCR
  - Molecular typing

- Vaccine information
  - Dates and types of diphtheria vaccination
  - Number of doses of diphtheria toxoid received
  - Manufacturer name
  - Vaccine lot number
  - If not vaccinated, reason
- Epidemiologic
  - Contact with a probable or confirmed case
  - Contact with immigrants or returning travelers from endemic-disease areas
  - Number of contacts cultured
  - Results of contact cultures
  - Local or international travel history: 6-week period before illness onset or date of presentation
  - Contact with domestic pets, horses, or dairy farm animals

IX. Vaccination

Primary diphtheria immunization with diphtheria-tetanus toxoids-acellular pertussis vaccine (DTaP) is recommended for all persons at least 6 weeks old but less than 7 years of age and without a history of contraindications. DTaP is the preferred vaccine for all doses in the infant and childhood vaccination series (including completion of the series for children who have received one or more doses of whole-cell DTP). The primary vaccination with DTaP series consists of a three-dose series, administered at ages 2, 4, and 6 months, with a minimum interval of 4 weeks between doses. The fourth (first booster) dose is recommended at 15–18 months of age to maintain adequate immunity during preschool years. The fourth dose should be administered at least 6 months after the third. If the interval from the third dose is 6 months or greater and the child is unlikely to return for a visit at the recommended age, the fourth dose of DTaP may be administered as early as age 12 months. The fifth (second booster) dose is recommended for children aged 4–6 years to confer continued protection against disease during the early years of schooling. A fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.[19]

Adolescents 11–18 years of age should receive a single dose of Tdap instead of Td for booster immunization against tetanus, diphtheria, and pertussis if they have completed the recommended childhood DTP/DTaP vaccination series. Thereafter, routine booster doses of Td vaccine should be given at 10-year intervals. Adolescents and adults who have never been vaccinated against diphtheria should receive a primary series of three doses of Td. The first two doses should be administered at least 4 weeks apart, and the third dose 6–12 months after the second dose. For added protection against pertussis, Tdap can substitute for any one dose in the 3-dose primary series. Td is preferred to TT for adults as part of wound management if the last dose of Td was received five or more years earlier. Up-to-date vaccination against diphtheria is especially important for travelers who will be living or working with local populations in countries where diphtheria is endemic.[20]

For added protection against pertussis, adults 19 years and older should receive a single dose of Tdap (ADACEL®, BOOSTRIX®) to replace a single routine booster dose of Td, if they received their last dose of Td 10 or more years earlier and have not previously received a dose of Tdap.[21, 22]

Healthcare providers should ensure that travelers to all countries with endemic or epidemic diphtheria are up-to-date with diphtheria vaccination. Information on countries with diphtheria is summarized in a recent publication by the World Health Organization[23] and updates can be found on the CDC website for travelers at http://www.cdc.gov/travel. Vaccine providers should carefully review the vaccine history of all travelers to areas with endemic and epidemic diphtheria to ensure that they are optimally protected according to the recommendations of the Advisory Committee on Immunization Practices.[19–23]

X. Treatment

Diphtheria antitoxin

The mainstay of treatment of a case of suspected diphtheria is prompt administration of diphtheria antitoxin. This should be given without waiting for laboratory confirmation of a diagnosis. The recommended dosage and route of administration depend on the extent and duration of disease. Diphtheria antitoxin is currently available for treatment of clinical cases of respiratory diphtheria in the United States only through CDC under an FDA-approved Investigational New Drug protocol. The healthcare provider should contact CDC Emergency Operations Center (770-488-7100) to obtain diphtheria antitoxin and assistance for its transport,[18] and notify the local and state health departments for public health investigation.

Antibiotics

Persons with suspected diphtheria should also receive antibiotics to eradicate carriage of *C. diphtheriae*, to limit transmission, and to halt further production of diphtheria toxin.[24] Treatment with erythromycin or penicillin is administered as a 14-day course.

Vaccination

Because diphtheria disease does not always confer immunity, an age-appropriate vaccine containing diphtheria toxoid should be administered during convalescence.

Contacting CDC

Providers should contact the CDC Emergency Operations Center (770-488-7100) to request diphtheria antitoxin.

XI. Enhancing Surveillance

Because diphtheria has occurred only rarely in the United States in recent years, many clinicians may not include diphtheria in their differential diagnoses. Clinicians are reminded to consider the diagnosis of respiratory diphtheria in patients with membranous pharyngitis and who are not up-to-date with vaccination against diphtheria. However, if diphtheria is suspected, appropriate laboratory confirmation may not be feasible locally because isolation of the organism requires selective media. Treatment with antibiotics before specimen collection may further decrease the probability of isolating the organism. Local health departments should assure the availability of laboratory capacity for isolation of *C. diphtheriae*, and at the state level, reference capacity for biotyping, and toxigenicity testing should be available. Laboratories should maintain proficiency in the necessary laboratory procedures.

In areas with endemic *C. diphtheriae* in the 1970s, public health officials should consider recommending routine screening for *C. diphtheriae* of clinical specimens obtained from patients in high-risk populations who have pharyngitis or ear drainage. High-risk populations are defined according to the epidemiology of diphtheria in the area. For consultation and assistance in deciding which populations may be at increased risk for *C. diphtheriae* infection, contact the state health department. See Chapter 19, "Enhancing Surveillance," for additional recommendations for enhancing surveillance of vaccine-preventable diseases.

XII. Case Investigation

Guidelines for investigating a suspected case and for managing contacts are published and are included in Appendix 2 (Figure 1.23).

Management of contacts of persons with suspected cases should include screening for possible respiratory or cutaneous diphtheria, obtaining nasopharyngeal cultures for *C. diphtheriae*, administering prophylactic antibiotics, assessing diphtheria vaccination status, and administering any necessary vaccinations. The CDC Diphtheria Worksheet may be used for guidelines in conducting a case investigation (see Appendix 3).

References

1. Gubler J, Huber-Schneider C, Gruner E, Altwegg M. An outbreak of nontoxigenic. *Corynebacterium diphtheriae* infection: single bacterial clone causing invasive infection among Swiss drug users. *Clin.Infect.Dis* 1998;27:1295–8.
2. CDC. Respiratory diphtheria caused by *Corynebacterium ulcerans*—Terre Haute, Indiana, 1996. *MMWR*. 1997;46:330–2.
3. Wong TP, Groman N. Production of diphtheria toxin by selected isolates of *Corynebacterium ulcerans* and *Corynebacterium pseudotuberculosis*. *Infect Immun* 1984;43:1114–6.
4. Chen RT, Broome CV, Weinstein RA, Weaver R, Tsai TF. Diphtheria in the United. States, 1971–81. *Am J Public Health* 1985;75:1393–7.
5. Bisgard KM, Hardy IR, Popovic T, Strebel PM, Wharton M, Chen RT, Hadler SC. Respiratory diphtheria in the United States, 1980 through 1995. *Am J Public Health* 1998;88:787–91.
6. CDC. Summary of notifiable diseases–United States, 2003. MMWR 2003;52:71–5.
7. CDC. Fatal respiratory diphtheria in a U.S. traveler to Haiti – 2003. *MMWR* 2003;52:1285–6.
8. CDC. Toxigenic *Corynebacterium diphtheriae* – Northern Plains Indian Community, August-October 1996. *MMWR* 1997;46:506–10.
9. Marston CK, Jamieson F, Cahoon F, Lesiak G, Golaz A, Reeves M, et al. Persistence of a distinct *Corynebacterium diphtheriae* clonal group within two communities in the United States and Canada where diphtheria is endemic. *J Clin Microbiol* 2001;39:1586–90.
10. Galazka AM, Robertson SE, Oblapenko GP. Resurgence of diphtheria. *Eur J Epidemiol* 1995;11:95–105.
11. Galazka A. Implications of the diphtheria epidemic in the former Soviet Union for immunization programs. *J Infect Dis* 2000;181 [Suppl 1]:S244–8.
12. Tharmaphornpilas P, Yoocharoan P, Prempree P, Youngpairoj S, Sriprasert P, Vitek CR. Diphtheria in Thailand in the 1990s. *J Infect Dis* 2001;184:1035–40.
13. Ohuabunwo CJ, Perevoscikovs J, Griskevica A, Gargiullo P, Brilla A, Viksna L, et al. Respiratory diphtheria among highly vaccinated military trainees in Latvia: improved protection from DT compared with Td booster vaccination. *Scand J Infect Dis* 2005;37:813–20.
14. US Department of Health and Human Services. Healthy People 2010. 2nd. ed. With understanding and improving health and objectives for improving health (2 vols.). Washington DC: US Department of Health and Human Services, 2000.
15. Council of State and Territorial Epidemiologists (CSTE). 2009 Position statements. CSTE Meeting, Buffalo, NY; Position statement 09-ID-05.
16. Nakao H, Popovic T. Development of a direct PCR assay for detection of the diphtheria toxin gene. *J Clin Microbiol* 1997;35:1651–5.
17. Roush S, Birkhead G, Koo D, Cobb A, Fleming D. Mandatory reporting of diseases and conditions by health care professionals and laboratories. *JAMA* 1999;282:164–70.
18. CDC. Availability of diphtheria antitoxin through an investigational new drug protocol. *MMWR* 2004;53:413.
19. CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2011;60(No. RR-2):3–61.
20. CDC. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55 (No. RR-3):1–34.

21. CDC. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR* 2006;55(No. RR-17):1–35.
22. CDC. Updated Recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. *MMWR* 2011; 60:13-15.
23. World Health Organization. WHO vaccine-preventable diseases monitoring system: 2006 global summary. Geneva, Switzerland: World Health Organization, 2006. Available at http://www.who.int/vaccines-documents/GlobalSummary/GlobalSummary.pdf. Accessed 6-9-2011.
24. Farizo KM, Strebel PM, Chen RT, Kimbler A, Cleary TJ, Cochi SL. Fatal respiratory disease due to *Corynebacterium diphtheriae*: case report and review of guidelines for management, investigation, and control. *Clin Infect Dis* 1993;16:59–68.