6 Diphtheria

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DT vaccine introduced in 1930s

DTP vaccine introduced in 1952/53

DTaP vaccine introduced in 1996

DTaP/IPV vaccine introduced in 2001

DTaP/IPV/Hib vaccine introduced in 2001

DTaP/IPV/Hib/HepB vaccine introduced in 2008

NOTIFIABLE

In some circumstances, advice in these guidelines may differ from that in the Summary of Product Characteristics (SmPC) of the immunisation product. When this occurs, NIAC advises that the recommendations in these guidelines, which are based on current expert advice from NIAC, are followed.

Contents

To view key changes please click **here.**

Acronyms used in this chapter

DAT	diphtheria antitoxin
ECDC	European Centre for Disease Prevention and Control
HCW	healthcare worker
HPRA	Health Products Regulatory Authority
HPSC	Health Protection Surveillance Centre
HSE	Health Service Executive
IU	international units
NCCS	National Cold Chain Service
PCR	polymerase chain reaction
SmPC	Summary of Product Characteristics
UKHSA	United Kingdom Health Security Agency
WHO	World Health Organization

Vaccine abbreviations used in this chapter

aP	full-dose acellular pertussis vaccine
ap	low-dose acellular pertussis vaccine
D	full-dose diphtheria vaccine
d	low-dose diphtheria vaccine
DT	diphtheria and tetanus vaccine
DTP	diphtheria, tetanus, pertussis vaccine
HepB	hepatitis B vaccine
Hib	*Haemophilus influenzae* type b vaccine
IPV	inactivated poliovirus vaccine
PCV	pneumococcal conjugate vaccine
Td	tetanus, low-dose diphtheria vaccine
Tdap	tetanus, low-dose diphtheria, low-dose acellular pertussis vaccine
4 in 1 (DTaP/IPV)	diphtheria, tetanus, acellular pertussis, inactivated poliovirus vaccine
5 in 1 (DTaP/IPV/Hib)	diphtheria, tetanus, acellular pertussis, inactivated poliovirus vaccine, *Haemophilus influenzae* type b
6 in 1 (DTaP/IPV/Hib/ HepB)	diphtheria, tetanus, acellular pertussis, inactivated poliovirus vaccine, *Haemophilus influenzae* type b, hepatitis B vaccine

Terms used for frequency of adverse events

Very common	≥1/10
Common	1/100 and <1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000

6.1 Introduction

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae,* an aerobic, pleomorphic, Gram-positive bacillus. It can also be caused by toxigenic strains of *Corynebacterium ulcerans* and rarely by *Corynebacterium pseudotuberculosis*. The toxin typically causes either respiratory or cutaneous symptoms (sometimes both), but on occasion can cause serious systemic illness affecting both the cardiovascular and neurologic systems. Before introduction of immunisation, epidemics occurred every few years, with mortality rates of up to 50%. Effective protection against the disease is provided by active immunisation. Diphtheria is a notifiable disease in Ireland but infections with non-toxigenic *C. diphtheriae, C. ulcerans* or *C. pseudotuberculosis* are not notifiable.

Since the introduction of vaccination against diphtheria, the disease has been eliminated from Ireland. However, the organism may still circulate, particularly in situations of poverty, overcrowding and poor hygiene. Thus, an immunisation rate of at least 85% must be maintained to protect against a possible resurgence of the disease following the introduction of cases or carriers of toxigenic strains from endemic countries or populations.

6.2 Epidemiology

Humans are presumed to be the only reservoir of *C. diphtheriae*; however, the bacteria have been recovered from other animals (horses and dogs) without confirmed transmission from humans. Disease can also be caused by toxin-producing strains of two other *Corynebacterium* species: *C. ulcerans* and *C. pseudotuberculosis.* Both species are zoonotic; infections have been documented in pigs, cattle, dogs, and cats.

Transmission results primarily from close contact with a patient or carrier. Spread is by droplet infection, and on rare occasions through contact with articles (fomites)

soiled by contact with skin lesions of infected people. Approximately five secondary infections will result from each index case in a fully susceptible population.

Prior to the introduction of vaccination, most people developed immunity (as measured by the Schick test) without experiencing clinical disease. There is now little likelihood of acquiring natural immunity from subclinical infection. One case was reported in Ireland in 2016 (*C. diphtheriae*) and in 2015 (*C. ulcerans*); no further cases have been notified since 2016. The last diphtheria case (and death) notified prior to 2015 was in 1967. In a major epidemic in the Russian Federation and former Soviet Republics in the 1990s, over 157,000 cases and 5,000 deaths were reported. Since the summer of 2022, many cases of diphtheria have been reported in the EU and the UK associated with reception centres for migrants. In 2024, a total of 25,149 cases of diphtheria were reported worldwide to the World Health Organization (WHO), but cases may be under-reported.

6.3 Effects of diphtheria

The incubation period is usually 2-5 days (range 1-10 days). The disease is communicable for up to six weeks without antibiotic treatment, but carriers may shed the organism for longer.

Classical (pharnygeal) diphtheria has an insidious onset of low-grade fever and sore throat. After 1-2 days, patchy exudates appear in the pharynx. These patches become confluent over 2-3 days. A greyish pseudomembrane may cover the entire pharynx, tonsils and soft palate. The pseudomembrane is typically firmly attached to the underlying tissue and attempts to remove it may result in bleeding. Obstructive laryngotracheitis and pneumonia may occur. There may be moderate enlargement of cervical lymph nodes and oedema of the soft tissue of the neck ("bull neck"). In untreated patients the membrane begins to slough off and systemic symptoms improve in about a week.

A toxin produced by diphtheria bacilli particularly affects myocardial, nervous and adrenal tissues and may result in life-threatening complications including myocarditis, arrhythmias and neurological problems such as vocal cord paralysis and ascending paralysis similar to Guillain-Barré syndrome. The neurological problems may not occur until 2-10 weeks after onset of the disease.

Laryngeal diphtheria presents with obstructive symptoms including a hoarse voice, croupy cough and progressive inspiratory distress. The pseudomembrane may extend into the trachea, bronchi and smaller airways, causing bronchopneumonia and severe airflow limitation.

Cutaneous diphtheria is an indolent infection which often occurs at burn or wound sites or exposed limbs in warmer climates and overcrowded conditions.

Rarely conjunctival, aural, and vaginal diphtheria may occur.

The case-fatality rate is highest in unimmunised very young and unimmunised elderly people; it usually ranges from 5-10% but is significantly higher in untreated cases (up to 50%). Most deaths are due to myocarditis or airway obstruction.

Fully immunised people may become asymptomatic carriers or may have a mild tonsillitis or pharyngitis.

6.4 Diagnosis

It is difficult clinically to differentiate early-stage diphtheria from other causes of membranous tonsillopharyngitis, such as Streptococcal or Ebstein-Barr virus infection, or from other causes of laryngotracheitis. If diphtheria is suspected, culture should be obtained from the edge or under the membrane and promptly inoculated into appropriate media. Polymerase chain reaction (PCR) is also useful.

6.5 Treatment and chemoprophylaxis

1. Antitoxin

Because the clinical condition of a person with diphtheria may deteriorate rapidly, diphtheria antitoxin (DAT) should be given by intravenous infusion as soon as clinically suspected. The amount given ranges from 20,000 to 100,000IU and depends on the extent of the local lesions and time since onset of symptoms. A clinician who suspects diphtheria should seek advice from an infectious disease consultant and also notify their Regional Department of Public Health.

In a recent large outbreak of diphtheria in Bangladesh between November 2017 and September 2018 there were 8,178 cases of diphtheria reported to the WHO. Diagnosis was clinical and not microbiologically confirmed. A subset of the reported cases, from 27 December 2017 to 11 September 2018, were analysed in detail. The WHO triage algorithm for the Bangladesh outbreak divided diphtheria cases into high-acuity and low-acuity. Of 5,080 cases who presented for care during this time, 3,097 were diagnosed as clinical cases and admitted. Of these, 2,388 were low-acuity and 709 were high-acuity. The 709 high-acuity cases were given DAT. Initially skin-sensitivity testing method was used to determine which patients were at high risk for hypersensitivity. However, this was abandoned within two weeks when clinicians found that skin-test results were poorly predictive of which patients experienced adverse reactions. In 2024, the WHO recommended against performing routine sensitivity testing prior to administration of DAT (strong recommendation, moderate certainty evidence).

About a quarter of the patients who received DAT experienced adverse events, three had anaphylaxis and 18 were retrospectively diagnosed as having anaphylaxis using criteria recommended by the National Academy of Allergy and Infectious Diseases. Common adverse reactions included cough in 115 patients (16%), skin reactions in 66 patients (9%), and itching in 37 patients (5%).

There was no statistically significant difference in the percentage of patients who had an adverse reaction in the group who received relatively low-dose DAT (25,000IU) compared with the group who received relatively high-dose DAT (26,000–80,000IU).

Of the 709 patients treated with DAT, 696 (98%) recovered and were discharged from the hospital. There were five deaths, one prior to DAT and four during or soon after DAT was administered. All deaths were considered to be due to advanced diphtheria as all were critically ill at presentation.

Supply of DAT is available from the HSE National Cold Chain Service. The NCCS is contactable 24 hours per day, seven days per week. **During office hours** the hospital account holder emails NCCS at vaccines@udd.ie and requests the required dosage of DAT. **Out of hours** the clinician should contact their Regional Department of Public Health on-call service to discuss, and an emergency delivery of DAT can be arranged through the National Health Protection Office on-call consultant.

2. Antibiotics

These are adjunctive therapy to antitoxin and hasten clearance of the organism. Seek advice from a microbiologist or infectious disease consultant on appropriate antibiotic treatment.

Elimination of the organism should be documented, as recommended by public health guidance available on the HPSC website.

3. Contacts of a diphtheria case or carriers of a toxigenic strain

Contacts of a case need to be identified and given an age-appropriate diphtheria vaccine booster (see below). Contacts will also require antibiotic prophylaxis and may require isolation or exclusion. Further information and advice can be obtained from a Regional Department of Public Health.

6.6 Diphtheria vaccine

Diphtheria vaccines are toxoids, which protect by stimulating the production of antibodies, also known as antitoxin, thus providing immunity to the effects of the toxin. After a primary series of three properly spaced doses, most infants (more than 94%) develop protective levels of diphtheria antibody while effectiveness in

outbreak contexts has been shown to exceed 95%.

Currently licensed diphtheria vaccines are all combination vaccines containing full or low doses of diphtheria toxoid. Full-dose diphtheria vaccines (D) are recommended for children under 10 years of age. Low-dose diphtheria vaccines (d) are recommended for all aged 10 years and older, as this minimises risk of injection site reactions but is still sufficient to produce a satisfactory immune response.

An up-to-date list of licensed vaccines is available on the Health Products Regulatory Authority (HPRA) website www.hpra.ie.

The list of the vaccines currently available from the National Cold Chain Service (NCCS) can be found at: https://www.hse.ie/eng/health/immunisation/hcpinfo/frequentlyaskedquestions/pilandspc/pilandspc.html.

Approximately 94-100% of vaccinated children achieve protective antibody levels after the three-dose primary series of diphtheria-containing vaccine but booster doses are needed to ensure continuing protection.

Diphtheria vaccines should be stored between +2°C and +8°C. If the vaccine has been frozen, it should not be used.

Dose, route of administration and schedule

The dose is 0.5ml given by intramuscular injection into the deltoid region or the anterolateral thigh according to the primary childhood immunisation schedule and catch-up schedules in Chapter 2.

6.7 Recommendations

6.7.1 Primary immunisation

The primary immunisation series consists of three doses given to infants aged two, four and six months, as 6 in 1 vaccine (DTaP/IPV/Hib/HepB).

When 6 in 1 vaccine is given concurrently with pneumococcal conjugate vaccine (PCV), 6 in 1 should be given first as it is less painful.

If the primary course is interrupted, it should be resumed but not repeated, allowing appropriate intervals between the remaining doses (see Chapter 2, Table 2.3 and Table 2.4).

If pertussis vaccine is refused by parents for their children, the only available pertussis-free diphtheria and tetanus vaccines are Td vaccine and Td/IPV vaccine. These contain low-dose diphtheria vaccine which is insufficient for primary immunisation in children under 10 years of age. Low dose diphtheria vaccines are not intended for use as part of the primary immunisation series and may not give a sufficient immune response if so used.

6.7.2 Booster immunisation

- A fourth dose is recommended at 13 months of age, as 6 in 1 vaccine (DTaP/IPV/Hib/HepB) for children born on or after 1 October 2024.
- A booster dose is recommended from the age of 4-5 years, usually in Junior Infants, as 4 in 1 vaccine (DTaP/IPV).*
- A further booster dose is recommended at 12-13 years in the first year of second-level school as Tdap vaccine.
- Additional booster doses (as a diphtheria-containing vaccine) may be given to adults every 10 years for life. See Chapter 4 for occupational risk categories and see Chapter 5 for travel risks.

*This is a fourth dose for children born before 1 October 2024 and a fifth dose for children born on or after 1 October 2024.

See Chapter 2, Table 2.2 for optimal and minimum recommended intervals between doses of 6 in 1 vaccine and the recommended interval between the 6 in 1 vaccine and the 4 in 1 vaccine.

6.7.3 Immunisation of cases

Fully vaccinated cases (i.e. received ≥5 diphtheria vaccine containing vaccines) should receive an age-appropriate* booster dose of diphtheria vaccine regardless of when the previous dose was given.

Unvaccinated or incompletely vaccinated cases should complete the age-appropriate* vaccination during convalescence and then should complete the age-appropriate vaccination schedule, as infection may not confer long-term immunity (see catch-up schedule in Chapter 2).

*The age-appropriate formulation of diphtheria containing vaccines is set out in the box below.

6.7.4 Immunisation of contacts and carriers

Fully vaccinated contacts (i.e. received ≥5 diphtheria vaccine containing vaccines) should receive an age-appropriate* booster dose of diphtheria vaccine.

Unvaccinated or incompletely vaccinated contacts should receive an age-appropriate* diphtheria- containing vaccine as soon as possible and then should

complete the age-appropriate vaccination schedule (see catch-up schedule in Chapter 2).

*The age-appropriate formulation of diphtheria containing vaccines is set out in the box below.

6.7.5 Delayed immunisation/late entrants to Irish healthcare system

For catch-up schedules for unvaccinated or incompletely vaccinated children and adults see Chapter 2 Table 2.3 and Table 2.4.

If diphtheria vaccine is indicated for those aged <10 years:

- Children aged <10 years should receive full-dose diphtheria vaccine (D) as 6 in 1 (DTaP/IPV/Hib/HepB) or 4 in 1 (DTaP/IPV).
- There should be an interval of at least six months± between booster doses of DTaP and the completion of a primary course of DTaP containing vaccines.
- DTaP-containing vaccines can be given at any interval following (an inappropriately administered) Td vaccine.

If diphtheria vaccine is indicated for those aged ≥10 years:

- Those aged ≥10 years should receive low-dose diphtheria vaccine (d) as Td or Td/IPV or Tdap depending on other vaccine requirements (see Chapter 2, Table 2.4).
- Tdap vaccine may be given at any interval following a Td-containing vaccine.

± If third dose of 6 in 1 is given later than six months of age but under 12 months, then the fourth dose of 6 in 1 should be given as scheduled at 13 months (i.e. ≥4 weeks after the third dose, see Chapter 2, Table 2.2).

Contraindications

Anaphylaxis to any of the vaccine constituents.

Precautions

Acute severe febrile illness, defer until recovery.

Type III (Arthus) hypersensitivity reaction to a previous dose (see Adverse reactions). People experiencing these reactions usually have very high serum diphtheria or tetanus antibody (i.e. antitoxin) levels; they should not be given further routine or emergency booster doses of tetanus or diphtheria containing vaccines more frequently than every 10 years.

Adverse reactions

Local:	Very common*: Injection site redness, pain, swelling. These reactions are more frequent with subsequent doses. Common: Injection site induration. Very rarely a Type III (Arthus) hypersensitivity reaction occurs, involving swelling and erythema of most of the diameter of the limb from the shoulder to the elbow or the hip to the knee. This usually begins 2-8 hours after vaccination and is more common in adults. This resolves without sequelae.
General:	Very common: Fever ≥38°C, vomiting, anorexia (feeding disturbance), headache, irritability, crying (abnormal), somnolence (drowsiness), fatigue, malaise, myalgia. Common: Fever >39.5°C, diarrhoea, insomnia (sleep disturbances), dizziness. Anaphylaxis is extremely rare (0.6-3 per million doses)

* Most of these reactions resolve with no treatment. A cold pack or ice wrapped in a cloth may be applied to the site for 20 minutes per hour as necessary. On occasions paracetamol or ibuprofen may be needed. Antibiotics are very rarely indicated.

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