

3.3 DIPHTHERIA

Bacteriology

Diphtheria is an acute illness caused by toxigenic strains of *Corynebacterium diphtheriae*, a Gram-positive, non-sporing, non-capsulate bacillus. The exotoxin produced by *C. diphtheriae* acts locally on the mucous membranes of the respiratory tract or, less commonly, on damaged skin, to produce an adherent pseudomembrane. Systemically, the toxin acts on cells of the myocardium, nervous system and adrenals.

Clinical features

The incubation period is 2 to 5 days. The disease is communicable for up to 4 weeks, but carriers may shed organisms for longer. Spread is by respiratory droplets or by direct contact with skin lesions or articles soiled by infected individuals. Pharyngeal diphtheria is characterised by an inflammatory exudate which forms a greyish or green membrane in the upper respiratory tract which can cause acute severe respiratory obstruction. Diphtheria toxin can cause neuropathy and cardiomyopathy, which may be fatal. The introduction of diphtheria antitoxin in the 1890s reduced the death rate to about 10%, but the mortality has not been further reduced by the use of antibiotics and other modern treatments.¹ Effective protection against diphtheria is achieved by active immunisation with diphtheria vaccine.

Epidemiology

In the early 1900s, diphtheria caused more deaths in Australia than any other infectious disease, but increasing use of diphtheria vaccines since World War II has led to its virtual disappearance.² The current epidemiology of diphtheria in Australia is similar to that in other developed countries. Almost all recent cases in the United Kingdom and the United States have been associated with imported infections.³ Hence, there is still the possibility of an imported case occurring in Australia, particularly from developing countries, as occurred in 2001 when a case, acquired in East Timor, was notified in Australia.⁴ There is now little possibility of acquiring natural immunity or boosting declining immunity with subclinical infection. It is therefore important for Australians to retain high levels of immunity through high vaccination coverage.

Disruption of vaccination programs following the collapse of the Soviet Union resulted in the re-emergence of diphtheria throughout the Newly Independent States. From 1991 to 1996, there were more than 140 000 cases and more than 4000 deaths.⁵ Cases also occurred in neighbouring European countries and in visitors to the area. Mass vaccination eventually brought the epidemic under control.^{6,7} This experience illustrates the importance of maintaining high levels of vaccination coverage against diphtheria.

Vaccines

Diphtheria toxoid is available in Australia only in combination with tetanus and other antigens.

The acronym DTPa, using capital letters, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines. The acronym dTpa is used for adolescent/adult formulations which contain substantially lesser amounts of diphtheria toxoid and pertussis antigens (see formulations).

Formulations for children aged <8 years

- **Infanrix hexa** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine-*Haemophilus influenzae* type b (Hib)). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. The vaccine *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. May also contain yeast proteins.
- **Infanrix-IPV** – GlaxoSmithKline (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin.
- **Infanrix Penta** – GlaxoSmithKline (DTPa-hepB-IPV; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin. May also contain yeast proteins.

Formulations for people aged ≥8 years

Adsorbed diphtheria-tetanus vaccine

- **ADT Booster** – Statens Serum Institut/CSL Biotherapies (dT; diphtheria-tetanus, adult formulation). Each 0.5 mL pre-filled syringe or monodose vial contains ≥2 IU diphtheria toxoid and ≥20 IU tetanus toxoid adsorbed onto 0.5 mg aluminium hydroxide.

Combination vaccines

- **Adacel** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3; 1.5 mg aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde.
- **Adacel Polio** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 1.5 mg aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin, neomycin and streptomycin.
- **Boostrix** – GlaxoSmithKline (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, adsorbed onto 0.5 mg aluminium hydroxide/phosphate; 2.5 mg phenoxyethanol as preservative. May contain traces of formaldehyde.
- **Boostrix-IPV** – GlaxoSmithKline (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polymyxin and neomycin.

Diphtheria vaccination stimulates the production of antitoxin, which protects against the toxin produced by the organism. The immunogen is prepared by treating a cell-free preparation of toxin with formaldehyde, thereby converting it into the innocuous diphtheria toxoid. Diphtheria toxoid is usually adsorbed onto an adjuvant, either aluminium phosphate or aluminium hydroxide, to increase

its immunogenicity. Antigens from *Bordetella pertussis*, in combination vaccines, also act as an effective adjuvant.

Circulating levels of antitoxin are closely related to protection from diphtheria. Antitoxin levels of <0.01 IU are poorly protective, 0.01 to 0.1 IU are usually protective, and titres of >0.1 IU are associated with more certain and prolonged protection.⁸ Complete immunisation induces protective levels of antitoxin lasting throughout childhood but, by middle age, at least 50% of vaccinees have levels <0.1 IU.⁹⁻¹¹ This has been confirmed in Australia by a recent national serosurvey.¹² Single low doses of toxoid in previously immunised adults induce protective levels within 6 weeks.¹³

Production of DT (CDT vaccine), registered for use in children <8 years of age, ceased in June 2005.

ADT Booster can be used for the booster dose of dT in people aged ≥8 years or, if necessary, for the primary dT course (see 'Variations from product information').

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.¹⁴ Store at +2°C to +8°C. Protect from light. Do not freeze.

Dosage and administration

The dose of diphtheria-containing vaccine is 0.5 mL by IM injection.

Do not mix DTPa-containing vaccines or dT vaccine with any other vaccine in the same syringe, unless specifically registered for use in this way.

Recommendations

(i) Vaccination in childhood

The recommended primary course of vaccination is at 2, 4 and 6 months of age. A booster dose of DTPa is given at 4 years of age. Immunity to diphtheria will not be compromised before the booster dose, as the serological response to the primary course of vaccination is usually sufficient for those years. A second booster, using the adolescent/adult formulation, dTpa, at 12–17 years of age, is essential for maintaining immunity to diphtheria in adults. Vaccination against diphtheria is part of the National Immunisation Program (NIP) schedule, diphtheria toxoid being given in combination with tetanus toxoid and acellular pertussis as DTPa vaccine. Before the 8th birthday, DTPa-containing vaccines should be given, as they contain a larger dose of diphtheria toxoid. After the 8th birthday, smaller doses of toxoid (dT or adolescent/adult formulation dTpa) should be given. Dose reduction is necessary because of the increased incidence of local and systemic reactions to diphtheria toxoid in older children and adults. For details on the management of children who have missed doses in the NIP schedule, see Section 1.3.5, *Catch-up*.

(ii) Vaccination of adults

Individuals who have not received any diphtheria vaccines are also likely to have missed tetanus vaccination. Three doses of dT should be received at minimum intervals of 4 weeks, followed by booster doses at 10 and 20 years after the primary course. It is prudent to give the first of these doses as dTpa, to also provide boosting to natural immunity from exposure to pertussis, which is almost universal in unvaccinated adults. In the event that dT vaccine is *not* available, dTpa can be used for all primary doses. This is not recommended routinely because there are no data on the safety, immunogenicity or efficacy of dTpa in multiple doses for primary vaccination.

All adults who reach the age of 50 years without having received a booster dose of dT in the previous 10 years should receive a further booster dose of dT, or preferably dTpa, if this has not been given previously, to also provide protection against pertussis.

(iii) Other people at special risk

Diphtheria can be a significant risk for travellers to some countries (particularly southeast Asia, the Newly Independent States of the former Soviet Union, Baltic countries or eastern European countries). Travellers to high-risk countries should receive a booster dose of dT (or dTpa) if they have not received one in the previous 10 years.

Contraindications

The only absolute contraindications to diphtheria vaccine are:

- anaphylaxis following a previous dose of the vaccine, or
- anaphylaxis following any component of the vaccine.

Adverse events

Mild discomfort or pain at the injection site persisting for up to a few days is common. Uncommon general adverse events following dT vaccine include headache, lethargy, malaise, myalgia and fever. Acute anaphylactic reactions, urticaria and peripheral neuropathy very rarely occur (brachial neuritis occurs in 0.001% of cases). (For specific adverse events following combination vaccines containing both diphtheria and pertussis antigens, see Chapter 3.14, *Pertussis*).

The public health management of diphtheria cases

A suspected case of diphtheria is of considerable public health importance, and should be notified immediately to the State/Territory public health authorities, who will advise on further management. In general, contacts of a proven or presumptive diphtheria case will require vaccination (either primary or booster, depending on vaccination status), and appropriate prophylactic antibiotics.¹⁵

Diphtheria antitoxin and penicillin should be given immediately to suspected cases. Do not wait for bacteriological confirmation of the disease. Diphtheria antitoxin derived from horse serum is used because sera of sufficient titre are not available from humans. Due to the presence of foreign protein, diphtheria antitoxin may provoke acute, severe, allergic reactions or serum sickness. Consequently, a test dose should be administered, and if there is evidence of hypersensitivity, it may be necessary to administer diphtheria antitoxin under corticosteroid, adrenaline, and antihistamine cover. The therapeutic dose of antitoxin will depend on the clinical condition of the patient, and may be given either intramuscularly or diluted for administration in an intravenous infusion. Expert advice should be sought with respect to antitoxin dose and special arrangements made if hypersensitivity is suspected. This can be coordinated through the relevant State/Territory health authority (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

- **Diphtheria antitoxin** – This is currently available only through the Special Access Scheme.

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

Variations from product information

The product information for both Infanrix hexa and Infanrix Penta states that these vaccines may be given as a booster dose at 18 months of age. NHMRC recommends that a booster dose of DTPa (or DTPa-containing vaccines) is not necessary at 18 months of age. However, DTPa-containing vaccine may be used for catch-up of the primary schedule in children <8 years of age.

The product information for Infanrix-IPV states that this vaccine may be used as a booster dose for children ≤6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. NHMRC recommends that booster doses of DTPa and IPV be given at 4 years of age; however, this product may be used for catch-up of the primary schedule or as a booster in children <8 years of age.

The product information for ADT Booster states that this vaccine is indicated for a booster dose only in children aged ≥5 years and adults who have previously received at least 3 doses of diphtheria and tetanus vaccines. NHMRC recommends that, where a dT vaccine is required for any person ≥8 years of age, ADT Booster can be used, including for primary immunisation against diphtheria and tetanus.

The product information for adolescent/adult formulations of dTpa-containing vaccines states that these vaccines are indicated for booster doses only. NHMRC recommends that, where dT is unavailable for the primary course, dTpa can be used.

The product information for Adacel and Boostrix (adolescent/adult formulations of dTpa) states that these vaccines are recommended for use in those aged >10 years. However, NHMRC recommends that they may be used in people aged ≥8 years. The product information also states that dTpa should not be given within 5 years of a tetanus toxoid-containing vaccine. However, NHMRC recommends that dTpa vaccines can be administered at any time following receipt of a diphtheria and tetanus toxoid-containing vaccine.

References

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.