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Chapter 7: Diphtheria

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AT A GLANCE

This chapter discusses pathogenesis, clinical features, epidemiology, vaccination, and surveillance of diphtheria.

Introduction

Keep in mind

The 14th edition of the "Pink Book" was published August 2021. Vaccine-specific recommendations may be outdated. Refer to the CDC website for updated Diphtheria, Tetanus, and Pertussis Vaccination Information for Healthcare Professionals.

Diphtheria

- Described by Hippocrates in 5th century BCE
- Epidemics described in 6th century
- Bacterium first observed in 1883 and cultivated in 1884
- Diphtheria toxoid developed in 1920s

Diphtheria is an acute, bacterial disease caused by toxin-producing strains of *Corynebacterium diphtheriae*. The name of the disease is derived from the Greek diphthera, meaning 'leather hide.' The disease was described in the 5th century BCE by Hippocrates, and epidemics were described in the 6th century AD by Aetius. The bacterium was first observed in diphtheritic membranes by Edwin Klebs in 1883 and cultivated by Friedrich Löffler in 1884. Beginning in the early 1900s, prophylaxis was attempted with combinations of toxin and antitoxin. Diphtheria toxoid was developed in the early 1920s but was not widely used until the early 1930s. It was incorporated with tetanus toxoid and pertussis vaccine and became routinely used in the 1940s.

Corynebacterium diphtheriae

Corynebacterium diphtheria

- Aerobic gram-positive bacillus
- Toxin production occurs when bacillus is infected by corynebacteriophages carrying *tox* gene
- Four biotypes: gravis, intermedius, mitis, and belfanti
- All isolates should be tested for toxigenicity

C. diphtheriae is an aerobic, gram-positive bacillus. Toxin production (toxigenicity) occurs only when the bacillus is itself infected (lysogenized) by specific viruses (corynebacteriophages) carrying the genetic information for the toxin (*tox* gene). Diphtheria toxin causes the local and systemic manifestations of diphtheria.

C. diphtheriae has four biotypes: gravis, intermedius, mitis, and belfanti. All biotypes can become toxigenic and cause severe disease. All isolates of *C. diphtheriae* should be tested for toxigenicity.

Pathogenesis

Diphtheria Pathogenesis

- Toxigenic diphtheria bacilli acquired in the nasopharynx
  - Produces a toxin that inhibits cellular protein synthesis, destroys local tissue, and forms a pseudomembrane
  - Responsible for major complications, including: myocarditis, polyneuropathies, nephritis, and thrombocytopenia
- Non-toxin-producing *C. diphtheriae* strains cause mild to severe exudative pharyngitis and sometimes lesions, endocarditis, bacteremia, and septic arthritis

Susceptible persons may acquire toxigenic diphtheria bacilli in the nasopharynx. The organism produces a toxin that inhibits cellular protein synthesis and is responsible for local tissue destruction and formation of the pseudomembrane that is characteristic of this disease. The toxin produced at the site of the membrane is absorbed into the bloodstream and then distributed to the tissues of the body. The toxin is responsible for major complications such as myocarditis, polyneuropathies, and nephritis, and can also cause thrombocytopenia.

Non-toxin-producing *C. diphtheriae* strains can cause mild to severe exudative pharyngitis. Severe cases with pseudomembranes caused by such strains have been reported rarely; it is possible that these infections were caused by toxigenic strains that were not detected because of inadequate culture sampling. Other manifestations of nontoxigenic *C. diphtheriae* infection include cutaneous lesions, endocarditis, bacteremia, and septic arthritis.

Clinical Features

EXPAND ALL +

Diphtheria Clinical Features

- Incubation period 2 to 5 days (range, 1 to 10 days)
- May involve any mucous membrane
- Classified based on site of disease
  - Respiratory (pharyngeal, tonsillar, laryngeal, nasal)
  - Non-respiratory (cutaneous and other mucus membranes)
- Most common sites of infection are the pharynx and tonsils

The incubation period for diphtheria is 2 to 5 days, with a range of 1 to 10 days. Disease can involve almost any mucous membrane. In untreated people, organisms can be present in discharges and lesions 2 to 6 weeks after infection. For clinical purposes, it is convenient to classify diphtheria by anatomic site: respiratory (pharyngeal, tonsillar, laryngeal, nasal) and non-respiratory (cutaneous and other mucus membranes) disease.

Pharyngeal and Tonsillar Diphtheria +

The most common sites of diphtheria infection are the pharynx and the tonsils. Infection at these sites is usually associated with substantial systemic absorption of toxin. The onset of pharyngitis is gradual. Early symptoms include malaise, sore throat, anorexia, and low-grade fever (less than 101°F). Within 2 to 3 days, a bluish-white membrane forms and extends, varying in size from covering a small patch on the tonsils to covering most of the soft palate. Often by the time a physician is contacted the membrane is greyish-green or, if bleeding has occurred, black. There is a minimal amount of mucosal erythema surrounding the membrane. The membrane is firmly adherent to the tissue, and forcible attempts to remove it cause bleeding. Extensive membrane formation may result in respiratory obstruction.

While some patients may recover at this point without treatment, others may develop severe disease. The patient may appear quite toxic, but the fever is usually not high. Patients with severe disease may develop marked edema of the submandibular areas and the anterior neck along with lymphadenopathy, giving a characteristic "bull neck" appearance. If enough toxin is absorbed, the patient can develop severe prostration, pallor, rapid pulse, stupor, and coma. Death can occur within 6 to 10 days.

Laryngeal Diphtheria

Laryngeal diphtheria can be either an extension of the pharyngeal form or can involve only this site. Symptoms include fever, hoarseness, and a barking cough. The membrane can lead to airway obstruction, coma, and death.

Anterior Nasal Diphtheria

The onset of anterior nasal diphtheria looks much like the common cold and is usually characterized by a mucopurulent nasal discharge that may become blood-tinged. A white membrane usually forms on the nasal septum. The disease is usually fairly mild because of apparent poor systemic absorption of toxin from this location, and it can be terminated rapidly by diphtheria antitoxin and antibiotic therapy.

Cutaneous Diphtheria

Skin infections may be manifested by a scaling rash or by ulcers with clearly demarcated edges and an overlying membrane, but any chronic skin lesion may harbor *C. diphtheriae* along with other organisms. Cutaneous diphtheria is quite common in the tropics and is probably responsible for the high levels of natural immunity found in these populations. Infection with toxigenic strains appears to result less frequently in systemic complications with cutaneous compared to other forms of diphtheria. *C. diphtheriae* isolated from cutaneous cases in the United States typically has been nontoxigenic, although recently a number of imported toxigenic cutaneous cases have been identified.

Other

Other rare sites of involvement include the mucous membranes of the conjunctiva and vulvovaginal area, as well as the external auditory canal.

Complications

Diphtheria Complications

- Most complications attributable to toxin
- Severity generally related to extent of local disease
- Most frequent complications are myocarditis and neuritis
- Death occurs in 5%-10%

Most complications of diphtheria, including death, are caused by effects of the toxin. The severity of the disease and complications are generally related to the extent of local disease. The toxin, when absorbed, affects organs and tissues distant from the site of invasion. The most frequent complications of diphtheria are myocarditis and neuritis.

Myocarditis may present as abnormal cardiac rhythms and can occur early in the course of the illness or weeks later. Myocarditis can lead to heart failure and, if it occurs early, it is often fatal.

Neuritis most often affects motor nerves and usually resolves completely. Paralysis of the soft palate is most frequent during the third week of illness. Paralysis of eye muscles, limbs, and the diaphragm can occur after the fifth week. Secondary pneumonia and respiratory failure may result from diaphragmatic paralysis.

Other complications include otitis media and respiratory insufficiency due to airway obstruction, especially in infants.

The estimated overall case fatality ratio for diphtheria is 5% to 10%.

Laboratory Testing

Diagnosis of respiratory diphtheria is usually made based on clinical presentation because it is imperative to begin presumptive therapy quickly. Non-respiratory diphtheria, such as cutaneous diphtheria, may not be clinically suspected and therefore diagnosis is typically based on the laboratory finding.

Confirmatory testing for diphtheria includes culture to identify the bacterial species and the Elek test to confirm diphtheria toxin production. Capacity for diphtheria culture may be available at public health or commercial laboratories. CDC's Pertussis and Diphtheria Laboratory routinely performs culture to confirm *C. diphtheriae* and is currently the only laboratory in the United States that tests for toxin production. It is critical to take a swab of the affected area, especially any ulcerations or pseudomembranes. The organism can be cultured on common laboratory media; culture on a selective medium containing tellurite allows for distinguishing *C. diphtheriae* and *C. ulcerans* from other Corynebacterium species that normally inhabit the nasopharynx and skin (e.g., diphtheroids). However, further biochemical tests are required to fully identify an isolate as *C. diphtheriae*. If *C. diphtheriae* or *C. ulcerans* are isolated, they must be tested for toxin production.

If antibiotic therapy was started prior to specimen collection from a suspected diphtheria case, and culture was negative for *C. diphtheriae*, two sources of evidence can help support presumptive diagnosis:

1. a positive polymerase chain reaction (PCR) test for diphtheria *tox* gene;
2. isolation of *C. diphtheriae* from cultures of specimens from close contacts.

Medical Management +

Diphtheria Antitoxin

Diphtheria antitoxin, produced in horses, has been used for treatment of respiratory diphtheria in the United States since the 1890s. It typically is not administered in cases of non-respiratory diphtheria and it is not indicated for prophylaxis of diphtheria patient contacts. Diphtheria antitoxin is available only from CDC, through an Investigational New Drug (IND) protocol. Diphtheria antitoxin does not neutralize toxin that is already fixed to tissues, but it will neutralize circulating toxin and prevent progression of disease.

After a provisional clinical diagnosis of respiratory diphtheria is made, appropriate specimens should be obtained for culture and the patient placed in isolation. Persons with suspected diphtheria should be promptly given diphtheria antitoxin and antibiotics in adequate dosage, without waiting for laboratory confirmation. Respiratory support and airway maintenance should also be provided as needed. Consultation on the use of and access to diphtheria antitoxin is available through the duty officer at CDC's Emergency Operations Center at 770-488-7100.

Antibiotics

In addition to diphtheria antitoxin, patients with respiratory diphtheria should also be treated with antibiotics. The disease is usually no longer contagious 48 hours after antibiotics have been given. Elimination of the organism should be documented by two consecutive negative cultures taken 24 hours apart, with the first specimen collected 24 hours after therapy is completed.

Preventive Measures +

Diphtheria disease might not confer immunity. Unvaccinated or incompletely vaccinated persons recovering from diphtheria should begin or complete active immunization with diphtheria toxoid during convalescence.

Vaccination history of close contacts of diphtheria patients should also be assessed: if vaccination history is incomplete or unknown, the contact should receive a dose of diphtheria toxoid-containing vaccine immediately, and the vaccination series should be completed according recommendations from the Advisory Committee on Immunization Practices (ACIP). If the contact is up-to-date according to ACIP recommendations but the last dose was more than 5 years ago, a diphtheria toxoid-containing vaccine should be immediately administered. In addition, close contacts should receive a single intramuscular dose of benzathine penicillin G or a 7- to 10-day course of oral erythromycin. Benzathine penicillin G should be given to contacts for whom surveillance cannot be maintained for 7 to 10 days. Contacts should be closely monitored and begin diphtheria antitoxin treatment at the first signs of illness.

Epidemiology

EXPAND ALL +

Diphtheria Epidemiology

- Reservoir
  - Human

- Transmission
  - Person-to-person through respiratory droplets
  - Exposure to infected skin lesions and fomites
- Temporal pattern
  - Winter and spring in temperate climates
- Communicability
  - As long as virulent bacilli are present in discharge and lesions

Occurrence +

Diphtheria occurs worldwide, particularly in countries with suboptimal vaccination coverage. Diphtheria is rare in industrialized countries, including the United States. Because it is a rare disease, seasonal and geographic distribution patterns are no longer observed.

Reservoir +

Humans are the reservoir for *C. diphtheriae*.

Transmission +

Transmission is most often person-to-person through respiratory droplets. Transmission may also occur from exposure to infected skin lesions or articles soiled with discharges from these lesions.

Temporal Pattern +

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

Communicability +

Transmission may occur as long as virulent bacilli are present in discharges and lesions. Effective antibiotic therapy promptly terminates shedding.

Secular Trends in the United States

Diphtheria Secular Trends in the United States

- 100,000-200,000 cases and 13,000-15,000 deaths reported annually in 1920s before vaccine
- Cases gradually declined after vaccines introduced in 1940s; cases rapidly declined after universal vaccination program introduction in late 1940s
- From 1996 to 2018, 14 cases and 1 death reported in the United States

During the 1920s, 100,000–200,000 cases of diphtheria (140–150 cases per 100,000 population) and 13,000–15,000 deaths were reported each year. After diphtheria toxoid-containing vaccines became available in the 1940s, the number of cases gradually declined to about 19,000 in 1945 (15 cases per 100,000 population). A more rapid decrease began with implementation of a universal childhood vaccination program which included diphtheria toxoid-containing vaccines beginning in the late 1940s.

From 1996 through 2018, 14 cases of diphtheria were reported in the United States, an average of less than 1 per year. One fatal case occurred in a 63-year-old male returning to the United States from a country with endemic diphtheria disease.

Within the United States, coverage with diphtheria toxoid childhood vaccines (DTaP) has been consistently high. Among children born during 2016–2017, 93.3% had received at least 3 doses of DTaP vaccine by age 24 months, and 80.6% had received at least 4 doses of DTaP vaccine by age 24 months. Coverage with the adolescent and adult diphtheria toxoid vaccines (Tdap or Td) is variable: Tdap coverage among adolescents age 13 through 17 years reached 90.2% in 2019.

Diphtheria Toxoid-containing Vaccines

Diphtheria Toxoid-containing Vaccines

- DT
- DTaP (Daptacel and Infanrix)
- Td (Tdvax and Tenivac)
- Tdap (Adacel and Boostrix)
- DTaP-HepB-IPV (Pediarix)
- DTaP-IPV/Hib (Pentacel)
- DTaP-IPV (Kinrix and Quadracel)
- DTaP-IPV-Hib-HepB (Vaxelis)

Diphtheria toxoid is produced by growing toxigenic *C. diphtheriae* in liquid medium.

Diphtheria toxoid is combined with tetanus toxoid as diphtheria and tetanus toxoid (DT) vaccine or tetanus and diphtheria toxoid (Td [Tenivac and Tdvax]) vaccine. Diphtheria toxoid is also combined with both tetanus toxoid and acellular pertussis vaccine as DTaP (Infanrix and Daptacel) or Tdap (Boostrix and Adacel) vaccines. Td contains reduced amounts of diphtheria toxoid compared with DT. DTaP and Tdap contain the same pertussis components, but Tdap contains a reduced quantity of some pertussis antigens and diphtheria toxoid. Boostrix contains a reduced quantity of tetanus toxoid compared to Infanrix.

Children younger than age 7 years should receive DTaP vaccine or DT vaccine (in instances where the pertussis vaccine component is contraindicated or where the physician decides that pertussis vaccine is not to be administered). Persons age 7 years or older should receive the Td vaccine or Tdap vaccine, even if they have not completed a series of DTaP or DT (Tdap would be off-label for children age 7 through 9 years but is still recommended by ACIP). Tdap (Boostrix) is approved for persons age 10 years or older; Tdap (Adacel) is approved for persons age 10 through 64 years. DTP vaccines are combined diphtheria and tetanus toxoids and whole cell pertussis vaccine, but none are currently licensed in the United States.

There are five combination vaccines that contain DTaP vaccine. DTaP-HepB-IPV (Pediarix) is licensed for the first 3 doses of the DTaP series among children age 6 weeks through 6 years. DTaP-IPV/Hib (Pentacel) is licensed for the first 4 doses of the component vaccines among children age 6 weeks through 4 years. DTaP-IPV (Kinrix) is licensed only for the fifth dose of DTaP and fourth dose of IPV among children age 4 through 6 years. DTaP-IPV (Quadracel) is licensed only for the fifth dose of DTaP and fourth or fifth dose of IPV among children age 4 through 6 years. DTaP-IPV-Hib-HepB (Vaxelis) is licensed for use in children age 6 weeks through 4 years.

Characteristics

Diphtheria Toxoid-containing Vaccine Characteristics

- Administered by intramuscular injection
- Contains aluminum as an adjuvant

Diphtheria toxoid-containing vaccines are administered by intramuscular injection. Each dose of diphtheria toxoid-containing vaccines contains aluminum as an adjuvant but no preservative. DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel), DTaP-IPV-Hib-HepB (Vaxelis), DTaP-IPV (Kinrix), and DTaP-IPV (Quadracel) contain neomycin and polymyxin B as antibiotics. DTaP-IPV-Hib-HepB (Vaxelis) contains streptomycin as an antibiotic. DTaP-HepB-IPV (Pediarix) and DTaP-IPV-Hib-HepB (Vaxelis) vaccines contain yeast protein. Presentations of some diphtheria toxoid-containing vaccines contain latex rubber.

Vaccination Schedule and Use

EXPAND ALL +

DTaP (Infanrix and Daptacel)

Diphtheria Toxoid-containing Vaccine Schedule

- DTaP
  - 3-dose primary series at age 2, 4, and 6 months
  - Primary series interval of 4- to 8-weeks and minimum interval 4 weeks
  - Boosters at age 15 through 18 months and age 4 through 6 years
  - Minimum interval for dose 4 is 6 months from dose 3 and minimum age is 12 months
  - If dose 4 is given on or after 4th birthday, the 5th dose is optional
  - DT is used in place of DTaP if child has a valid contraindication to pertussis vaccine

DTaP (diphtheria, tetanus toxoids, and acellular pertussis vaccine) is recommended for children age 6 weeks through 6 years. The routine schedule is a primary series of 3 doses at age 2, 4, and 6 months, a booster dose between age 15 through 18 months, and another booster dose between age 4 through 6 years (total of 5 doses). The first 3 doses should be given at 4- to 8-week intervals (minimum of 4 weeks). Dose 4 should follow dose 3 by no less than 6 months and should not be administered before age 12 months.

Dose 4 of both brands of DTaP is recommended to be administered at age 15 through 18 months (15 through 20 months for Daptacel). Dose 4 may be given as early as age 12 months if at least 6 months have elapsed since dose 3 and, in the opinion of the vaccine provider, the child is unlikely to return for an additional visit between age 15 through 18 months.

Children who received 4 doses before their fourth birthday should receive a fifth dose of DTaP before entering school. The fifth dose is not necessary (but may be given) if dose 4 in the series was given on or after the fourth birthday. Administering the fifth dose increases antibody levels and may decrease the risk of school-age children transmitting the disease to younger siblings who are not fully vaccinated.

If a child has a valid contraindication to pertussis vaccine, DT should be used to complete the vaccination series. If the child was younger than age 12 months when the first dose of DT was administered (as DTP, DTaP, or DT), the child should receive a total of 4 DT doses. If the child was age 12 months or older at the time the first dose of DT was administered, 3 doses (with dose 3 administered 6 through 12 months after dose 2) will complete the primary DT series. If dose 4 of DTP, DTaP, or DT is administered before the fourth birthday, a fifth dose is recommended at age 4 through 6 years.

DTaP-HepB-IPV (Pediarix)

DTaP-HepB-IPV vaccine is approved for use as a 3-dose series for children age 6 weeks through 6 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-HepB-IPV vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-HepB-IPV vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-HepB-IPV vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-HepB-IPV vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV/Hib (Pentacel)

DTaP-IPV/Hib vaccine is approved for use as a 4-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, 6, and 15 through 18 months. The minimum intervals for DTaP-IPV/Hib vaccine are determined by the DTaP component. The first 3 doses must be separated by at least 4 weeks between doses. Dose 4 must be separated from dose 3 by at least 6 months, and should not be administered before age 12 months. When DTaP-IPV/Hib vaccine is used to provide 4 doses at age 2, 4, 6, and between 15 through 18 months (based on the DTaP and Hib schedules), an additional booster dose with IPV-stand alone or DTaP-IPV vaccine should be administered at age 4 through 6 years. This will result in a 5-dose IPV vaccine series, which is acceptable.

DTaP-IPV-Hib-HepB (Vaxelis)

DTaP-IPV-Hib-HepB is approved for use as a 3-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-IPV-Hib-HepB vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-IPV-Hib-HepB vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-IPV-Hib-HepB vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-IPV-Hib-HepB vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV (Kinrix)

DTaP-IPV (Kinrix) vaccine is approved only for dose 5 of DTaP vaccine and dose 4 of IPV vaccine in children age 4 through 6 years whose previous DTaP vaccine doses have been with Infanrix and/or Pediarix for dose 1, 2, and 3 and Infanrix for dose 4. However, if DTaP-IPV (Kinrix) vaccine is administered to children who received another brand of DTaP vaccine for prior DTaP vaccine doses, or if administered as dose 1, 2, 3, or 4 of the DTaP vaccine series or dose 1, 2, or 3 of the IPV vaccine series, the dose of DTaP-IPV (Kinrix) does not need to be repeated.

DTaP-IPV (Quadracel)

DTaP-IPV (Quadracel) vaccine is approved only for dose 5 of DTaP vaccine and dose 4 or 5 of IPV vaccine in children age 4 through 6 years who have received 4 doses of Pentacel and/or Daptacel vaccine. However, if DTaP-IPV (Quadracel) vaccine is administered to children who received another brand of DTaP vaccine for prior DTaP vaccines doses, or if administered as dose 1, 2, 3, or 4 of the DTaP vaccine series or dose 1, 2, or 3 of the IPV series, the dose of DTaP-IPV (Quadracel) does not need to be repeated.

Diphtheria Toxoid-containing Vaccine Schedule

- Tdap
  - 1 dose at age 11 through 18 for adolescents who have completed DTaP series
  - Booster dose of Td or Tdap every 10 years for all persons

Tdap (Boostrix and Adacel) and Td (Tenivac and Tdvax)

Use of Tdap

- 1 dose Tdap during each pregnancy (off-label use)
- 1 dose Tdap for the following with no previous documentation of Tdap: adults, adolescents and adults who have or anticipate having close contact with an infant younger than age 12 months, and health care personnel
- 3 doses of tetanus- and diphtheria-containing vaccine (1 dose should be Tdap) for adolescents and adults without documentation of a primary series

Both Tdap vaccines are approved by the FDA for a booster dose for persons who have completed the recommended childhood DTP/DTaP vaccination series. Boostrix is approved for persons age 10 years or older. Adacel is approved for a single dose in persons age 10 through 64 years. A second dose of Adacel is also licensed for administration 8 or more years after the first Tdap dose and for use for tetanus prophylaxis when indicated for wound management if at least 5 years have elapsed since the previous receipt of any tetanus toxoid-containing vaccine. Both Td vaccines are approved for use in persons age 7 years or older.

A single Tdap dose is recommended for adolescents age 11 through 18 years who have completed the recommended childhood DTP/DTaP vaccination series, preferably at age 11 through 12 years. Adults age 19 years or older who have not previously received Tdap should receive a single dose of Tdap. To reduce the burden of pertussis in infants, a dose of Tdap has been recommended during each pregnancy since 2012, although this practice is an off-label use.

All adolescents and adults should have received a primary series of at least 3 documented doses of tetanus and diphtheria toxoids-containing vaccine (i.e., DTaP, DTP, DT, or Td) during their lifetime. A person without such documentation should receive a series of 3 doses of tetanus- and diphtheria-containing vaccine. One of these doses, preferably the first, should be Tdap. The remaining 2 doses should be either Td or Tdap.

For persons age 7 to 9 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap dose should be administered at age 11 through 12 years. If a Tdap dose is administered at age 10 years or older, the Tdap dose may count as the adolescent Tdap dose. Either brand of Tdap may be used.

Adults age 19 years or older who previously have not received Tdap should receive a single dose of Tdap to protect against pertussis and reduce the likelihood of transmission. For adults age 19 through 64 years, either brand of Tdap may be used. Adults age 65 years or older should be vaccinated with Boostrix, if feasible. However, either vaccine administered to a person age 65 years or older is immunogenic and would provide protection. A dose of either vaccine would be considered valid.

Adolescents and adults who have not previously received Tdap, and have or anticipate having close contact with an infant younger than age 12 months (e.g., parents, siblings, grandparents, child care providers, and health care personnel) should receive a single dose of Tdap to protect against pertussis. Ideally, these persons should receive Tdap at least 2 weeks before beginning close contact with the infant.

Health care personnel should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap, regardless of the time since their most recent Td vaccination.

When Tdap is indicated (e.g., routine vaccination, catch-up vaccination, or pregnancy), it can be administered regardless of the interval since the last tetanus- or diphtheria-toxoid-containing vaccine. After receipt of Tdap, persons should continue to receive a dose of Td or Tdap for routine booster immunization against tetanus and diphtheria every 10 years unless needed sooner for tetanus prophylaxis as part of wound management.

Immunogenicity and Vaccine Efficacy +

Diphtheria Toxoid-containing Vaccine Efficacy

- More than 95% of recipients develop protective antibody levels after 3 doses and booster (infants) or 3 doses (adults).

After a primary series of 3 properly spaced doses of diphtheria toxoid-containing vaccines in infants and a booster dose at age 15 through 18 months or 3 properly spaced doses in adults, a protective level of antitoxin (defined as greater than 0.1 IU of antitoxin/mL) is reached in more than 95% of vaccine recipients. Diphtheria toxoid-containing vaccine has been estimated to have an efficacy of 97%.

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Contraindications to combination vaccines that contain DTaP include the contraindications to the individual component vaccines (e.g., IPV, hepatitis B, Hib), but specific ingredients might differ. DTaP-HepB-IPV (Pediarix) and DTaP-IPV-Hib-HepB (Vaxelis) vaccines contain yeast. Presentations of some diphtheria toxoid-containing vaccines contain latex rubber. DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel), DTaP-IPV-Hib-HepB (Vaxelis), DTaP-IPV (Kinrix), and DTaP-IPV (Quadracel) contain neomycin and polymyxin B. DTaP-IPV-Hib-HepB (Vaxelis) contains streptomycin.

Encephalopathy not attributable to another identifiable cause occurring within 7 days after vaccination with DTaP, DTP, or Tdap is a contraindication for DTaP and Tdap vaccination.

A progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy is a precaution for DTaP and Tdap vaccination. For persons with a known or suspected neurologic condition, vaccination with DTaP or Tdap should be delayed until the condition has been evaluated, treatment initiated, and the condition stabilized. These conditions include the presence of an evolving neurologic disorder (e.g., uncontrolled epilepsy, infantile spasms, and progressive encephalopathy); a history of seizures that has not been evaluated; or a neurologic event that occurs between doses of vaccine. A family history of seizures or other neurologic diseases, or stable or resolved neurologic conditions (e.g., controlled idiopathic epilepsy, cerebral palsy, developmental delay), are neither contraindications nor precautions to DTaP or Tdap vaccination.

Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine is a precaution for DTaP, Tdap, DT, and Td vaccination.

A history of Arthus-type hypersensitivity reactions after a previous dose of diphtheria toxoid-containing or tetanus toxoid–containing vaccine is a precaution for DTaP, Tdap, DT, and Td vaccination; vaccination should be deferred until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine.

Vaccine Safety

Diphtheria Toxoid-containing Vaccine Safety

DTaP

- Pain, redness, or swelling
  - 20%-40%
  - More frequent after dose 4 or 5
- Temperature of 101°F
  - 3%-5%

- Moderate or severe systemic reactions
  - Fewer than 1 in 10,000 doses
- Arthus-type reactions are rare

Tdap, Td

- Pain, redness, or swelling
  - 21%-75%
- Temperature of 100.4°F or higher
  - 1.1%-5%

DTaP vaccine may cause local reactions, such as pain, redness, or swelling. Local reactions have been reported in 20% to 40% of children after each of the first 3 doses. Local reactions appear to be more frequent after the fourth and/or fifth doses. Mild systemic reactions such as drowsiness, fretfulness, and low-grade fever may also occur. Temperature of 101°F or higher is reported in 3% to 5% of DTaP recipients. These reactions are self-limited and can be managed with symptomatic treatment with acetaminophen or ibuprofen.

Moderate or severe systemic reactions (such as fever of 105°F or higher, febrile seizures, persistent crying lasting 3 hours or longer, and hypotonic-hyporesponsive episodes) have been reported after administration of DTaP, but occur less frequently than among children who received whole-cell DTP. Rates of moderate or severe systemic reactions vary by symptom and vaccine but generally occur in fewer than 1 in 10,000 doses.

Exaggerated local (Arthus-type) reactions are rarely reported but may occur following receipt of a vaccine containing diphtheria or tetanus toxoids.

The most common adverse reaction following vaccination with both brands of Tdap is a local reaction, such as pain (66% to 75%), redness (25%), or swelling (21%) at the site of injection. Temperature of 100.4°F or higher was reported by 1.4% to 5% of Tdap recipients and 1.1% to 5% of Td recipients. Tdap recipients also reported a variety of nonspecific systemic events, such as headache, fatigue and gastrointestinal symptoms.

The Institute of Medicine reported in 2011 that the evidence was inadequate to accept or reject a causal relation between receipt of diphtheria toxoid and tetanus toxoid–containing vaccine and encephalitis, encephalopathy, infantile spasms, seizures, ataxia, autism, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, onset of multiple sclerosis in adults, relapse of multiple sclerosis in adults, relapse of multiple sclerosis in children, Guillain-Barré syndrome, chronic inflammatory disseminated polyneuropathy, opsoclonus myoclonus syndrome, or Bell's palsy.

The most frequently reported adverse events after DTaP in the Vaccine Adverse Effect Reporting System (VAERS) and Vaccine Safety Datalink (VSD), two post-licensure surveillance systems, were consistent with observations from pre-licensure studies of these vaccines. When VAERS DTaP reports for each vaccine brand were compared individually with reports for all other inactivated vaccines in the VAERS database, no concerning patterns of adverse events were observed.

Routine VAERS surveillance for and VSD studies on adverse events following receipt of Tdap vaccines in persons aged 10 through 64 years have provided reassuring data consistent with the prelicensure clinical trial safety data and have not demonstrated any associations between Tdap and the following rare adverse events: encephalopathy-encephalitis-meningitis; paralytic syndromes; seizures; cranial nerve disorders; and Guillain-Barré syndrome.

Vaccine Storage and Handling

DTaP, Td, and Tdap vaccines should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit [PDF].

Surveillance and Reporting of Diphtheria Disease

In January 2019, the Council of State and Territorial Epidemiologists modified its diphtheria case definition. This modification specifies that toxigenic diphtheria infections from any anatomic site (such as skin), not only respiratory infections, should be reported. In addition, confirmed case classification requires verification of toxin production by the *C. diphtheriae* isolate. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases.

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SOURCES

CONTENT SOURCE:
National Center for Immunization and Respiratory Diseases (NCIRD)