

4 Diphtheria

4.1 Introduction

Diphtheria has been known since ancient times, although in the pre-microbiological age it was not clearly distinguished from streptococcal infections. The first accurate description of the disease was by Bretonneau in 1826. Epidemics of diphtheria occurred in France, Norway and Denmark during the early part of the 19th century. In 1858 there was a sudden widespread appearance of severe diphtheria, and within a year it had spread all over the world, including New Zealand. Very young children were most at risk, with few cases being reported in individuals over 10 years of age. Klebs described the morphological appearance of the organism in a diphtheritic membrane in 1883, and a year later Loeffler isolated the organism.

The incidence of diphtheria had been declining before the introduction of immunisation, which accelerated the decline. Although immunisation is more effective at preventing disease than preventing infection, it does create herd immunity and reduces carriage and therefore transmission.¹ To prevent major community outbreaks it has been suggested that 70 percent or more of the childhood population must be immune to diphtheria.^{2,3} This may explain the control of diphtheria in New Zealand despite relatively poor coverage. A larger dose of diphtheria vaccine is recommended for children (signified by capital D, eg, DTaP) than for adults (signified by a small d, eg Td) (see section 4.5).

4.2 The illness

Diphtheria is a serious, often fatal disease caused by *Corynebacterium diphtheriae*, a non-sporulating, non-encapsulated, non-motile, pleomorphic gram-positive bacillus. This disease causes a membranous inflammation of the upper respiratory tract, and it can also cause infection at other sites, notably the skin, where disease tends to be less serious. The organism is not usually invasive but produces a powerful toxin that damages the myocardium (leading to myocarditis and heart failure), peripheral nerves (resulting in demyelination and paralysis), the kidneys (resulting in tubular necrosis) and other organs. The neuropathy begins two to eight weeks after disease onset, while the myocarditis can be early or late.

C. diphtheriae may be toxin producing (toxigenic) or non-toxin producing (non-toxigenic). Immunisation leads to the disappearance of toxigenic strains, but toxigenicity can be rapidly conferred on non-toxigenic strains via phage conversion.⁴ This makes the return of epidemic diphtheria a real threat when there is insufficient herd immunity, as happened in the states of the former Soviet Union during 1990–97.

The incubation period is usually from one to five days, but can be up to 10 days. The disease remains communicable for up to four weeks, but carriers of diphtheria may continue to shed the organism and be a source of infection for much longer periods.

The clinical illness has a gradual onset over one to two days, characterised by the development of a mildly painful tonsillitis or pharyngitis with an associated greyish membrane. Diphtheria should be suspected particularly if the membrane extends to the uvula and soft palate. The nasopharynx may also be obstructed by a greyish membrane, which leaves a bleeding area if disturbed. It is stated that the breath of a patient with diphtheria has a characteristic mousy smell.

The majority of diphtheria deaths are due to the effects of toxin on the myocardium, and the earlier the electrocardiographic changes occur, the worse the prognosis. The case fatality rate in the United States (US) for pharyngeal diphtheria has remained at about 10 percent since 1920. The mortality in the recent Russian outbreak was much lower, at just over 2 percent, but was variable by age and region.

4.3 Epidemiology

Humans are the only known host for diphtheria, and the disease is spread by close personal contact with a case or carrier. In the pre-immunisation era diphtheria was predominantly a disease of children under 15 years of age, and most adults acquired immunity without experiencing clinical diphtheria. Asymptomatic carriage was common (3–5 percent) and important in perpetuating both endemic and epidemic diphtheria. Immunisation appears to reduce carriage, and therefore reduces exposure to infection (herd immunity).

The incidence of diphtheria dropped dramatically during the 20th century. Although immunisation played a large part in this reduction it may not be wholly responsible. Diphtheria is rare in industrialised countries like New Zealand, although small outbreaks may occur. A Swedish outbreak in 1984–86 was caused by a single strain and occurred mainly in a group of destitute alcoholics and drug users.⁵ It occurred after more than 25 years without indigenous diphtheria, and was notable for not spreading to the general population, despite 70 percent of women and 50 percent of men having no detectable antibody against diphtheria (ie, an antibody titre < 0.01 IU/mL).⁶ Limited contact between affected individuals and the general population, as well as outbreak control measures such as immunising hospital personnel, may have accounted for the lack of spread.

In June 1995 the World Health Organization (WHO) declared the diphtheria epidemic affecting the former Soviet Union to be an international health emergency. The epidemic began in Russia in 1990 and had affected almost all states of the former Soviet Union by 1994. Although other factors (ie, social disruption, mass population movements, inadequate immunisation coverage among children and the introduction of a new strain) were relevant, the importance of waning immunity and/or lack of immunity among adults were highlighted by the epidemiology. More than 115,000 cases and 3000 deaths were reported between 1990 and 1997 in the Russian Federation. Most of the cases and deaths occurred in adults, although the incidence rate for diphtheria was higher among children.⁷ Mass immunisation of adults and improved childhood immunisation controlled the epidemic, but has not

yet eliminated the circulation of diphtheria in the region. A case control study in the Ukraine found that three doses of vaccine were 98 percent effective in preventing disease in children under 15 years of age,⁸ thus showing that poor vaccine efficacy was not responsible for the epidemic.

Diphtheria remains endemic in many parts of the non-industrialised world but is being controlled by immunisation. In industrialised countries diphtheria has become increasingly rare; for example, in the US there were 853 notifications of non-cutaneous diphtheria during the 1970s,⁹ but only 41 cases between 1980 and 1995.¹⁰ However, continuing endemic cutaneous diphtheria in indigenous communities has been reported from the US, Canada and Australia.

The virtual disappearance of diphtheria in industrialised countries has removed the opportunity for infection to either produce or boost immunity. In all developed countries that have undertaken surveys, many adults have been shown to lack diphtheria antibodies.¹¹ In Australia, where infant vaccination against diphtheria was introduced from 1940 to 1945, a report from the national serosurvey using samples taken during 1996–99 showed that about 99 percent of children aged five to nine years had diphtheria antitoxin levels ≥ 0.01 IU/mL and were considered immune or partially immune.¹² Eighty-one percent of those aged 20–29 years were considered immune or partially immune, whereas in subjects aged 50–59 years, who were born between 1937 and 1948, only 59 percent had antitoxin levels considered immune or partially immune to diphtheria.

Despite these findings there has been minimal disease in developed countries, suggesting that antibody levels may not be a reliable guide to protection and that other factors may be operating.¹³ For example, a high proportion of the adult German population have antibody levels indicating susceptibility yet this has not led to diphtheria outbreaks despite Germany's relative proximity to the former Soviet Union.¹⁴

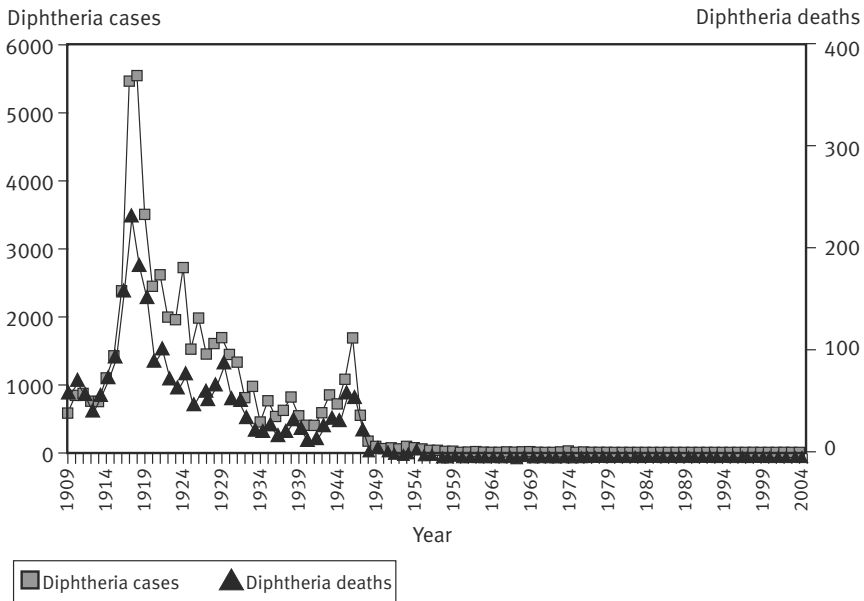
Diphtheria continues to occur each year in less developed countries in Asia and the Western Pacific Region. For sources of further information see Appendix 11.

New Zealand epidemiology

Between 1917 and 1921 there were 794 reported deaths in non-Māori from diphtheria.¹⁵ Regular epidemics of infection occurred in New Zealand until 1950, and further outbreaks occurred in Milton and the Waikato in the 1960s. In 1998 the first case of diphtheria was reported in New Zealand since 1979, and this was the first toxigenic isolate since 1987.¹⁶ In 2002 a four-year-old child was reported after a toxigenic strain was isolated from a hip aspirate. The child had no toxin related symptoms and had been fully vaccinated for age; this would not be regarded as a vaccine failure. (See Figure 4.1.)

There is no current data on the proportion of New Zealand adults susceptible to diphtheria. The 1985 National Serum Survey found that 73 percent of five year olds, 65 percent of 10 year olds and 53 percent of 15 year olds had protective levels of diphtheria antibody.¹⁷ The decline apparent with age suggests that there is likely to be a large and increasing pool of adults susceptible to diphtheria in New Zealand. This was the reason for the introduction of adult tetanus diphtheria (Td) vaccination in 1994.

Figure 4.1: Number of cases of diphtheria and diphtheria mortality, 1909–2004



History of the New Zealand Immunisation Schedule

During the 1920s the Department of Health, at the instigation of individual school medical officers or medical officers of health, began delivering diphtheria immunisation in a few selected schools and orphanages, but there was no national policy. By 1941 diphtheria immunisation was offered routinely to children under seven years of age through the School Medical Service and the Plunket Society. From 1960 the Department of Health programme was delivered by general practitioners using three doses of non-adsorbed triple vaccine (diphtheria, tetanus and whole cell pertussis vaccine – DTWP) at three, four and five months of age, and a dose of double (diphtheria and tetanus – DT) vaccine before school entry at five years of age. In 1964 a DT booster at 18 months was added to the schedule. There was a change in 1971 to an adsorbed (ie, adjuvant added) vaccine that was more immunogenic, and the dose given at four months of age was dropped. In 1980 the dose of DT given at five years of age was replaced by the monovalent tetanus toxoid (TT) given at 15 years of age, as part of a move from 10-yearly to 20-yearly boosters for tetanus.

There was a return to a three dose primary series for DTwP (by the addition of a dose at six weeks of age) in 1984, because two doses of DTwP had been inadequate to control pertussis.

Emerging concerns about the lack of adult immunity to diphtheria, prompted by outbreaks and epidemics overseas, led to the introduction of Td in 1994. Td replaced the TT vaccine given to 15 year olds and as adult boosters. The recommendation for boosters was changed from 20-yearly to 10-yearly in the hope this would increase uptake. In 1996 the timing of the adolescent booster of Td was changed from age 15 years to age 11 years. Td was continued at age 11 years until the introduction of the adult diphtheria, tetanus, acellular pertussis and inactivated polio vaccine (dTAp-IPV) in February 2006. From 2002 Td boosters for adults have been recommended at age 45 and 65 years, as a pragmatic attempt to improve the uptake of adult booster doses.

From 1996 the vaccine used for infants was the combination vaccine of diphtheria, tetanus, whole cell pertussis and *Haemophilus influenzae* type b vaccine (DTwPH). In August 2000 the vaccines were changed to diphtheria, tetanus and acellular pertussis (DTaP) during the first year, and diphtheria, tetanus, acellular pertussis and *H. influenzae* type b (DTaP/Hib) at age 15 months. In 2002, with the change to inactivated polio vaccine (IPV), DTaP-IPV was given during the first year of life at age six weeks, and at three and five months. A booster of DTaP-IPV was added at the age of four years before school entry to improve pertussis control and boost diphtheria immunity.

From 2006 the schedule is three doses of a diphtheria containing vaccine (DTaP-IPV) in the first year of life, and a fourth dose at age four years. At age 11 years (school year 7) dTap-IPV will be given, and adult boosters will continue to be recommended at age 45 and 65 years. The diphtheria, tetanus and acellular pertussis vaccine dose at 15 months has been dropped. However, it is expected that young children will have adequate protection from diphtheria from the end of the first year and the dose at age four years (see chapter 6: Pertussis for further details).

4.4 Vaccines

Diphtheria toxoid is prepared from cell free purified diphtheria toxin treated with formaldehyde. It is a relatively poor immunogen, which, to improve its efficacy, is usually adsorbed onto an adjuvant – either aluminium phosphate or aluminium hydroxide.

The diphtheria vaccine is only available as a component of combination vaccines. From 2006 the publicly funded vaccine for the infant series and the booster at age four years is diphtheria, tetanus, acellular pertussis and inactivated polio vaccine (DTaP-IPV – INFANRIX™-IPV, GSK). A smaller adult dose of diphtheria and pertussis vaccine together with tetanus and inactivated polio vaccine (dTAp-IPV – BOOSTRIX®-IPV, GSK) is given at age 11 years (school year 7) (see section 4.5 below, and sections 6.4 and 8.4).

There are other diphtheria vaccines available that are publicly funded for children requiring an alternative to a pertussis containing vaccine. These vaccines include adsorbed diphtheria tetanus (DT–CDT™, CSL) for children six years of age and under, and the adult tetanus-diphtheria vaccine (Td–ADT®, CSL), with a reduced dose of diphtheria toxoid for individuals seven years of age and over (see section 4.5). Because the age cut off for changing from the childhood to the adult vaccine varies between countries, the manufacturer's inserts may suggest different age cut offs. The Australian guidelines use a cut off age of eight years, the British 10 years and the American guidelines seven years.

Efficacy of vaccine

Although there are no randomised controlled studies on the efficacy of the vaccine, between 87 and 98 percent protection has been demonstrated. Immunised cases have been shown to have less severe disease, as highlighted during the outbreak in the former Soviet Union.

Dosage

The dose of DTaP-IPV, dTap-IPV, DT or Td is 0.5 mL given by intramuscular injection. (See section 2.3 for needle sites and sizes.)

4.5 Recommended immunisation schedule

Primary immunisation

From 2006 the diphtheria containing vaccine for infants and children up to and including six years of age is DTaP-IPV, which is given at six weeks, three months and five months of age. A further dose of DTaP-IPV is given at four years of age, prior to school entry, and at age 11 years (school year 7) a dose of dTap-IPV is given. The dTap-IPV vaccine will be given to children aged 11 years in 2006/07, because these children have not received four doses of polio vaccine. Children receiving a fifth dose of a polio (IPV) containing vaccine are unlikely to experience adverse events. After this it is expected dTap will be given.

If a course of immunisation is interrupted for any reason, it may be resumed, without repeating prior doses, to complete four doses of diphtheria toxoid. The fifth dose is given at age 11 years.

Maximum number of doses for children

Children who did not receive the pertussis vaccine (DTwPH, DTaP or DTaP-IPV) as infants, but subsequently wish to have pertussis vaccine, will receive additional doses of diphtheria and tetanus vaccine because pertussis is only available in the DTaP-IPV combination. In general, children should not have more than six doses of tetanus and diphtheria vaccines by their fourth birthday. For an individual child, the vaccinator may be guided by the extent of any local reaction in determining whether to give future doses. The only danger from the additional doses is a local reaction, and this needs to be balanced against the need to protect against pertussis.

Immunisation of individuals seven years of age and over, including adults

When immunising individuals seven years of age and over the adult tetanus diphtheria (Td) vaccine should be used. This is because of the risk of severe local reactions if the larger dose of diphtheria toxoid contained in the childhood vaccines (DTaP-IPV, DT and other combinations) is administered to partially immune individuals seven years of age and over. For full primary immunisation in this age group, three doses of 0.5 mL Td vaccine should be given by intramuscular injection at not less than monthly intervals. For previously unimmunised adults a course of three doses of Td at zero, one and six months is recommended.

As at 2006, dTap and dTap-IPV are licensed for distribution for booster doses only. However, there are expected to be no safety concerns to giving three doses of dTap-IPV to previously unimmunised older children and adults. Therefore, using dTap should be considered for all catch up and adult schedules for primary and booster immunisation.

Dose intervals between Td and dTap-IPV

It is recommended that for students who have recently received a tetanus diphtheria (Td) vaccine booster, eg, at the time of an injury, the age 11 (year 7), dTap-IPV immunisation should be delayed until two years after the dose of Td, and offered before the student reaches the age of 16 years. Students who would normally receive the year 7 event at school should be referred to their general practitioner for follow up and recall.

Booster doses for adults

Studies overseas show that many adults lack protective levels of the antibody, and this has led to concern about waning immunity and recommendations for booster doses beyond childhood. Most authorities recommend maintenance of diphtheria immunity by periodic reinforcement using Td.¹⁸

In New Zealand, following the dose of dTap-IPV at age 11 years, booster doses of Td are recommended at 45 and 65 years of age. The age specific recommendations may facilitate the linkage of adult immunisation to the delivery of other preventive health measures.

Booster doses before travel

If someone is travelling to an area endemic for diphtheria, or there is another reason to ensure immunity, a booster dose should be given if it is more than 10 years since the last dose. If adults have not received a primary series of diphtheria containing vaccine, a course of three doses should be given (at zero, one and six months). For website sources of further information see Appendix 11.

4.6 Expected responses and adverse events following immunisation (AEFI)

Expected responses

There is limited data on reactions to the diphtheria toxoid because it is usually given in combination with tetanus, pertussis and other vaccines. The 1994 Institute of Medicine review of vaccine reactions did not identify any reaction where the evidence favoured or established a causal relation for diphtheria toxoid.¹⁹ However, local and systemic reactions do occur with diphtheria vaccine, especially when the infant vaccine is used in older children and adults.

Adverse events following immunisation

For further information on adverse events following a vaccine containing diphtheria/tetanus/pertussis antigens (DTaP, DTaP-IPV, dTap-IPV) and events following the fourth and fifth dose of a DTaP containing vaccine, see chapter 6: Pertussis.

There was an increase in the number of reports (although the rates are not known) of AEFI in adults following the change from TT to Td in New Zealand, and the majority of these were local reactions. Studies in the US have found that booster doses of Td are associated with fever in 0.5 to 7 percent of recipients, but that temperatures above 39°C are rare. Other systemic symptoms such as headache or malaise are reported less frequently, and severe adverse events are reported in 2.1 events per million doses of Td.²⁰

Any severe or unexpected reactions should be reported to CARM, PO Box 913, Dunedin, using the prepaid postcard HP3442 (see section 2.4) or via online reporting at <http://carm.otago.ac.nz>. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

4.7 Contraindications

See section 1.9 for general contraindications for all vaccines. There are no specific contraindications to diphtheria vaccine (or Td/DT), except for a serious reaction to a previous dose. See also section 6.7 for contraindications to a pertussis containing vaccine.

Td must be used for individuals seven years of age and over because of the increased risk of local reactions with the higher dose of diphtheria toxoid contained in the childhood formulation.

4.8 Control measures

All cases of diphtheria should be notified immediately on suspicion to the local medical officer of health. Alert the laboratory that culture for *C. diphtheriae* is requested. If *C. diphtheriae* is isolated it should be sent to the Institute of

Environmental Science and Research (ESR) reference laboratory to determine whether it is a toxigenic strain. All patients with *C. diphtheriae* isolated from a clinical specimen should be discussed with the medical officer of health.

Household and close contacts of a case of diphtheria or a carrier should be given a complete course of vaccine or a booster dose according to the following schedule.

- Fully immunised children up to and including six years of age who have not received a booster dose of diphtheria containing vaccine within the last five years: give one injection of DTaP-IPV.
- Fully immunised individuals seven years of age and over who have not received a booster dose of a diphtheria containing vaccine within the last five years: if aged 7–15 years give one injection of dTap-IPV or dTap; if aged over 15 years give one injection of Td. (See section 4.5.)
- Unimmunised children up to and including six years of age: follow the catch up schedules outlined in Appendix 2.
- Unimmunised individuals seven years of age and over: give two injections of Td followed by one dose of dTap-IPV if aged 7–15 years; give three doses of Td at monthly intervals for adults. Alternatively three doses of dTap-IPV may be given (see section 4.5). See also Appendix 2 for catch-up schedules for other vaccines.

All close contacts should:

- have pharyngeal cultures taken
- remain under observation for seven days
- receive immunisation as described above
- be treated with erythromycin 40 to 50 mg/kg per day (maximum 2 g/day) for seven days. If compliance is uncertain, a single intramuscular dose of benzathine penicillin 600,000 to 1,200,000 units may be used (600,000 units for children weighing <30 kg and 1,200,000 units for children weighing ≥30 kg and adults). Cotrimoxazole 960 mg bd (adult dose) has been recommended in cases of erythromycin intolerance
- have a repeat pharyngeal culture to document eradication of infection (this should be taken from contacts that have been proven to be carriers, two weeks after completion of their therapy).

Child contacts should be excluded from school, early childhood services and community gatherings until they are known to be culture negative. Adult contacts who are food handlers or work with children should be excluded from work until known to be culture negative. Cases should be excluded from school until recovery has taken place and two negative throat swabs have been collected one day apart and one day after cessation of antibiotics.

For more details on control measures, refer to *Control of Communicable Diseases Manual*.²¹

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