Introduction
Diphtheria is an acute infectious disease affecting the upper respiratory tract and occasionally the skin. It is caused by toxigenic strains of *Corynebacterium diphtheria*, an aerobic, pleomorphic, Gram-positive bacillus or occasionally by *C. ulcerans*. Before introduction of immunisation, epidemics occurred every 10 years, with mortality rates of up to 50%. Effective protection against the disease is provided by active immunisation.

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 the possibility of a resurgence of the disease which could follow the introduction of cases or carriers of toxigenic strains from endemic countries or populations.
Chapter 6 Diphtheria

Epidemiology
Humans are the only known reservoir of *Corynebacterium diphtheriae*. 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 persons. Approximately 5 secondary infections will result from each index case in a fully susceptible population.

Prior to the introduction of vaccination, most persons developed immunity as measured by the Schick test without experiencing clinical disease. There is now little likelihood of acquiring natural immunity from sub-clinical infection. However, while no cases have been recently reported in Ireland, they have occurred in the UK, the former USSR states, India, China, and Bangladesh among other countries. In a major epidemic in the Russian Federation in the 1990s, over 150,000 cases and 4,500 deaths were reported. In 2014, 7,321 cases of diphtheria were reported worldwide to the WHO, but many cases are likely to be unreported.

Effects of diphtheria
The incubation period is usually 2-5 days, but occasionally can be longer. The disease is communicable for up to 6 weeks without antibiotic treatment, but carriers may shed the organism for longer.

Classical (pharyngeal) 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. 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 affects particularly 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 the 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
airs, causing bronchopneumonia and severe airflow limitation. 

**Cutaneous** diphtheria is an indolent infection which generally occurs at burn or or wound sites, in warmer climates and overcrowded conditions.

Rarely conjunctival, aural, and vaginal diphtheria may occur.

The case-fatality rate is highest in the young and the elderly; it usually ranges from 5-10%, but is significantly higher in untreated cases. Most deaths are due to myocarditis or airway obstruction.

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

**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 (transport, Loefflers, Tellurite, blood agar). PCR is also useful.

**Treatment and Chemoprophylaxis**

1. **Antitoxin**: Because the clinical condition of a person with diphtheria may deteriorate rapidly, diphtheria antitoxin should be given by IV infusion as soon as clinical or laboratory diagnosis is made. The amount given ranges from 20,000 to 120,000 units depending on the extent of the local lesions and time since onset of symptoms. If the patient has a history of a local or general reaction to a previous dose of antitoxin or has a known allergic condition such as asthma or eczema, desensitisation should be tried.

Supply of diphtheria antitoxin is available from the HSE National Cold Chain Service (phone 01 463 7770 or 086 7700846).

2. **Antibiotics**: These are adjunctive therapy to antitoxin, and hasten clearance of the organism. Treatment is with erythromycin orally (40 mg/kg/day; maximum, 2 gm/day) for 14 days, or procaine penicillin G for 14 days (see the SmPC for dosage).

The disease is usually not contagious 48 hours after antibiotics are instituted. Elimination of the organism should be documented by two consecutive negative cultures after therapy is completed.

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

Contacts of a case need to be identified, given an age-appropriate diphtheria vaccine booster and will require antibiotic prophylaxis. Further information and advice can be obtained from the local Department of Public Health.
Diphtheria vaccine

Diphtheria vaccines are toxoids, which protect by stimulating the production of antitoxin thus providing immunity to the effects of the toxin. After a primary series of 3 properly spaced doses in adults and 4 doses in infants, efficacy is estimated at over 97%.

Currently licensed diphtheria vaccines are all combination vaccines containing high or low doses of diphtheria toxoid. High dose diphtheria vaccines (D) are recommended for children up to 10 years of age. Low dose diphtheria vaccines (d) are recommended for all aged 10 years and older.

An up-to-date list of licensed vaccines can be accessed on the HPRA website www.hpra.ie

Almost 100% of vaccinated persons achieve protective antibody levels. However, immunity decreases with age and with time since vaccination; over 50% may have insufficient protection 10 years after a booster diphtheria vaccine. A survey in the U.S showed protective levels (0.1 IU/ml or greater) of diphtheria antibodies decreased progressively with age, from 91% at ages 6-11 years to approximately 30% at ages 60-69 years. It is important that high uptake of vaccination in children continues, in order to achieve herd protection.

A list of the vaccines currently available from the National Cold Chain Service can be found at www.immunisation.ie

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

Dose and route of administration
The dose is 0.5 ml given by intramuscular injection into the deltoid region or the anterolateral thigh.

Indications

1. Primary immunisation
The primary course consists of 3 doses given at 2, 4 and 6 months as part of a 6 in 1 vaccine (DTaP/IPV/Hib/Hep B).

When 6 in 1 vaccine is given concurrently with PCV, it 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 catch-up schedule in Chapter 2).

If pertussis vaccine is refused by parents for their children, the only available pertussis-free diphtheria and tetanus vaccines are Td and Td/IPV which 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 vaccine schedule and may not give a sufficient immune response if so used.

2. Booster immunisation
A first booster dose is recommended at 4-5 years of age as 4 in 1 vaccine (DTaP/IPV). In the event of this vaccine being unavailable, Tdap/IPV may be given from 4 years.

Children who have received four doses of diphtheria vaccine before their fourth birthday should receive a DTaP/IPV (or Tdap/IPV) booster at least 6 months after the 4th dose.

A second booster is recommended at 11-14 years as Tdap vaccine.

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

Unvaccinated or partially vaccinated cases should complete the age appropriate vaccination schedule during convalescence as infection may not confer long-term immunity.

4. Vaccination of contacts and carriers
Fully vaccinated contacts (i.e. received 5 diphtheria vaccine containing vaccines) should receive an age appropriate dose of diphtheria vaccine.

Unvaccinated or partially vaccinated contacts should complete the age appropriate vaccination schedule (see catch up schedule in Chapter 2).

5. Adults
Additional booster doses (as Tdap) may be given every 10 years for life.
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Children under 10 years should receive full dose diphtheria vaccine (D) as DTaP/IPV/Hib/Hep B or DTaP/IPV (or Tdap/IPV in the event of a temporary shortage).

All aged 10 years and over should receive low dose diphtheria vaccine (d) as Td or Td/IPV or Tdap or Tdap/IPV depending on other vaccine requirements.

If diphtheria vaccine is indicated
for those aged <10 years
There should be an interval of at least 6 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.

for those aged 10 years and older
Tdap or Tdap/IPV can be given at any interval following a Td containing vaccine.

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). Persons experiencing these reactions usually have very high serum diphtheria or tetanus 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: Pain, palpable lump, swelling and erythema occur in up to 20% of recipients. They are more frequent with subsequent doses. Most of these reactions resolve with no treatment. A cold pack or ice wrapped in a cloth applied to the site for 20 minutes per hour as necessary may be required. On occasions paracetamol or ibuprofen may be needed. Antibiotics are very rarely indicated.

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:** Malaise, transient fever and headache are uncommon. Temperature over 40°C is rare. Dyspnoea, urticaria, angioedema, and neurological reactions are very rare and are not a contraindication to further vaccination.

Anaphylaxis is extremely rare (0.6-3 per million doses).

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**Bibliography**


Department of Health UK (2013) Immunisation against Infectious Diseases (The Green Book) www.dh.gov.uk/greenbook

