Chapter 10
Diphtheria

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Diphtheria Infection

Etiology

Diphtheria is caused by toxin-producing strains of *Corynebacterium diphtheriae*. The bacterial pathogen is an aerobic, Gram-positive, pleomorphic, non-spore-forming bacillus. The organism's key virulence factor, diphtheria toxin, is a potent exotoxin encoded by a bacteriophage that is present in toxigenic strains. After the bacteriophage infects the bacterium, phage DNA integrates into the bacterial genome. Nontoxigenic strains of *C. diphtheriae* can cause disease, but are much less virulent. Some strains of *C. pseudotuberculosis* and *C. ulcerans* are also infected with the phage, explaining how they produce illness so similar to diphtheria.

Diphtheria toxin comprises two segments, A and B. After segment B recognizes and binds to the target cell surface receptor, segment A enters the cell's cytoplasm and inactivates the host tRNA translocase (elongation factor 2). Loss of this enzyme blocks cellular protein synthesis in all cell types, but disproportionately affects cardiac myocytes, renal tubular cells, and neurons. Toxin also triggers the formation of a pseudomembrane at the site of the initial infection.

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Epidemiology

Worldwide, although outbreaks of diphtheria are uncommon, they still occur in countries with poor routine vaccination coverage and/or substantial pockets of unimmunized children. In the USA, during the prevaccine era, between 100,000 and 200,000 cases of diphtheria and 15,000 associated deaths occurred annually, with most of the disease burden among children under 5 years of age. Diphtheria vaccines emerged during the mid-1930s, but global uptake across low- and middle-income countries was not widespread until 1974 when the World Health Organization included diphtheria, tetanus, and whole cell pertussis (DTP) vaccine as a component of the Expanded Programme on Immunization. In 1980, 97,160 cases of diphtheria were reported to the World Health Organization, 80% of which occurred in just 6 countries (Table 10.1). Since 1980, the general trend has been a gradual decline in diphtheria cases, largely due to widespread immunization efforts (Fig. 10.1). By 2010, the total number of cases reported had reached historic lows, dropping 95% to fewer than 5000 cases per year. National crises such as civil unrest and/or war-like conditions are associated with outbreaks such as the 2018 surges in cases in Yemen and Venezuela, while other areas struggle more consistently to control the disease. For nearly four decades, year after year, the nation of India has ranked number one in reported cases, at times accounting for nearly 75% of the world's total cases. Other nations that have regularly ranked in the top six for the numbers of reported cases include Pakistan, Indonesia, and Nigeria. Nations that rank in the top six repeatedly are highlighted using a country-specific color (Table 10.1; India in blue, Pakistan in green, Indonesia in orange, and Nigeria in pink).

Transmission

Humans are the only known reservoir for *C. diphtheriae.* The primary modes of transmission are via respiratory droplets and through direct contact with infected skin lesions. The usual incubation period between exposure and development of symptoms is 2–5 days. The diagnosis of diphtheria is made primarily on clinical

Table 10.1 Countries reporting the most cases of diphtheria in 1980, 1990, 2000, 2010, and 2018

	1980		1990		2000		2010		2018	
Rank	Nation	Cases Reported	Nation	Cases Reported	Nation	Cases Reported	Nation	Cases Reported	Nation	Cases Reported
1	India	39231	India	8425	India	5125	India	3434	India	8788
2	Pakistan	14328	Indonesia	2200	Nigeria	3995	Indonesia	432	Yemen	2609
3	China	9767	Nigeria	1768	Russia	771	Nepal	146	Nigeria	1870
4	Kenya	6395	Pakistan	1371	Ukraine	365	Philippines	107	Indonesia	1026
5	Brazil	4646	Sudan	1342	Nepal	268	Iran	106	Venezuela	775
6	Indonesia	3674	Russia	1211	Latvia	264	Thailand	77	Pakistan	413
Global		97160	Global	22127	Global	11615	Global	4603	Global	16651

*Nations that rank in the top 6 repeatedly are highlighted using a country -specific color; India in blue, Pakistan in green, Indonesia in orange, and NIgeria in pink).

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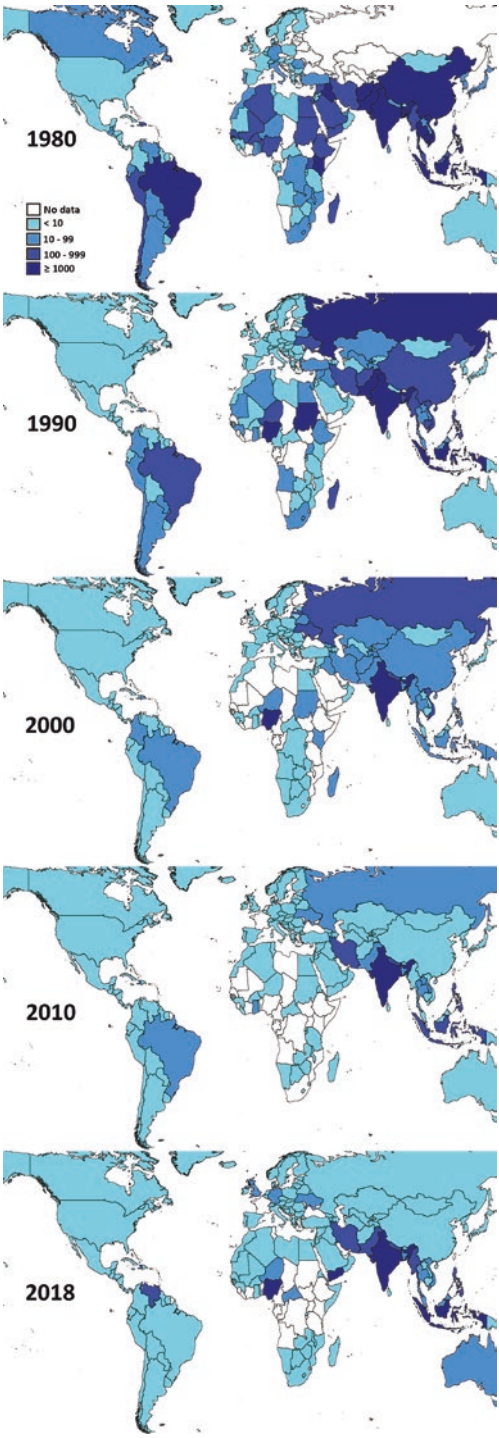

Fig. 10.1 Diphtheria cases reported to the World Health Organization in 1980, 1990, 2000, 2010, and 2018 by country. See also Table 10.1. (Data Source to generate maps: World Health Organization https://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencediphtheria.html)

Table 10.2 Forms of diphtheria based on anatomic site involved

Cutaneous diphtheria
Respiratory diphtheria
Pharyngeal and tonsillar
Nasal and nasopharyngeal
Laryngeal
Conjunctival

grounds based on the classic presentation; however, diagnostic microbiology studies provide confirmation of toxin production and an isolate for epidemiologic tracking. Droplet precautions are necessary for patients with pharyngeal diphtheria until two consecutive negative cultures are obtained from both the nose and the throat 24 hours after completing antibiotic therapy. Contact precautions are sufficient for those with cutaneous diphtheria until two negative skin lesion cultures are obtained 24 hours apart, 24 hours after completion of therapy. The only effective control measure against diphtheria is immunization using a diphtheria-toxoid-containing vaccine. Close contacts of patients diagnosed with diphtheria should receive a booster dose of vaccine in addition to a 7- to 10-day regimen of oral erythromycin. Another 10-day course of erythromycin may be indicated if posttreatment pharyngeal cultures are positive, indicating persistent colonization. A single intramuscular dose of benzathine penicillin may be given as an alternative.

Clinical Presentation

Diphtheria is classified into different clinical forms based on the location of the disease (Table 10.2). Fever, when present, is of low grade. The respiratory infection caused by *C. diphtheriae* usually presents with membranous pharyngitis with or without bloody nasal discharge. Patients with pharyngeal diphtheria may develop palatal palsy, a condition that can be recognized when the patient develops a highly nasal quality to their speech. Laryngeal and/or conjunctival involvement is less common. Anterior and posterior cervical lymphadenopathy and the associated soft tissue edema can give the appearance of a "bull neck" in severe cases. Cutaneous diphtheria is a much less common form of the infection that presents as a nonhealing skin ulcer. In all forms of the infection, diphtheria toxin causes the formation of a local pseudomembrane that is comprised of fibrin clots and necrotic cellular debris. This dense, gray, friable matted collection adheres to the local mucosa or skin.

Management

Careful attention to maintaining airway patency is the most essential aspect of managing patients with respiratory diphtheria. In addition, treatment with diphtheria antitoxin and appropriate antibiotics should not be delayed. A single dose of

Table 10.3 Available combination vaccines that include diphtheria toxoid

Combination vaccine	Brand name	Manufacturer	Diseases targeted for prevention
DT	None	Sanofi Pasteur	Diphtheria Tetanus
Td	Tenivac	Sanofi Pasteur	Tetanus Diphtheria
DTaP	Daptacel Infanrix	Sanofi Pasteur Glaxo Smith Kline	Diphtheria Tetanus Pertussis
TdaP	Adacel Boostrix	Sanofi Pasteur Glaxo Smith Kline	Tetanus Diphtheria Pertussis
DTaP, Hep-B, IPV	Pediarix	Glaxo Smith Kline	Diphtheria Tetanus Pertussis Hepatitis B Polio
DTaP, IPV	Kinrix Quadracel	Glaxo Smith Kline Sanofi Pasteur	Diphtheria Tetanus Pertussis Polio
DTaP, IPV, Hib	Pentacel	Sanofi Pasteur	Diphtheria Tetanus Pertussis Polio *Haemophilus influenzae* type b
DTaP, IPV, Hep-B, Hib	Vaxelis	MSP Vaccine Company	Diphtheria Tetanus Pertussis Polio Hepatitis B *Haemophilus influenzae* type b

equine-derived diphtheria antitoxin should be given any time the clinical suspicion for diphtheria is high, even without laboratory confirmation of the infection. A scratch test should be performed prior to administration to determine whether the patient has pre-existing hypersensitivity to horse serum. Diphtheria antitoxin should be administered intravenously in an effort to neutralize systemic diphtheria toxin as quickly as possible. Antibiotics are administered to stop toxin production, eradicate *C. diphtheriae* from the respiratory tract, and prevent further transmission to others. Oral or intravenous erythromycin is the drug of choice.

Diphtheria Vaccine

Diphtheria vaccine is among the most simple and elegant immunizations available. The vaccine immunogen, diphtheria toxoid, is a derivative of diphtheria toxin that has been rendered nontoxic. Monovalent vaccine formulations of diphtheria toxoid are not

currently available anywhere in the world. Instead, diphtheria toxoid is 1 of 2 or more components included in a growing variety of combination vaccine formulations. All formulations of diphtheria vaccine in use presently also include tetanus toxoid (abbreviated DT and Td) and all those that contain immunogens beyond diphtheria and tetanus toxoids all include pertussis antigens (DTaP and TdaP) (see Table 10.3). Lower case "d" is used to indicate the lesser amount of total diphtheria toxoid included in vaccines used in formulations given as booster doses to individuals older than 7 years (Td and TdaP). The DT vaccine formulation is not commonly used, but is available to provide protection against diphtheria and tetanus in infants and young children for whom pertussis vaccination is contraindicated. For younger children, quadrivalent (adding in polio immunogens; abbreviated DTaP-IPV), pentavalent (adding either hepatitis B or *Haemophilus influenzae* type B; DTaP-IPV-Hep-B and DTaP-IPV-HIB), and hexavalent (adding both hepatitis B or *Haemophilus influenzae* type B immunogens; DTaP-IPV-Hep-B-HIB) combination vaccines are also widely used throughout the world. During young childhood, five doses of diphtheria- (capital "D") and tetanus-toxoid-containing vaccines are recommended to be administered at ages 2, 4, 6, and 15–18 months and 4–6 years. The first dose may be administered as early as 6 weeks of age. The use of pentavalent or hexavalent vaccines at 2, 4, and 6 months has the benefit of reducing the number of injections needed at each immunization visit (Fig. 10.2). Other benefits of combination vaccines are discussed in Chap. 35.

Starting at age 7 years, and throughout adulthood, vaccine formulations that contain the lesser amount of diphtheria toxoid, as indicated in the vaccine abbreviation with a lower case "d," as in Td and TdaP, are used. The immune systems of older children and adults have already been primed and boosted with diphtheria toxoid at 2, 4, 6, 15–18 months and 4–6 years of age, so the lower antigen dose is more than sufficient to boost existing immunity. The unintentional administration of a vaccine formulation containing the higher amount of diphtheria toxoid beyond age 6 years is not harmful, per se, but would likely be associated with a high rate of self-limiting injection site reactions. Such reactions result, at least in part, from the robust immune memory response to the prior doses. Pediatricians are keenly aware of the relative frequency with which this occurs already following the appropriate administration of DTaP-containing vaccines, particularly in preschool-aged children 1–2 days after receiving their fifth dose.

The Advisory Committee on Immunization Practices (ACIP) recommends that booster injections of diphtheria toxoid be given every 10 years for life. TdaP vaccine is recommended for all 11- or 12-year-old children, primarily to boost their pre-existing immunity to pertussis. ACIP recommendations state that either Td or TdaP vaccine may be used for subsequent, every 10-year boosters. Td or TdaP vaccine is also used for tetanus wound prophylaxis, since monovalent tetanus toxoid vaccine is no longer available. Anytime a diphtheria-toxoid-containing combination vaccine is used in such contexts to boost immunity to tetanus or pertussis, the dose is valid to reset the 10-year clock for the next recommended dose. This guidance aligns nicely with the routine booster recommendations for tetanus toxoid booster vaccines every 10 years and explains why monovalent tetanus toxoid vaccines are no longer made available for use.

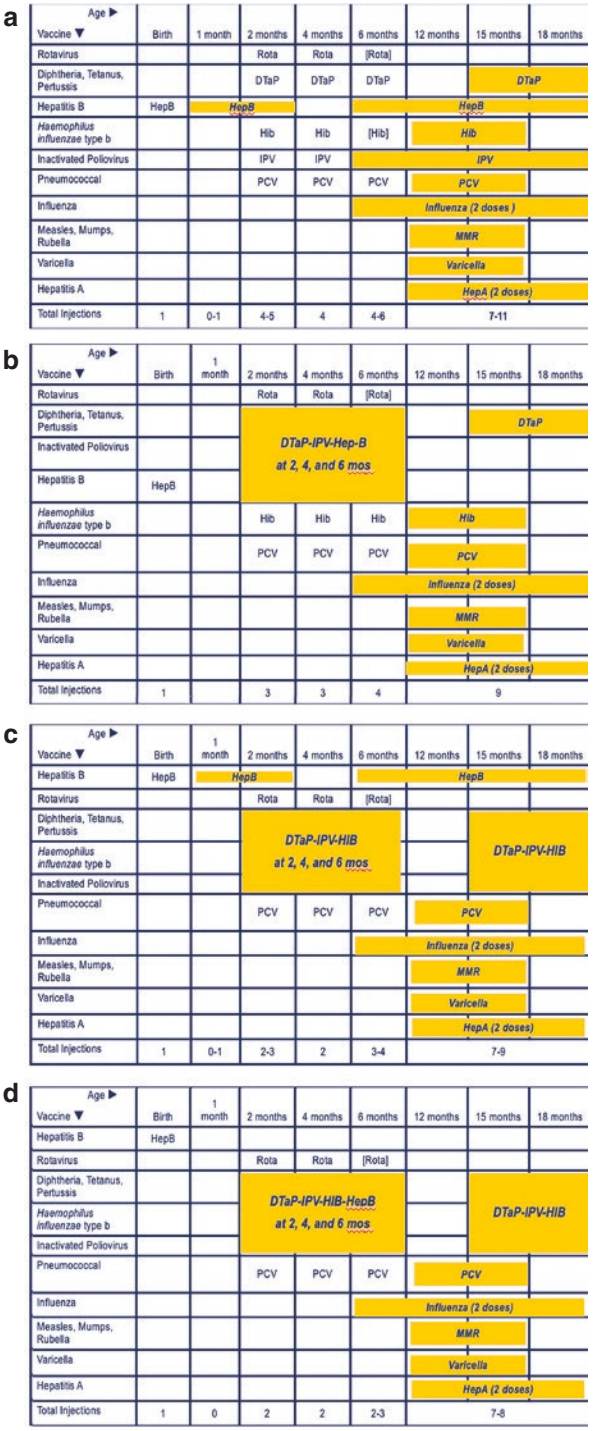

Fig. 10.2 Pediatric immunization schedule from birth to 18 months of age when using (**a**) DTaP with individual component vaccines, (**b**) DTaP-IPV-Hep-B combination vaccine, (**c**) DTaP-IPV-HIB combination vaccine, and (**d**) DTaP-IPV-HIB-Hep-B combination vaccine

Immunizing Antigen

Diphtheria toxoid is used as the immunogen in all combination vaccines that include diphtheria antigen. Diphtheria toxoid is derived from diphtheria toxin produced in industrial cultures of toxigenic *C. diphtheriae* grown under carefully defined conditions. When the bacterial cultures are ready for harvest, diphtheria toxin is concentrated from the culture medium using ultrafiltration, then purified by ammonium chloride precipitation, and dialysis. Toxin is then inactivated with formaldehyde to produce a bulk lot of diphtheria toxoid for use in all of the available combination vaccine products.

Additives and Excipients

All diphtheria-toxoid-containing vaccines include an aluminum salt adjuvant that is added during the final manufacturing steps. Monovalent diphtheria toxoid vaccines are not available for use. For a list of additives and excipients in diphtheria-toxoid-containing vaccines, see details provided in Chap. 4.

Contraindications to Vaccine

Diphtheria-toxoid-containing vaccines are contraindicated for use in individuals who developed a severe allergic reaction to a prior dose, and for those with a known severe allergy to any vaccine component.

Side Effects and Adverse Events

Mild-to-moderate, self-limiting local injection site reactions are common with all diphtheria-toxoid-containing vaccines. Since infants who receive diphtheria-toxoid-containing vaccines also typically receive other vaccines during the same visit, vaccine-specific and antigen-specific side effects are usually difficult to identify with any certainty. Fortunately, all of the diphtheria-toxoid-containing vaccines are very well tolerated. For example, in one study involving more than 27,000 infants who received DTaP at 2, 4, and 6 months of age, crying for 3 hours or longer was reported at a rate of 0.44 per 1000 doses, fever ≥40 °C at a rate of 0.35 per 1000 doses, seizures at 0.07 per 1000 doses, and no reported episodes of hypotonic-hyporesponsive episodes (an uncommon reaction known to occur following the administration of whole cell DTP vaccine at rates of 0.67 per 1000 doses). Adolescents and adults who receive Td vaccine experience injection site pain

(75–80%), redness (16–26%), or swelling (15–17%), which are rarely severe in nature. Fever between 38 °C and 39 °C occurs uncommonly (0.8–1.6%). Headache (23–25%), weakness (17–32%), malaise (15–17%), and joint pains (11–16%) are self-limiting and only rarely severe in quality.

Vaccine Immunogenicity

Protection against diphtheria results from the development of neutralizing antibodies to the diphtheria toxin/toxoid. Serum antibody at concentrations of 0.01 IU/mL is the lowest level to provide some degree of protection; a serum concentration of 0.1 IU/mL or higher is considered protective. Clinical trials consistently show that diphtheria-toxoid-containing vaccines induce protective antibody concentrations in the protective range in 100% of recipients who have completed a three-dose primary series. The global epidemiology of diphtheria from 1980 to the present (Fig. 10.1, Table 10.1) is quite telling. Diphtheria can be controlled by prioritizing and paying careful attention to vaccination. Lack of attention and/or a failure to prioritize vaccination will, eventually, lead to the emergence or re-emergence of disease. The immune response to diphtheria vaccination provides excellent protection against the effects of diphtheria toxin, but the induced immunity does not eliminate the pathogen's natural reservoir, because it has no effect on reducing human nasopharyngeal colonization with *C. diphtheriae*. Regions that struggle most with outbreaks are those that are most densely populated (India), are experiencing war or war-like conditions (Yemen), have undergone a recent collapse in infrastructure (Venezuela), and/or continue to suffer from extreme poverty (Haiti, Nigeria).

References and Suggested Reading

World Health Organization

https://www.who.int/immunization/diseases/diphtheria/en/

U.S. Centers for Disease Control and Prevention

https://www.cdc.gov/diphtheria/index.html

Vaccine Information Sheets

https://www.cdc.gov/vaccines/hcp/vis/visstatements/dtap.html
https://www.cdc.gov/vaccines/hcp/vis/vis-statements/tdap.html
https://www.cdc.gov/vaccines/hcp/vis/vis-statements/td.html

FDA Aapproved Package Inserts

Daptacel

https://www.fda.gov/vaccines-blood-biologics/vaccines/daptacel

DT vaccine

https://www.fda.gov/media/119411/download

Infanrix

https://www.fda.gov/vaccines-blood-biologics/vaccines/infanrix

Kinrix

https://www.fda.gov/vaccines-blood-biologics/vaccines/kinrix

Pediarix

https://www.fda.gov/media/79830/download

Pentacel

https://www.fda.gov/media/74385/download

Quadracel

https://www.fda.gov/vaccines-blood-biologics/vaccines/quadracel

Tenivac

https://www.fda.gov/media/76610/download

Vaxelis

https://www.fda.gov/vaccines-blood-biologics/vaxelis

Adacel

https://www.fda.gov/media/119862/download

Boostrix

https://www.fda.gov/media/124002/download

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