# 15

# Diphtheria

**NOTIFIABLE**

## The disease

Diphtheria is an acute infectious disease affecting the upper respiratory tract, and occasionally the skin, caused by the action of diphtheria toxin produced by toxigenic *Corynebacterium diphtheriae* or by *Corynebacterium ulcerans*. The most characteristic features of diphtheria affecting the upper respiratory tract are a membranous pharyngitis (often referred to as a pseudo-membrane) with fever, enlarged anterior cervical lymph nodes and oedema of soft tissue giving a 'bull neck' appearance. The pseudo-membrane may cause respiratory obstruction. In the UK, the classical disease is now very rare and clinicians may not recognise it. Milder infections (without toxin production) resemble streptococcal pharyngitis and the pseudo-membrane may not develop, particularly in vaccinated individuals. Carriers may be asymptomatic. Diphtheria toxin affects the myocardium, nervous and adrenal tissues, causing paralysis and cardiac failure.

The incubation period is from two to five days. Patients with untreated disease may be infectious for up to four weeks, but carriers may potentially transmit the infection for longer. Transmission of the infection is by droplet and through contact with articles (such as clothing or bed linen) soiled by infected persons.

In countries where hygiene is poor, cutaneous diphtheria is the predominant clinical manifestation and source of infection. The normal reservoir of *C. ulcerans* is cattle. Infections in humans are associated with the consumption of raw dairy products and contact with animals. Person-to-person spread cannot be ruled out, although it is probably uncommon (Bonnet and Begg, 1999).

There is little likelihood of developing natural immunity from sub-clinical infection acquired in the UK. Based on sero-surveillance studies, approximately 50% of UK adults over 30 years are susceptible to diphtheria. The proportion susceptible increases to over 70% in older age cohorts (Edmunds *et al.*, 2000). High immunisation uptake must be maintained in order to prevent the resurgence of disease which could follow the introduction of cases or carriers of toxigenic strains from overseas.

## History and epidemiology of the disease

Prior to the 1940s, diphtheria was a common disease in the UK. The introduction of immunisation against diphtheria on a national scale during the 1940s resulted in a dramatic fall in the number of notified cases and deaths from the disease. In 1940, more than 61,000 cases with 3,283 deaths were notified in the UK, compared with 38 cases and six deaths in 1957 (see Figure 15.1).

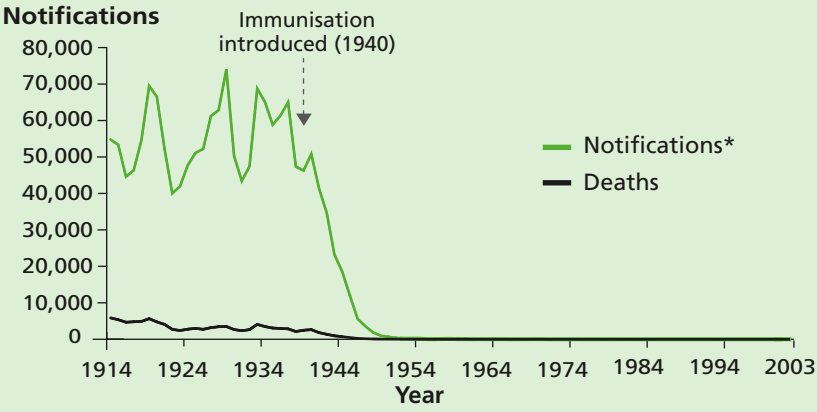
From 1986 to 2002, 56 isolates of toxigenic *C. diphtheriae* and 47 isolates of toxigenic *C. ulcerans* were identified in England and Wales by the Health Protection Agency (HPA) Streptococcus and Diphtheria Reference Unit (formerly the Public Health Laboratory Service). Of these, eight patients with *C. diphtheriae* infection and six patients with *C. ulcerans* presented with classical pharyngeal diphtheria: the remainder had mild pharyngitis or were asymptomatic. Two deaths from diphtheria occurred between 1986 and 2002: in 1994 an unvaccinated 14-year-old died with a *C. diphtheriae* infection following a visit to Pakistan, and in 2000 an elderly woman died with a *C. ulcerans* infection acquired in the UK.



An increase in notifications of diphtheria since 1992 has been due to a rise in isolations of non-toxigenic strains of *C. diphtheriae* which do not cause classical diphtheria disease (Reacher *et al.*, 2000). These may be associated with a mild sore throat without signs of toxicity.

Diphtheria cases continue to be reported in South-East Asia, South America, Africa and India. A large number of UK citizens travel to and from these regions, maintaining the possibility of the reintroduction of *C. diphtheriae* into the UK. Most cases of diphtheria that have occurred in recent years in the UK have been imported from the Indian subcontinent or from Africa; four cases of cutaneous diphtheria were reported in travellers returning in 2002 (De Benoist *et al.*, 2004). Secondary cases are rare but do occur in the UK.

There was a resurgence of diphtheria in the former Soviet Union, starting with an initial peak in the 1980s and followed by a larger epidemic from 1990 (Dittmann *et al.*, 2000). The epidemic rapidly disseminated, affecting all newly independent states, and peaked in 1994–95. From 1990 to 1998, more than 157,000 cases and 5000 deaths had been reported to the World Health Organization (WHO) (Dittmann *et al.*, 2000). This epidemic was caused by low immunisation coverage in young children, waning immunity in adults and large-scale population movements. Several importations of diphtheria occurred from former Soviet Union countries into Western Europe, including one case into the UK in 1997 (CDR, 1997).




Source: Office for National Statistics; Health Protection Agency
* Notifications up to 1985, laboratory-confirmed cases 1986–2002
† Death data for 2002 are provisional

Figure 15.1 Diphtheria cases and deaths, England and Wales (1914–2003)



## The diphtheria vaccination

The vaccine is made from a cell-free purified toxin extracted from a strain of *C. diphtheriae*. This is treated with formaldehyde, which converts it into diphtheria toxoid. This is adsorbed on to an adjuvant – either aluminium phosphate or aluminium hydroxide – to improve its immunogenicity.

Diphtheria vaccines are produced in two strengths according to the diphtheria toxoid content:

- vaccines containing the higher dose of diphtheria toxoid (abbreviated to 'D') contain not less than 30IU
- vaccines containing the lower dose of diphtheria toxoid (abbreviated to 'd') contain approximately 2IU.

Vaccines containing the higher dose of diphtheria toxoid (D) are used to achieve satisfactory primary immunisation of children under ten years of age. Vaccines containing the lower dose of diphtheria toxoid (d) should be used for primary immunisation in individuals aged ten years or over, where they provide a satisfactory immune response and the risk of reactions is minimised. This precautionary advice is particularly pertinent when the early immunisation

history and possibility of past exposure are uncertain. Low-dose preparations are also recommended for boosting (see 'Reinforcing immunisation' section, below).

The diphtheria vaccine is only given as part of combined products:

- diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/ *Haemophilus influenzae* type b (DTaP/IPV/Hib)
- diphtheria/tetanus/acellular pertussis/inactivated polio vaccine (dTaP/IPV or DTaP/IPV)
- tetanus/diphtheria/inactivated polio vaccine (Td/IPV).

The above vaccines are thiomersal-free. They are inactivated, do not contain live organisms and cannot cause the diseases against which they protect.



Td/IPV vaccine should be used where protection is required against tetanus, diphtheria or polio in order to provide comprehensive long-term protection against all three diseases.

Monovalent diphtheria vaccine is not available.

## Storage

Vaccines should be stored in the original packaging at +2˚C to +8˚C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

## Presentation

Diphtheria vaccine is only available as part of combined products. It is supplied as a cloudy white suspension, either in a single dose ampoule or pre-filled syringe. The suspension may settle during storage, so the vaccine should be shaken to distribute the suspension uniformly before administration.

## Dosage and schedule

- First dose of 0.5ml of a diphtheria-containing vaccine.
- Second dose of 0.5ml, one month after the first dose.
- Third dose of 0.5ml, one month after the second dose.
- Fourth and fifth doses of 0.5ml should be given at the recommended intervals (see below).

## Administration

Vaccines are routinely given intramuscularly into the upper arm or anterolateral thigh. This is to reduce the risk of localised reactions, which are more common when vaccines are given subcutaneously (Mark *et al.*, 1999, Diggle and Deeks, 2000; Zuckerman, 2000). However, for individuals with a bleeding disorder, vaccines should be given by deep subcutaneous injection to reduce the risk of bleeding.

Diphtheria-containing vaccines can be given at the same time as other vaccines such as MMR, MenC and hepatitis B. The vaccines should be given at a separate site, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each vaccine was given should be noted in the individual's records.

## Disposal

Equipment used for vaccination, including used vials or ampoules, should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box (UN-approved, BS 7320).



# Recommendations for the use of the vaccine

The objective of the immunisation programme is to provide a minimum of five doses of a diphtheria-containing vaccine at appropriate intervals for all individuals. For most circumstances, a total of five doses of vaccine at the appropriate intervals are considered to give satisfactory long-term protection.

To fulfil this objective, the appropriate vaccine for each age group is also determined by the need to protect individuals against tetanus, pertussis, Hib and polio.

## Primary immunisation

### Infants and children under ten years of age

The primary course of diphtheria vaccination consists of three doses of a D-containing product. DTaP/IPV/Hib is recommended to be given at two, three and four months of age but can be given at any stage from two months to ten years of age. If the primary course is interrupted it should be resumed but not repeated, allowing an interval of one month between the remaining doses.

### Children aged ten years or over, and adults

The primary course of diphtheria vaccination consists of three doses of a d-containing product with an interval of one month between each dose. Td/IPV is recommended for all individuals aged ten years or over. If the primary course is interrupted it should be resumed but not repeated, allowing an interval of one month between the remaining doses.

## Reinforcing immunisation

Children under ten years should receive the first diphtheria booster combined with tetanus, pertussis and polio vaccines. The first booster of a diphtheria-containing vaccine should ideally be given three years after completion of the primary course, normally when the child is between three-and-a-half and five years of age. When primary vaccination has been delayed, this first booster dose may be given at the scheduled visit – provided it is one year since the third primary dose. This will re-establish the child on the routine schedule. DTaP/IPV or dTaP/IPV should be used in this age group. Td/IPV should not be used routinely for this purpose in this age group because it does not contain pertussis and has not been shown to give an equivalent diphtheria antitoxin response compared with other recommended preparations.



Individuals aged ten years or over who have only had three doses of a diphtheria-containing vaccine should receive the first diphtheria booster combined with tetanus and polio vaccines (Td/IPV).

The second booster dose of Td/IPV should ideally be given to all individuals ten years after the first booster dose. Where the previous doses have been delayed, the second booster should be given at the school session or scheduled appointment – provided a minimum of five years have elapsed between the first and second boosters. This will be the last scheduled opportunity to ensure long-term protection.

If a person attends for a routine booster dose and has a history of receiving a vaccine following a tetanus-prone wound, attempts should be made to identify which vaccine was given. If the vaccine given at the time of the injury was the same as that due at the current visit and given after an appropriate interval, then the routine booster dose is not required. Otherwise, the dose given at the time of injury should be discounted as it may not provide long-term protection against all antigens, and the scheduled immunisation should be given. Such additional doses are unlikely to produce an unacceptable rate of reactions (Ramsay *et al.*, 1997).

## Vaccination of children with unknown or incomplete immunisation status

Where a child born in the UK presents with an inadequate immunisation history, every effort should be made to clarify what immunisations they may have had (see Chapter 11). A child who has not completed the primary course should have the outstanding doses at monthly intervals. Children may receive the first booster dose as early as one year after the third primary dose to re-establish them on the routine schedule. The second booster should be given at the time of school leaving to ensure long-term protection at this time. Wherever possible, a minimum of five years should be left between the first and second boosters.

Children coming to the UK who have a history of completing immunisation in their country of origin may not have been offered protection against all the antigens currently used in the UK. They will probably have received diphtheria-containing vaccines in their country of origin. For country-specific information, please refer to www.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm.

Children coming from developing countries, from areas of conflict, or from hard-to-reach population groups may not have been fully immunised. Where there is no reliable history of previous immunisation, it should be assumed that they are unimmunised and the full UK recommendations should be followed (see Chapter 11 on vaccine schedules).

Children coming to the UK may have had a fourth dose of a diphtheria-containing vaccine that is given at around 18 months in some countries. This dose should be discounted as it may not provide satisfactory protection until the time of the teenage booster. The routine pre-school and subsequent boosters should be given according to the UK schedule.

## Travellers and those going to live abroad

All travellers to epidemic or endemic areas should ensure that they are fully immunised according to the UK schedule. Additional doses of vaccines may be required according to the destination and the nature of travel intended, for example for those who are going to live or work with local people in epidemic or endemic areas (Department of Health, 2001). Where tetanus, diphtheria or polio protection is required and the final dose of the relevant antigen was received more than ten years ago, Td/IPV should be given.

## Diphtheria vaccination in laboratory and healthcare workers

Individuals who may be exposed to diphtheria in the course of their work, in microbiology laboratories and clinical infectious disease units, are at risk and must be protected (see Chapter 12).

## Contraindications

There are very few individuals who cannot receive diphtheria-containing vaccines. When there is doubt, appropriate advice should be sought from a consultant paediatrician, immunisation co-ordinator or consultant in communicable disease control, rather than withholding the vaccine.



The vaccine should not be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of a diphtheria-containing vaccine, or
- a confirmed anaphylactic reaction to any of the components of the vaccine.

Confirmed anaphylaxis occurs extremely rarely. Data from the UK, Canada and the US point to rates of 0.65 to 3 anaphylaxis events per million doses of vaccine given (Bohlke *et al.*, 2003; Canadian Medical Association, 2002). Other allergic conditions may occur more commonly and are not contraindications to further immunisation. A careful history of the event will often distinguish between anaphylaxis and other events that are either not due to the vaccine or are not life-threatening. In the latter circumstance, it may be possible to continue the immunisation course. Specialist advice must be sought on the vaccines and circumstances in which they could be given. The risk to the individual of not being immunised must be taken into account.

## Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

## Systemic and local reactions following a previous immunisation

This section gives advice on the immunisation of children with a history of a severe or mild systemic or local reaction within 72 hours of a preceding

vaccine. Immunisation with diphtheria-containing vaccine **should** continue following a history of:

- fever, irrespective of its severity
- hypotonic-hyporesponsive episodes (HHEs)
- persistent crying or screaming for more than three hours
- severe local reaction, irrespective of extent.

Children who have had severe reactions as above have continued and completed immunisation with diphtheria-containing vaccines without recurrence (Vermeer-de Bondt *et al.*, 1998; Gold *et al.*, 2000).

In Canada, a severe general or local reaction to DTaP/IPV/Hib is not a contraindication to further doses of the vaccine (Canadian Medical Association, 1998). Adverse events after childhood immunisation are carefully monitored in Canada (Le Saux *et al.*, 2003), and experience there suggests that further doses were not associated with recurrence or worsening of the preceding events (S Halperin and R Pless, pers. comm., 2003).



## Pregnancy and breast-feeding

Diphtheria-containing vaccines may be given to pregnant women when the need for protection is required without delay. There is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with inactivated viral or bacterial vaccines or toxoids (Plotkin and Orenstein, 2004).

## Premature infants

It is important that premature infants have their immunisations at the appropriate chronological age, according to the schedule. The occurrence of apnoea following vaccination is especially increased in infants who were born very prematurely.

Very premature infants (born ≤ 28 weeks of gestation) who are in hospital should have respiratory monitoring for 48-72 hrs when given their first immunisation, particularly those with a previous history of respiratory immaturity. If the child has apnoea, bradycardia or desaturations after the first immunisation, the second immunisation should also be given in hospital, with respiratory monitoring for 48-72 hrs (Pfister *et al.*, 2004; Ohlsson *et al.*, 2004; Schulzke *et al.*, 2005; Pourcyrous *et al.*, 2007; Klein *et al.*, 2008).

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

## Immunosuppression and HIV infection

Individuals with immunosuppression or with HIV infection (regardless of CD4 counts) should be considered for diphtheria-containing vaccines in accordance with the recommendations above. However, these individuals may not develop a full antibody response if they are immunosuppressed, and vaccine protective efficacy has not been studied. Re-immunisation should be considered after treatment is finished and recovery has occurred. Specialist advice may be required.

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk), the British HIV Association (BHIVA) *Immunisation guidelines for HIV-infected adults* (BHIVA, 2006) and the Children's HIV Association of UK and Ireland (CHIVA) immunisation guidelines (www.bhiva.org/chiva).



## Neurological conditions

### Pre-existing neurological conditions

The presence of a neurological condition is not a contraindication to immunisation. Where there is evidence of a neurological condition in a child, the advice given in the flow chart in Figure 15.2 should be followed.

If a child has a stable pre-existing neurological abnormality such as spina bifida, congenital abnormality of the brain or perinatal hypoxic-ischaemic encephalopathy, they should be immunised according to the recommended schedule. When there has been a documented history of cerebral damage in the neonatal period, immunisation should be carried out unless there is evidence of an evolving neurological abnormality.

If there is evidence of current neurological deterioration, including poorly controlled epilepsy, immunisation should be deferred and the child should be referred to a child specialist for investigation to see if an underlying cause can be identified. If a cause is not identified, immunisation should be deferred until the condition has stabilised. If a cause is identified, immunisation should proceed as normal.

A family history of seizures is not a contraindication to immunisation. When there is a personal or family history of febrile seizures, there is an increased risk of these occurring after any fever, including that caused by immunisation. Seizures associated with fever are rare in the first six months of life, and most common in the second year of life. After this age the frequency falls, and they are rare after five years of age.

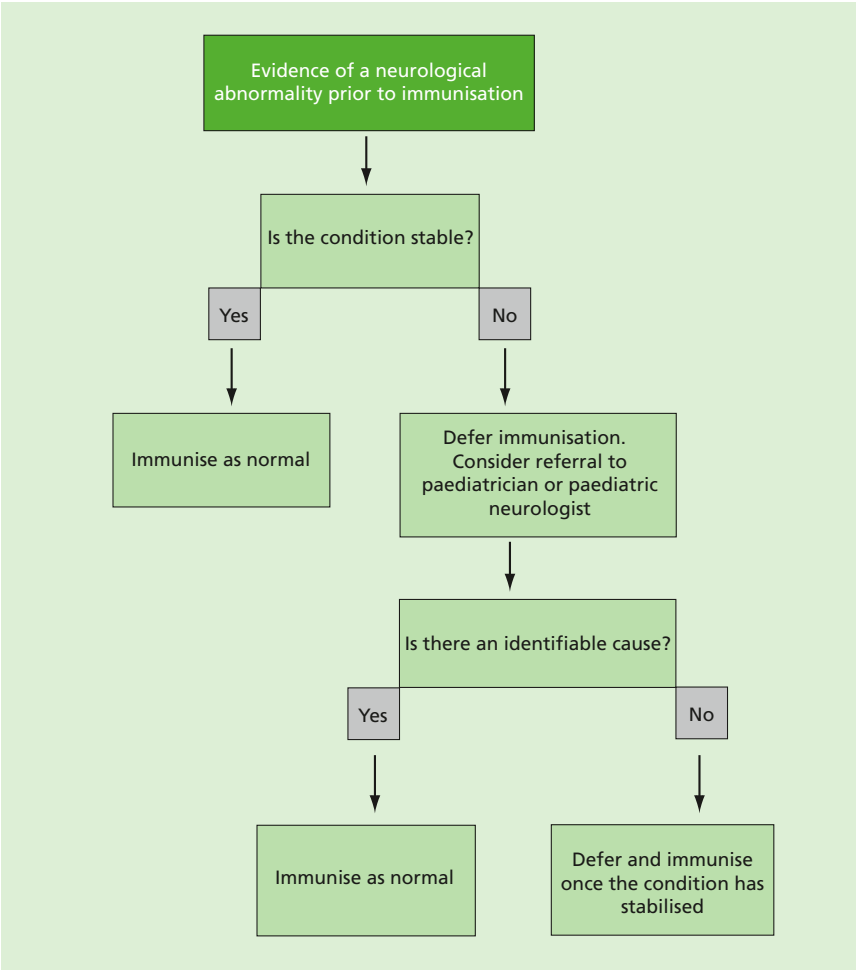



Figure 15.2 Flow chart for immunisation procedure if there is evidence of a neurological condition before immunisation

When a child has had a seizure associated with fever in the past, with no evidence of neurological deterioration, immunisation should proceed as recommended. Advice on the prevention and management of fever should be given before immunisation.

When a child has had a seizure that is not associated with fever, and there is no evidence of neurological deterioration, immunisation should proceed as recommended. When immunised with DTP vaccine, children with a family or personal history of seizures had no significant adverse events and their developmental progress was normal (Ramsay *et al.*, 1994).

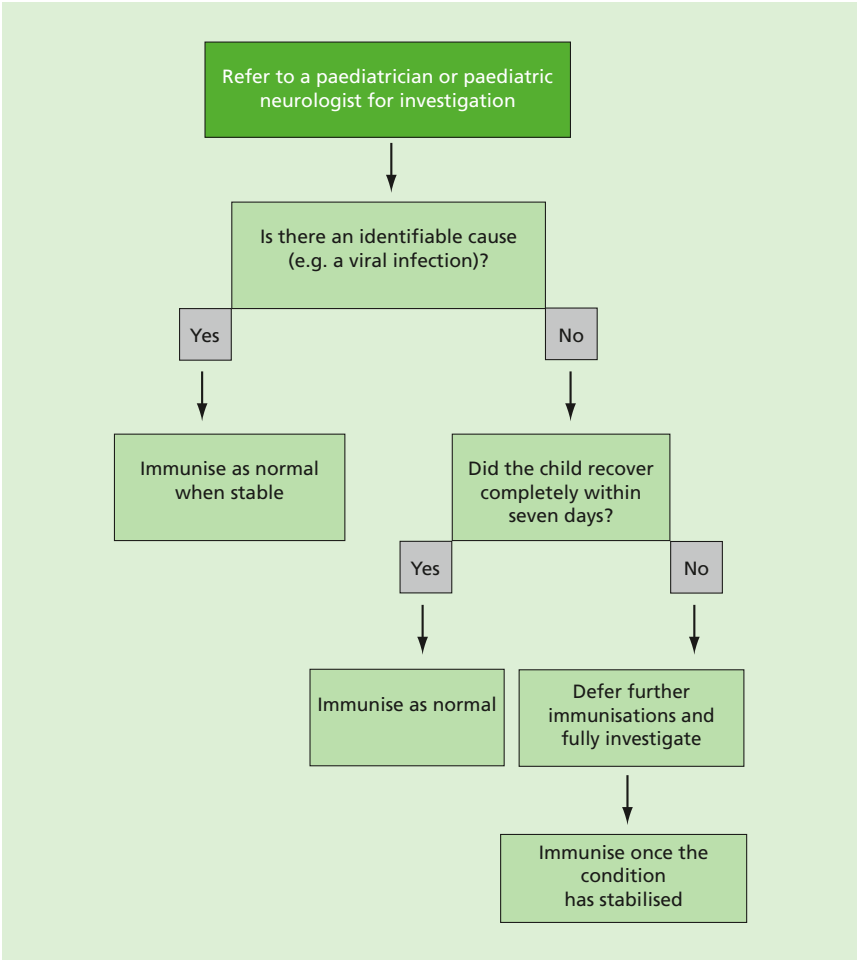



Figure 15.3 Flow chart for encephalitis or encephalopathy occurring within seven days of immunisation

## Neurological abnormalities following immunisation

If a child experiences encephalopathy or encephalitis within seven days of immunisation, the advice in the flow chart in Figure 15.3 should be followed. It is unlikely that these conditions will have been caused by the vaccine, and they should be investigated by a specialist. Immunisation should be deferred until the condition has stabilised in children where no underlying cause was found, **and** the child did not recover completely within seven days. If a cause is identified or the child recovers within seven days, immunisation should proceed as recommended.

If a seizure associated with a fever occurs within 72 hours of an immunisation, further immunisation should be deferred if no underlying cause has been found **and** the child did not recover completely within 24 hours, until the condition is stable. If a cause is identified or the child recovers within 24 hours, immunisation should continue as recommended.

## Deferral of immunisation

There will be very few occasions when deferral of immunisation is required (see above). Deferral leaves the child unprotected; the period of deferral should be minimised so that immunisation can commence as soon as possible. If a specialist recommends deferral, this should be clearly communicated to the general practitioner and he or she must be informed as soon as the child is fit for immunisation.



## Adverse reactions

Pain, swelling or redness at the injection site are common and may occur more frequently following subsequent doses. A small, painless nodule may form at the injection site; this usually disappears and is of no consequence. The incidence of local reactions is lower with diphtheria vaccines combined with acellular pertussis vaccines than with whole-cell pertussis vaccines, and similar to that after DT vaccine (Miller, 1999; Tozzi and Olin, 1997).

Fever, convulsions, high-pitched screaming, and episodes of pallor, cyanosis and limpness (HHE) occur rarely but with equal frequency after both DTaP and DT vaccines (Tozzi and Olin, 1997).

Confirmed anaphylaxis occurs extremely rarely. Data from the UK, Canada and the US point to rates of 0.65 to 3 anaphylaxis events per million doses of vaccine given (Bohlke *et al.*, 2003; Canadian Medical Association, 2002). Other allergic conditions may occur more commonly and are not contraindications to further immunisation.

All suspected adverse reactions to vaccines occurring in children, or in individuals of any age after vaccines labelled with a black triangle (▼), should be reported to the Commission on Human Medicines using the Yellow Card scheme. Serious suspected adverse reactions to vaccines in adults should also be reported through the Yellow Card scheme.

## Management of cases, contacts, carriers and outbreaks

As diphtheria is a notifiable disease in the UK, for public health management of cases, contacts and outbreaks, all suspected cases should be notified to the local health protection unit immediately.

### Management of cases

Diphtheria antitoxin is only used in suspected cases of diphtheria in a hospital setting. Tests to exclude hypersensitivity to horse serum should be carried out. Diphtheria antitoxin should be given without waiting for bacteriological confirmation. It should be given according to the manufacturer's instructions, the dosage depending on the clinical condition of the patient.



Diphtheria antitoxin is based on horse serum and therefore severe, immediate anaphylaxis occurs more commonly than with human immunoglobulin products. If anaphylaxis occurs, adrenaline (0.5ml or 1ml aliquots) should be administered immediately by either intramuscular (0.5ml of 1:1000 solution) or intravenous (1ml of 1:10,000 solution) injection. This advice differs from that for treatment of anaphylaxis after immunisation because the antitoxin is being administered in the hospital setting.

In most cutaneous infections, large-scale toxin absorption is unlikely and therefore the risk of giving antitoxin is usually considered substantially greater than any benefit. Nevertheless, if the ulcer in cutaneous diphtheria infection were sufficiently large (i.e. more than $2cm^2$) and especially if it were membranous, then larger doses of antitoxin would be justified.

Antibiotic treatment is needed to eliminate the organism and to prevent spread. The antibiotics of choice are erythromycin, azithromycin, clarithromycin or penicillin (Bonnet and Begg, 1999).

The immunisation history of cases of toxigenic diphtheria should be established. Partially or unimmunised individuals should complete immunisation according to the UK schedule. Completely immunised individuals should receive a single reinforcing dose of a diphtheria-containing vaccine according to their age.

## Management of contacts

Contacts of a case or carrier of toxigenic diphtheria should be promptly investigated, kept under surveillance and given antibiotic prophylaxis and vaccine. The immunisation history of all individuals exposed to toxigenic diphtheria should be established. Partially immunised or unimmunised individuals should complete immunisation according to the UK schedule (see above). Completely immunised individuals should receive a single reinforcing dose of a diphtheria-containing vaccine according to their age.

Contacts of a case or carrier of toxigenic diphtheria should be given a prophylactic course of erythromycin or penicillin. Contacts of cases of toxigenic *C. ulcerans* do require prophylaxis as, although it is rare, person-to-person transmission cannot be ruled out (Bonnet and Begg, 1999).



# Supplies

## Vaccines

- Pediacel (diphtheria/tetanus/5-component acellular pertussis/inactivated polio vaccine/*Haemophilus influenzae* type b (DTaP/IPV/Hib) – manufactured by Sanofi Pasteur MSD.
- Repevax (diphtheria/tetanus/5-component acellular pertussis/inactivated polio vaccine (dTaP/IPV)) – manufactured by Sanofi Pasteur MSD.
- Infanrix IPV (diphtheria/tetanus/3-component acellular pertussis/inactivated polio vaccine (DTaP/IPV)) – manufactured by GlaxoSmithKline.
- Revaxis (tetanus/diphtheria/inactivated polio vaccine (Td/IPV)) – manufactured by Sanofi Pasteur MSD.

These vaccines are supplied by Healthcare Logistics (Tel: 0870 871 1890) as part of the national childhood immunisation programme.

In Scotland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from Scottish Healthcare Supplies (Tel: 0141 282 2240).

Diphtheria antitoxin is supplied by the Butantan Institute, in 10ml vials containing 10,000IU. It is distributed in the UK by the Health Protection Agency, Centre for Infections, Immunisation Department (Tel: 020 8200 6868).

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