4.2 DIPHTHERIA

4.2.1 Bacteriology

Diphtheria is an acute illness caused by toxigenic strains of Corynebacterium diphtheriae, a Gram-positive, non-sporeforming, 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.

4.2.2 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 aerosol transmission or by direct contact with skin lesions or articles soiled by infected persons. The disease can involve almost any mucous membrane. Pharyngeal diphtheria, by far the commonest form of disease in the unimmunised, is characterised by an inflammatory exudate that forms a greyish or green membrane in the upper respiratory tract, which can cause acute severe respiratory obstruction. Life-threatening complications from diphtheria toxin include myocarditis and neuritis (usually affecting motor nerves). The case-fatality rate in the last three decades has been reported as up to 16%. Diphtheria antitoxin, which neutralises unbound toxin, was first used in the 1890s. Together with antibiotics, antitoxin is the mainstay of treatment for diphtheria, but this may not always be successful. The first death from diphtheria in Australia for over 20 years occurred in 2011 in an unvaccinated person. Effective protection against diphtheria is only achieved by active immunisation with diphtheria toxoid-containing vaccines.

4.2.3 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. 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. In Australia, there have been two imported infections identified, one case in 2001 and one imported infection in 2011, resulting in two additional cases, including one death. The 2011 fatal case of pharyngeal diphtheria occurred in an unvaccinated person infected by a friend who acquired diphtheria in a less developed country.

4.2.4 Vaccines

Diphtheria toxoid is available in Australia only in combination with tetanus, with or without other antigens such as pertussis, inactivated poliomyelitis, hepatitis B and Haemophilus influenzae type b. The acronym DTPa, using capital letters, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines. The acronym dTpa is used for formulations that contain substantially lesser amounts of diphtheria toxoid and pertussis antigens than child (DTPa-containing) formulations; dTpa vaccines are usually used in adolescents and adults.

Diphtheria vaccination stimulates the production of antitoxin, which protects against the toxin produced by the organism. The immunogen is prepared by treating a cell-suspending 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.

The circulating levels of antitoxin required for protection from diphtheria are well described. Antitoxin levels of <0.01 IU/mL are poorly protective, 0.01 to 0.1 IU/mL are usually protective, and titres of >0.1 IU/mL are associated with more certain and prolonged protection. Complete immunisation induces protective levels of antitoxin lasting throughout childhood, but, by middle age, at least 50% of persons not vaccinated since childhood have levels <0.1 IU/mL. This has been confirmed in Australia by a national serosurvey. Single low doses of toxoid in previously immunised adults induce protective levels within 6 weeks.

Formulations for children aged <10 years

- Hexaxim – Sanofi-Aventis Australia Pty Ltd (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b). Each 0.5 mL pre-filled syringe contains ≥20 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 10 µg recombinant HBsAg, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1), 32 D-antigen units type 3 (Saukett) and 12 µg purified Hib capsular polysaccharide (PRP) conjugated to 22–36 µg tetanus toxoid, adsorbed onto 0.6 mg aluminium as aluminium hydroxide. May contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B.
- **Infanrix** – GlaxoSmithKline Australia Pty Ltd (DTPa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial or pre-filled syringe contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg pertactin (PRN), adsorbed onto 0.5 mg aluminium as aluminium hydroxide.

- **Infanrix hexa** – GlaxoSmithKline Australia Pty Ltd (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-**Haemophilus influenzae** type b). The vaccine consists of both a 0.5 mL pre-filled syringe containing ≥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 poliovirus 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, polysorbate 80, polysorbate 20, 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. May contain yeast proteins.

- **Infanrix IPV** – GlaxoSmithKline Australia Pty Ltd (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). 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 poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide; traces of formaldehyde, polysorbate 80, polysorbate 20, polymyxin and neomycin.

- **Quadrixel** – GlaxoSmithKline Australia Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 1.5 mg aluminium phosphate; ≤50 ng bovine serum albumin; phenoxethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin and neomycin.

- **Tripacel** – Sanofi-Aventis Australia Pty Ltd (DTPa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vials contain ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 10 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3; 1.5 mg aluminium phosphate; 3.4 mg phenoxethanol.

**Reduced antigen formulations for adults, adolescents and children aged ≥10 years**

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

- **Adacel** – Sanofi-Aventis Australia Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vials contain ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3; 0.33 mg aluminium as aluminium phosphate; phenoxethanol; traces of formaldehyde and glutaraldehyde.

- **Adacel Polio** – Sanofi-Aventis Australia Pty Ltd (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL monodose vial or pre-filled syringe 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 poliovirus type 1 (Mahoney); 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 0.33 mg aluminium as aluminium phosphate; phenoxethanol; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin, neomycin and streptomycin.

- **Boostrix** – GlaxoSmithKline Australia Pty Ltd (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 as aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80 and glycine.

- **Boostrix-IPV** – GlaxoSmithKline Australia Pty Ltd (dTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). 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 poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto 0.5 mg aluminium as aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polymyxin and neomycin.

### 4.2.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5.* Store at +2°C to +8°C. Do not freeze. Protect from light.

Infanrix hexa must be reconstituted by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at room temperature for not more than 8 hours.
4.2.6 Dosage and administration
The dose of all diphtheria-containing vaccines is 0.5 mL, to be given by IM injection.

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

4.2.7 Recommendations

Infants and children

Primary doses
Diphtheria toxoid is given in combination with tetanus toxoid and acellular pertussis as DTPa-containing vaccines. The recommended 3-dose primary schedule is at 2, 4 and 6 months of age. The 1st dose can be given as early as 6 weeks of age, due to the high morbidity and occasional mortality associated with pertussis in very young infants. If the 1st dose is given at 6 weeks of age, the next scheduled doses should still be given at 4 months and 6 months of age (refer to 4.12 Pertussis).

Booster doses
Two booster doses of DTPa-containing vaccine are recommended during childhood (at 18 months and 4 years of age) to provide ongoing protection against pertussis through to early adolescence (refer to 4.12 Pertussis).

For details on the management of children who require catch-up vaccination for diphtheria, including minimum acceptable intervals between vaccine doses, refer to 2.1.5 Catch-up.

Older children and adolescents
An additional booster dose (i.e. in addition to those recommended for young children, refer above) is recommended for adolescents between 10 and 17 years of age, using the reduced antigen content dTpa. The optimal age for administering this dose is 11–13 years, particularly due to waning of the pertussis antibody response following the booster dose recommended at 4 years of age (refer to 4.12 Pertussis). This adolescent booster dose of diphtheria-containing vaccine is essential for maintaining immunity to diphtheria (and tetanus and pertussis) into adulthood.

It is recommended to use the reduced antigen content dTpa for booster doses. However, when necessary, dT can also be used for the booster dose or, if necessary, for the primary dT course, in persons aged ≥10 years (refer to 4.2.12 Variations from product information below).

For details on the management of children and adolescents who require catch-up vaccination for diphtheria, refer to 2.1.5 Catch-up.

Adults

Booster doses
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 diphtheria booster dose. This should be given as dTpa, to also provide protection against pertussis (refer to 4.12 Pertussis). This stimulates further production of circulating diphtheria antibodies at an age when waning of diphtheria and tetanus immunity is commencing in the Australian population.11

A single booster dose of dTpa is also recommended for adults aged ≥65 years (if not received in the previous 10 years), for protection against pertussis (refer to 4.12 Pertussis).

Diphtheria can be a significant risk for travellers to some countries (particularly Southeast Asia, New Guinea, the states of the former Soviet Union, Baltic countries or eastern European countries). Travellers to countries where health services are difficult to access should be adequately protected against diphtheria before departure. They should receive a booster dose of dT (or dTpa if not given previously) if more than 10 years have elapsed since the last dose of dT-containing vaccine.

For persons undertaking travel to a country in which there is a high risk of diphtheria, consider giving a booster dose of either dTpa or dT (as appropriate) if more than 5 years have elapsed since the last dose of a dT-containing vaccine.

Persons who may be occupationally exposed to toxigenic Corynebacterium diphtheriae should consider a booster dose of either dTpa or dT (as appropriate) if more than 10 years have elapsed since the last dose of dT-containing vaccine. Serology should be conducted at an interval of not less than 10-yearly.

Primary doses
Persons who have not received any diphtheria vaccines are also likely to have missed tetanus vaccination. Therefore, 3 doses of dT should be given at minimum intervals of 4 weeks, followed by booster doses at 10 and 20 years after the primary course. One of these 3 doses (preferably the 1st) should be given as dTpa, to also provide additional protection against pertussis. In the event that dT vaccine is not available, dTpa can be used for all primary doses.14
For additional information on adults with no history of a primary course of dT vaccine requiring catch-up, refer to 2.1.5 Catch-up.

**Interval between tetanus/diphtheria-containing vaccines**

In some circumstances where protection against pertussis is required as soon as possible, a single dose of dTpa vaccine can be administered at any time after a dose of tetanus- and diphtheria-containing vaccine (refer to 4.12 Pertussis). If providing dT or dTpa vaccine as part of a dT catch-up schedule in adults or children aged ≥10 years, the recommended minimum intervals between doses should be met (refer to 2.2 Administration of vaccines).

### 4.2.8 Pregnancy and breastfeeding

Although dT vaccines are not routinely recommended for pregnant women, they can be given under certain circumstances, such as for management of a tetanus-prone wound (refer to 4.19 Tetanus).<sup>15</sup>

dTpa vaccine is recommended for pregnant women (in the third trimester of each pregnancy) to prevent pertussis in pregnant women and their newborns (refer to 4.12 Pertussis).

dT or dTpa vaccines can be given to breastfeeding women.

Refer to 3.3 Groups with special vaccination requirements, Table 3.3.1 Recommendations for vaccination in pregnancy for more information.

### 4.2.9 Contraindications

The only absolute contraindications to diphtheria-containing vaccines are:

- anaphylaxis following a previous dose of any diphtheria-containing vaccine
- anaphylaxis following any vaccine component.

### 4.2.10 Adverse events

Mild discomfort or pain at the injection site persisting for up to a few days is common. Administration of more than 1 dose of a dT-containing vaccine in a 5-year period in previously immunised adults had previously been thought to be associated with an increased risk of injection site reactions. However, recent studies indicate that, in adults and adolescents, the adverse reactions to a single dose of dTpa are similar whether administered shortly (18 months) or at a longer interval after a previous dose of a vaccine containing tetanus/diphtheria toxoids.<sup>16-19</sup> (Refer also to 4.12 Pertussis.)

Uncommon general adverse events following dT vaccine include headache, lethargy, malaise, myalgia and fever. Anaphylaxis, urticaria and peripheral neuropathy occur very rarely. Brachial neuritis (inflammation of a nerve in the arm, causing weakness or numbness) has been described following the administration of tetanus toxoid-containing vaccines, with an estimated excess risk of approximately 0.5–1 in 100 000 doses in adults.<sup>20,21</sup> For specific adverse events following combination vaccines containing both diphtheria and pertussis antigens, refer to 4.12 Pertussis.

### 4.2.11 Public health management of diphtheria

Diphtheria is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of diphtheria, including management of cases of diphtheria and their contacts, should be obtained from state/territory public health authorities (refer to Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control).

Confirmed or suspected diphtheria is of considerable public health importance and should be notified immediately to state/territory public health authorities. 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<sup>22</sup> (refer to 4.12 Pertussis).

Advice should be sought with respect to diphtheria antitoxin access and dosage, and special arrangements made if hypersensitivity is suspected; this can be coordinated through the relevant state/territory health authority (refer to Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control and Part 5 Passive immunisation).

### 4.2.12 Variations from product information

The product information for Infanrix states that this vaccine is indicated for primary immunisation of infants from the age of 2 months to 12 months and as a booster dose for children from 15 months to 6 years of age who have previously been vaccinated against diphtheria, tetanus and pertussis. The ATAGI recommends that this vaccine may also be used for catch-up of the primary schedule or as a booster in children <10 years of age. The ATAGI also recommends that the primary schedule may be commenced at 6 weeks of age, if required.
The product information for Infanrix hexa states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks and as a booster dose for children 18 months of age if boosting is required for all antigens. The ATAGI recommends that this vaccine may also be used for catch-up of the primary schedule or as a booster in children <10 years of age.

The product information for Infanrix IPV states that this vaccine is indicated for use in a 3-dose primary schedule for immunisation of infants from the age of 6 weeks and as a single booster dose for children ≤6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. In addition, the ATAGI recommends that this product may also be used for catch-up of the primary schedule or as a booster in children <10 years of age.

The product information for Quadracel states that this vaccine is indicated for use in a 3-dose primary schedule from the age of 2 months to 12 months and may also be used as a booster dose for children from 15 months to 6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years. The ATAGI also recommends that the primary schedule may be commenced at 6 weeks of age, if required.

The product information for ADT Booster states that this vaccine is indicated for use as a booster dose only in children aged ≥5 years and adults who have previously received at least 3 doses of diphtheria and tetanus vaccines. The ATAGI recommends instead that, where a dT vaccine is required, ADT Booster can be used, including for primary immunisation against diphtheria and tetanus (for any person ≥10 years of age).

The product information for Adacel and Boostrix (reduced antigen content dTpa) states that these vaccines are indicated for booster doses only. The ATAGI recommends instead that, when a 3-dose primary course of diphtheria/tetanus toxoids is given to an adolescent/adult, dTpa should replace the 1st dose of dT, with 2 subsequent doses of dT. If dT is not available, dTpa can be used for all 3 primary doses.

The product information for Adacel states that vaccination in pregnancy is not recommended unless there is a definite risk of acquiring pertussis. The product information for Boostrix states that the vaccine should be used during pregnancy only when clearly needed, and the possible advantages outweigh the possible risks for the fetus. The ATAGI recommends that pregnant women receive a dose with every pregnancy.

The product information for Adacel and Boostrix states that there is no recommendation regarding the timing and frequency of booster doses against pertussis in adults. However, the ATAGI recommends that pregnant women receive a booster dose with every pregnancy and that other adults in contact with infants and/or at increased risk from pertussis can receive a booster dose every 10 years.

The product information for Boostrix, Boostrix-IPV and Adacel states that dTpa-containing vaccine should not be given within 5 years of a tetanus toxoid-containing vaccine. The product information for Adacel Polio states that dTpa-containing vaccine should not be given within 3 years of a tetanus toxoid-containing vaccine. The ATAGI recommends instead that, if protection against pertussis is required, dTpa-containing vaccines can be administered at any time following receipt of a dT-containing vaccine.

The product information for Adacel, Adacel Polio, Boostrix, Boostrix-IPV, Infanrix, Infanrix hexa, Infanrix IPV, Quadracel and Tripacel states that these vaccines are contraindicated in children with encephalopathy of unknown aetiology or with neurologic complications occurring within 7 days following a vaccine dose. The ATAGI recommends instead that the only contraindication is a history of anaphylaxis to a previous dose or to any of the vaccine components.

References
A full reference list is available on the electronic Handbook or website www.immunise.health.gov.au.


13. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months – Advisory Committee on Immunization Practices (ACIP), 2011. MMWR. Morbidity and Mortality Weekly Report 2011;60:1424-6.

