16

Haemophilus influenzae type b (Hib)

***H. INFLUENZAE* MENINGITIS NOTIFIABLE (EXCEPT IN SCOTLAND)**

The disease

Haemophilus influenzae can cause serious invasive disease, especially in young children. Invasive disease is usually caused by encapsulated strains of the organism. Six typeable capsular serotypes (a–f) are known to cause disease; non-typeable encapsulated strains can occasionally cause invasive disease. Before the introduction of vaccination, type b (Hib) was the prevalent strain. The proportion of typeable to non-typeable strains depends largely on the prevalence of the type b strain. Non-encapsulated strains are mainly associated with respiratory infections such as exacerbation of chronic bronchitis and otitis media.

The most common presentation of invasive Hib disease is meningitis, frequently accompanied by bacteraemia. This presentation accounts for approximately 60% of all cases (Anderson *et al.*, 1995). Fifteen per cent of cases present with epiglottitis, a potentially dangerous condition that presents with airway obstruction. Bacteraemia, without any other concomitant infection, occurs in 10% of cases. The remainder is made up of cases of septic arthritis, osteomyelitis, cellulitis, pneumonia and pericarditis. The sequelae following Hib meningitis may include deafness, seizures, and intellectual impairment. In studies conducted in Wales and Oxford, 8 to 11% had permanent neurological sequelae (Howard *et al.*, 1991; Tudor-Williams *et al.*, 1989). The case fatality rate from Hib meningitis is 4–5%.

Individuals can carry Hib bacteria in their nose and throat without showing signs of the disease. Before Hib vaccine was introduced, about four in every 100 pre-school children carried the Hib organism; after the vaccine was introduced, carriage rates fell below the level of detection (McVernon *et al.*, 2004). Hib is spread through coughing, sneezing or close contact with a carrier or an infected person.

History and epidemiology of the disease

Before the introduction of Hib immunisation, the estimated annual incidence of invasive Hib disease was 34 per 100,000 children under five years of age. One in every 600 children developed some form of invasive Hib disease before their fifth birthday (Booy *et al.*, 1994). The disease was rare in children under three months of age, but the incidence rose progressively during the first year, reaching a peak between 10 and 11 months of age. Thereafter, the incidence declined steadily to four years of age after which infection was uncommon.

Vaccines against Hib were first produced in the early 1970s and they contained purified capsular polysaccharide. These vaccines were effective in children over 18 months of age, but failed to protect younger children, in whom the risk of disease was highest. The development of conjugate Hib vaccines overcame this problem. In conjugate vaccines, the capsular polysaccharides were linked to proteins, improving the vaccine's immunogenicity, particularly in children less than one year of age. In 1992, Hib conjugate vaccine was introduced into the routine UK immunisation schedule. Hib conjugate vaccine was originally administered as a separate vaccine. In 1996, combination vaccines (DTwP/Hib) were introduced, and in 2004, Hib vaccine combined with DTaP and IPV (DTaP/IPV/Hib) became available.

The efficacy and safety of the conjugate Hib vaccines have been demonstrated in large field trials in Finland, the United States and in the UK, where efficacy ranged from 83 to 100% (Black *et al.*, 1991a; Black *et al.*, 1991b; Eskola *et al.*, 1990). Studies comparing different vaccines, using the present UK primary schedule, have shown that 90 to 99% of children developed protective levels of antibodies following three doses of vaccine (Booy *et al.*, 1994). Cases of invasive disease in fully vaccinated children (vaccine failures) have been reported from some countries, including the UK (Heath and McVernon, 2002). A small proportion of such cases have underlying conditions, such as immunoglobulin deficiency, predisposing the child to vaccine failure.

Since the introduction of Hib immunisation in the UK, disease incidence has fallen (see Figure 16.1). In 1998, only 21 cases of invasive Hib were reported in England and Wales in children under five years of age (0.65 per 100,000) compared with 803 in 1991 (20.5 per 100,000). In infants under one year of age, the highest risk age group for disease, reported cases fell by over 95% (from 300 to 7). Notifications of *H. influenzae* meningitis for the same period declined from 485 to 29. In 1998, coverage by the second birthday was 95%.

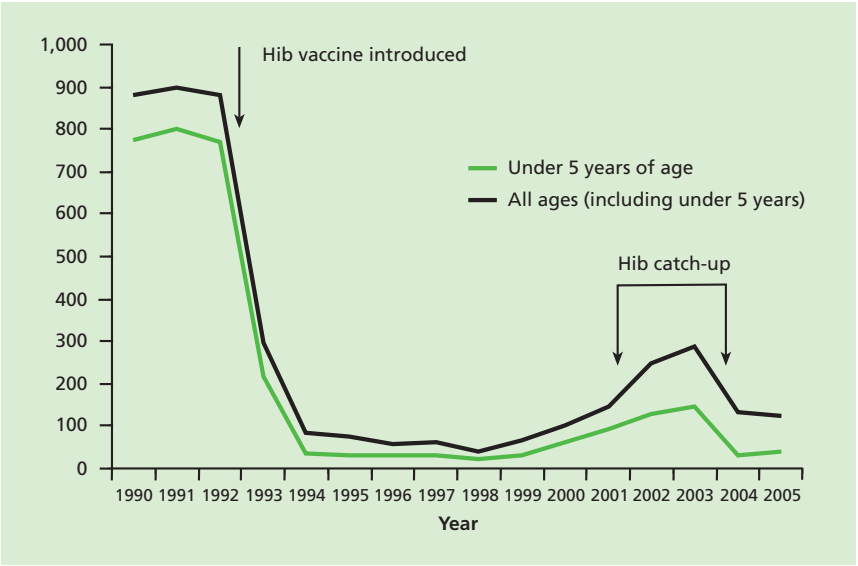

Figure 16.1 Laboratory reports of Hib disease in England and Wales (1990–2005)

From 1999, there was a small but gradual increase in the number of cases of Hib disease reported, mostly in children less than four years of age. However, this increase was most notable among children born in 2000 and 2001 (McVernon *et al*., 2003). Reasons for this increase in vaccine failures are thought to include an effect of the DTaP/Hib combination vaccine which was in use at that time and a waning of the impact of the catch-up programme when the vaccine was introduced. In this latter group, who were immunised at an older age, the efficacy was higher than in children vaccinated routinely as infants.

In 2003, a booster campaign was implemented with call-back of children aged six months to four years (Chief Medical Officer *et al*., 2004). Following the campaign, cases have begun to return to the low levels achieved previously (see Figure 16.1). In 2006, following studies that showed that protection against Hib waned during the second year of life (Trotter *et al*., 2003), a booster dose (combined with MenC as Hib/MenC) was introduced.

The Hib vaccination

Hib-containing vaccines are made from capsular polysaccharide that has been extracted from cultures of Hib bacteria. The polysaccharide is linked (conjugated) to a protein, according to the manufacturer's methodology. In the UK, Hib vaccines have been used that have been conjugated with either

CRM_{197} (a non-toxic variant of diphtheria toxin) or tetanus toxoid. The conjugation increases the immunogenicity, especially in young children, in whom the plain polysaccharide vaccines are not immunogenic.

Some DTaP/Hib combination vaccines have been shown to attenuate the Hib response in comparison with DTwP/Hib combinations (Trotter *et al*., 2003). The Hib-containing vaccine (Pediacel) chosen for primary immunisation in the UK programme has been shown not to have this problem (Miller *et al*., 2003).

The Hib vaccine is given as part of a combined product:

- diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/ *H. influenzae* type b (DTaP/IPV/Hib) vaccine, or
- Hib/MenC conjugate.

The Hib/MenC conjugate vaccine is made from capsular polysaccharides of *H. influenzae* type b and group C *Neisseria meningitidis,* which are conjugated to tetanus toxoid. The vaccine has been shown to elicit booster responses to both Hib and MenC when given in the second year of life to children who were primed in infancy with Hib and MenC conjugate vaccines.

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

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

Hib vaccines are available as part of combined products DTaP/IPV/Hib or Hib/MenC. The combined product, DTaP/IPV/Hib is supplied as a cloudy white suspension either in a single dose ampoule or pre-filled syringe. The suspension may sediment during storage and should be shaken to distribute the suspension uniformly before administration.

Hib/MenC is supplied as a vial of white powder and 0.5ml of solvent in a pre-filled syringe. The vaccine must be reconstituted by adding the entire contents of the pre-filled syringe to the vial containing the powder. After

addition of the solvent, the mixture should be shaken well until the powder is completely dissolved. After reconstitution, the vaccine should be administered promptly, or allowed to stand between +2˚C and +8˚C and used within 24 hours.

Dosage and schedule

For children under one year of age:

- First dose of 0.5ml of a Hib-containing vaccine.
- Second dose of 0.5ml, one month after the first dose.
- Third dose of 0.5ml, one month after the second dose.
- A fourth booster dose of 0.5ml of a Hib-containing vaccine should be given at the recommended interval (see below).

For children over one year of age and under ten years of age who have either not been immunised or not completed a primary course of diphtheria, tetanus, pertussis or polio, DTaP/IPV/Hib vaccination should be used. Children over one year and under ten years of age who have completed a primary course of diphtheria, tetanus, pertussis or polio should have Hib/MenC.

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.

Hib-containing vaccines can be given at the same time as other vaccines such as MMR, MenC, hepatitis B, and pneumococcal. 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 patient'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 protect individuals under ten years of age, and individuals older than this who may be at elevated risk from invasive Hib disease.

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

Primary immunisation

Infants and children under ten years of age

The primary course of Hib vaccination in infants consists of three doses of a Hib-containing product with an interval of one month between each dose. DTaP/IPV/Hib is recommended for all children from two months up to ten years of age. Although one dose of Hib vaccine is effective from one year of age, three doses of DTaP/IPV/Hib should be given to children who have either not been immunised or who have not completed a primary course, in order to be fully protected against diphtheria, tetanus, pertussis and polio. If the primary course is interrupted it should be resumed but not repeated, allowing an interval of one month between the remaining doses.

Children of one to ten years of age who have completed a primary course of diphtheria, tetanus, pertussis and polio but have not received Hib-containing vaccines, should receive a single dose of Hib/MenC vaccine.

Reinforcing immunisation

A reinforcing (booster) dose of Hib/MenC is recommended at 12 months for children who have received a complete primary course of three Hib-containing vaccine injections. The Hib/MenC vaccine can be given at the same time as the pneumococcal conjugate and MMR vaccines.

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, on immunisation schedule). A child who has not completed the primary course should have the outstanding doses at monthly intervals.

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 may not have received Hib-containing vaccines in their country of origin (www-nt.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).

Children and adults with asplenia, splenic dysfunction or complement deficiency

Children and adults with asplenia or splenic dysfunction may be at increased risk of invasive Hib infection. Children and adults with early complement deficiency (e.g. C1, 2, 3 or 4 deficiencies) may also be at increased risk of invasive Hib infection (Figueroa *et al.*, 1991).

Given the increased risk, additional vaccinations against Hib disease are advised for individuals who develop asplenia or splenic dysfunction or when complement deficiency is diagnosed depending on age and vaccination history. For the full list of immunisations for these groups, see Table 7.1 in chapter 7.

Children under two years of age

These individuals should be vaccinated according to the UK routine childhood schedule, which includes a booster of Hib/MenC and PCV given at 12 months of age. A dose of MenACWY conjugate vaccine should be given at least one month after the Hib/MenC and PCV boosters.

After the second birthday, an additional dose of Hib/MenC should be given. If the individual received their routine pneumococcal booster dose as PCV7 (before April 2010) an additional dose of PCV13 should be offered at the same time, followed by a dose of PPV two months later. If the child was routinely boosted with PCV13 (after April 2010) a dose of PPV should be given with the Hib/MenC booster.

Fully vaccinated individuals over two and under five years of age

These individuals should receive one additional dose of Hib/MenC and PCV13 (as they will have received PCV7). One month after this, they

should receive a dose of MenACWY conjugate vaccine. PPV should be given at least two months after the last dose of PCV13.

Previously unvaccinated individuals over two and under five years of age

These individuals should receive one additional dose of Hib/MenC and PCV13 (as they will have received PCV7). One month after this, they should receive a dose of MenACWY conjugate vaccine. PPV should be given at least two months after the last dose of PCV13.

Individuals over five years of age regardless of vaccination status

These individuals should receive one dose of Hib/MenC vaccine with a dose of PPV. One month after this, a dose of MenACWY conjugate vaccine should be given.

Contraindications

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

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

- a confirmed anaphylactic reaction to a previous dose of a Hib-containing vaccine, or
- a confirmed anaphylactic reaction to any 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 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 Hib-containing vaccine should continue following a history of:

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

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 their experience 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

Hib-containing vaccines may be given to pregnant women when 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 and HIV infection (regardless of CD4 count) should be given Hib-containing vaccines in accordance with the recommendations above. These individuals may not make a full antibody response. 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 (RCPCH) (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 16.2 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.

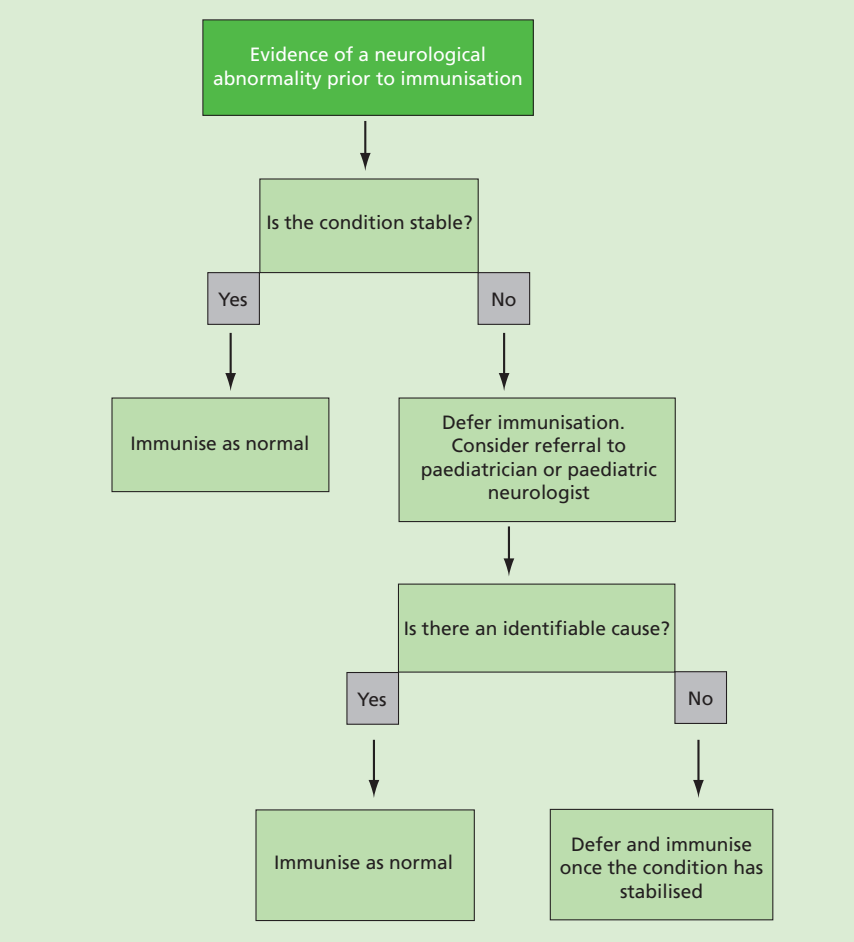

Figure 16.2 Flow chart for immunisation procedure if there is evidence of a neurological condition before immunisation

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.

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).

Neurological abnormalities following immunisation

If a child experiences encephalopathy or encephalitis within seven days of immunisation, the advice in the flow chart in Figure 16.3 should be followed. It is unlikely that these conditions will have been caused by the vaccine and should be investigated by a specialist. Immunisation should be deferred in children where no underlying cause is found and the child does not recover completely within seven days, until the condition has stabilised. 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 until the condition is stable if no underlying cause has been found and the child does not recover completely within 24 hours. 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 tetanus vaccines combined with acellular pertussis vaccines than with whole-cell pertussis vaccines, and similar to that after diphtheria (DT) vaccine (Miller, 1999; Tozzi and Olin, 1997).

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

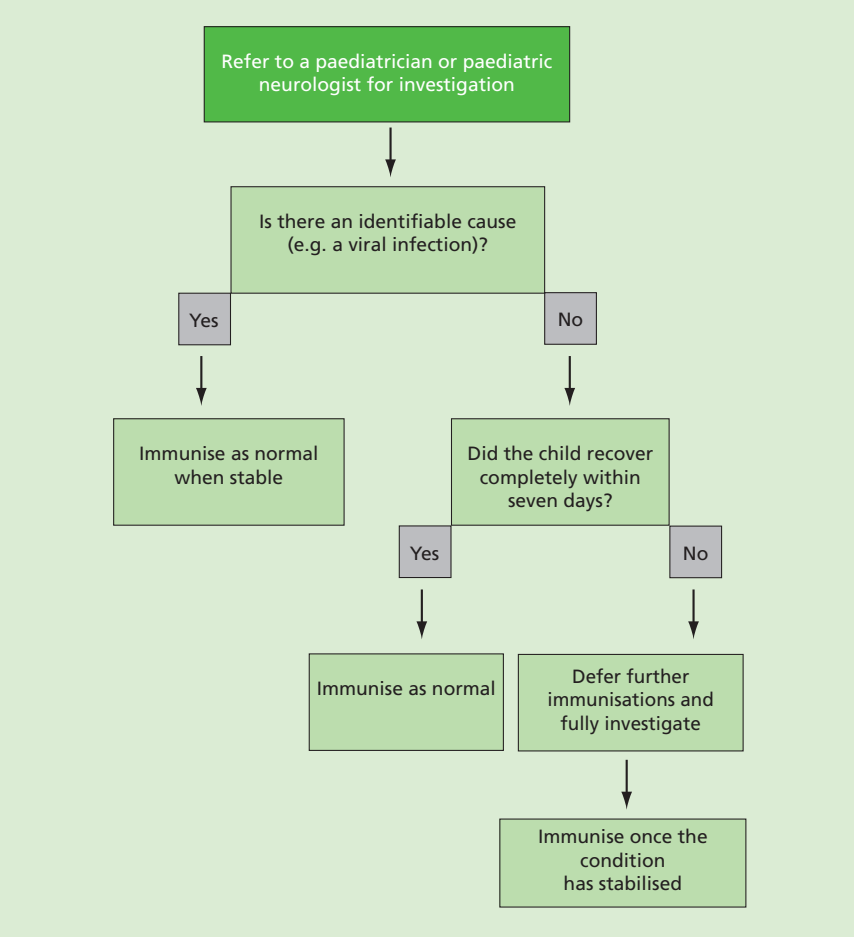

Figure 16.3 Flow chart for encephalitis or encephalopathy occurring within seven days of immunisation

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.

Hib/MenC conjugate vaccine

Mild side effects such as irritability, loss of appetite, pain, swelling, redness at the site of the injection and slightly raised temperature commonly occur.

Less commonly crying, diarrhoea, vomiting, atopic dermatitis, malaise and fever over 39.5˚C have been reported.

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 be reported through the Yellow Card scheme.

Management of cases and contacts

Unimmunised cases up to the age of ten years should be immunised according to their age-appropriate schedule after recovery from infection. Previously vaccinated cases should have their convalescent antibody levels measured, and booster vaccination may be advised. Where antibody testing is not possible, an additional dose of Hib-containing vaccine should be given after recovery from infection.

Household contacts of a case of invasive Hib disease have an increased risk of contracting the disease. Unimmunised children under ten years of age are at substantial risk. Contacts of cases should be managed following the advice of the local health protection unit, as follows:

- children who have never received any immunisations should receive three doses of DTaP/IPV/Hib vaccine if below ten years of age.
- children who have never received Hib vaccine, but who have been immunised against diphtheria, tetanus, pertussis and polio, should receive three doses of Hib/MenC vaccine if under one year, and one dose if aged between one and ten years.
- children aged between one and ten years who have received Hib vaccine in infancy, but who did not receive a booster dose of Hib containing vaccine after the age of 12 months, should receive a single dose of Hib/MenC vaccine.

Where there is any individual in the household of a case who is also at risk, the index case and all household contacts should be given rifampicin prophylaxis. Those at risk in the household include all children under ten years of age and vulnerable individuals of any age (e.g. those who are immunosuppressed or asplenic) regardless of their immunisation status. The purpose of this recommendation is to prevent transmission of Hib to vulnerable individuals within a household. Further information is available at:

www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/HaemophilusInfluenzaeTypeB/Guidance/

When a case occurs in a playgroup, nursery, crèche or school, the opportunity should be taken to identify and vaccinate any unimmunised children under ten years of age. When two or more cases of Hib disease have occurred in a playgroup, nursery, crèche or school within 120 days, chemoprophylaxis should be offered to all room contacts – teachers and children. This is a precautionary measure as there is little evidence that children in such settings are at significantly higher risk of Hib disease than the general population of the same age.

Vaccines

- Pediacel (diphtheria/tetanus/5-component acellular pertussis/inactivated polio vaccine/*H. influenzae* type b (DTaP/IPV/Hib) – manufactured by Sanofi Pasteur MSD.
- Menitorix (Hib/MenC) – manufactured by GlaxoSmithKline.

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).

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