

3.4 HAEMOPHILUS INFLUENZAE TYPE B (HIB)

Bacteriology

Haemophilus influenzae is a Gram-negative coccobacillus that is a normal part of upper respiratory tract flora. Strains isolated from respiratory tract specimens such as sputum and middle ear or sinus fluid usually do not have a capsule, and are known as non-typable (NT). Six capsular types (a to f) have been described and, before the introduction of vaccination against *Haemophilus influenzae* type b (Hib), almost all *H. influenzae* isolates from sterile sites (blood, cerebrospinal fluid, joint or pleural fluid) were of the b capsular type.

Before Hib immunisation, invasive disease caused by Hib rarely occurred after the age of 5 years. This was because the prevalence of antibody to Hib progressively increased from the age of 2 years, thought to be related to exposure to Hib (or cross-reacting organisms) colonising the nasopharynx or other sites. Children <2 years of age are usually unable to mount an antibody response to the type b capsular polysaccharide, even after invasive disease.¹

Clinical features

Clinical categories of invasive disease caused by Hib include meningitis, epiglottitis and a range of other infections such as septic arthritis, cellulitis and pneumonia. Hib is rarely isolated from the blood without a focal infection such as the above being evident or developing subsequently. The classical clinical signs of meningitis – neck stiffness and photophobia – are often not detected in infants, who present with drowsiness, poor feeding and high fever. Epiglottitis (inflammation of the epiglottis) presents with respiratory obstruction, associated with soft stridor and often drooling in a pale, febrile, anxious child who remains upright to maximise his or her airway. Meningitis and epiglottitis are almost invariably fatal without appropriate treatment. There are no specific clinical features of any of the focal infections due to Hib which enable them to be differentiated from those due to other organisms. However, before the introduction of Hib vaccines, epiglottitis was due to Hib in over 95% of cases.²

Epidemiology

(i) Before Hib vaccination

Before the introduction of routine Hib vaccination in 1993, there were at least 500 cases of Hib disease in Australian children <6 years of age every year, and a total of 10 to 15 deaths.³ Hib meningitis accounted for approximately 60% of all invasive Hib disease, most cases occurring in children <18 months of age. The case fatality rate for Hib meningitis was approximately 5%, and up to 40% of the survivors had neurological sequelae such as deafness and intellectual impairment.⁴ Hib epiglottitis was a more common disease presentation than

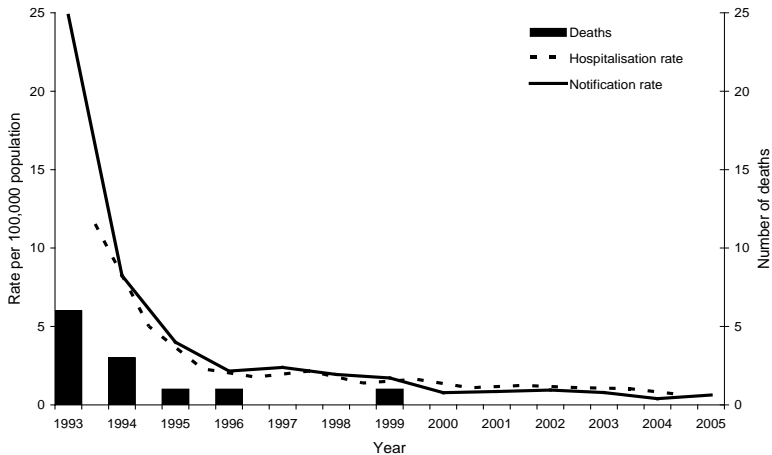
in many other countries,⁵ and usually occurred in children >18 months of age. Other manifestations such as cellulitis, septic arthritis and pneumonia occurred at a similar age to meningitis.⁶

The incidence of Hib disease in Aboriginal and Torres Strait Islander children, especially those in remote and rural areas, was considerably higher than in non-Indigenous children.⁷ Most importantly, the onset of Hib disease in this population was at a much younger age, manifesting mostly as meningitis, with epiglottitis being rare. Rates of death and long-term morbidity following Hib meningitis were similar to those observed in non-Indigenous children.⁷

(ii) After the introduction of Hib vaccination

Since Hib vaccines were included in the routine vaccination schedule in 1993, there has been a reduction of >90% in notified cases of Hib disease from 502 in 1992 to an average of 30 cases per year between 1999 and 2002, with approximately 15 cases per year currently reported in Australia (see Figure 3.4.1).⁸ This reduction has been particularly marked in Indigenous children.⁹ Similar impressive reductions in Hib disease have been seen in other countries with routine childhood vaccination.^{5,10} Since Hib disease has become relatively rare, cases of epiglottitis can no longer be assumed to be due to *H. influenzae* type b and, moreover, even when *H. influenzae* is isolated from a normally sterile site, it may not be type b. Thus, laboratory confirmation of *H. influenzae* infection and serotype should always be sought before vaccination failure is assumed.^{11,12}

Figure 3.4.1: *Haemophilus influenzae* type b (Hib) notifications, presumed Hib hospitalisations and deaths* of children aged 0 to 4 years from Hib, Australia 1993 to 2005†§



* Hospitalisations and deaths include those for *Haemophilus meningitidis* for the period up to 30 June 2005 (hospitalisations) and 31 December 2004 (deaths).

† Notifications where the month of diagnosis was between July 1993 and December 2005; hospitalisations where the month of admission was between 1 July 1993 and 30 June 2005; deaths where the date of death was recorded between January 1993 and December 2004.

Vaccines

The first generation Hib vaccines, consisting of purified polysaccharide (PRP) from the Hib capsule, were not effective in children <18 months of age. A review of the efficacy data for the second generation Hib vaccines, which consist of PRP chemically linked ('conjugated') to a variety of carrier proteins, found 3 of the 4 Hib vaccines to be immunogenic against invasive Hib disease, PRP-OMP, PRP-T and HbOC.¹³ The fourth vaccine, PRP-D, was not found to be highly protective in high-risk populations, such as Indigenous children.¹³

There are 2 main groups of carrier proteins associated with a different temporal pattern of PRP antibody response. The vaccine using the outer membrane protein of *Neisseria meningitidis* as a carrier protein (PRP-OMP) (COMVAX, Liquid PedvaxHIB) gives protective PRP antibody responses after the first dose, and requires only 2 doses to complete the primary course. For this reason, its main application worldwide has been in populations with a high incidence of early onset disease.⁵ Vaccines using other protein carriers such as tetanus (PRP-T) (Hiberix, Infanrix hexa) and diphtheria (HbOC) toxoids do not achieve protective PRP antibody levels until at least a second dose has been given, and

require 3 doses to complete primary immunisation. No or minimal immunologic interference has been observed when children are vaccinated with 7vPCV and Infanrix hexa at the same immunisation visit.^{14,15}

Many Hib combination vaccines containing acellular pertussis are known to produce lower Hib antibody responses than similar formulations containing whole-cell pertussis.¹⁶ When administered according to the United Kingdom's schedule as 3 primary doses at 2, 3 and 4 months of age without a booster, their use has been associated with an increased risk of vaccine failure.¹⁷ In other European countries that routinely give a fourth dose around the time of the 1st birthday, as is included in the Australian schedule, no loss of effectiveness has been observed.^{18,19}

- **Liquid PedvaxHIB** – CSL Biotherapies/Merck & Co Inc (PRP-OMP). Each 0.5 mL monodose vial contains 7.5 µg PRP conjugated to 125 µg meningococcal protein; liquid formulation with 35 µg borax and 225 µg aluminium hydroxide.
- **Hiberix** – GlaxoSmithKline (PRP-T). Each 0.5 mL monodose lyophilised vaccine contains 10 µg PRP conjugated to 30 µg tetanus toxoid (with a lactose stabiliser) for reconstitution with 0.9% saline.

Combination vaccines that include Hib

- **COMVAX** – CSL Biotherapies/Merck & Co Inc (Hib (PRP-OMP)-hepatitis B). Each 0.5 mL monodose vial contains 7.5 µg PRP conjugated to 125 µg meningococcal protein, 5 µg hepatitis B surface antigen; 225 µg aluminium hydroxide; 35 µg borax. May contain yeast proteins.
- **Infanrix hexa** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine-*Haemophilus influenzae* type b (Hib)). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. The vaccine *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. May also contain yeast proteins.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.²⁰ Store conjugate Hib vaccines at +2°C to +8°C. Do not freeze.

Dosage and administration

The dose of Hib vaccine is 0.5 mL to be given by IM injection. Conjugate Hib vaccines may be administered in separate sites on the same day as any of the other childhood vaccines such as the 7-valent pneumococcal conjugate (7vPCV), meningococcal serogroup C conjugate (MenCCV), hepatitis B, DTPa-containing and monovalent IPV (or IPV-containing) vaccines.

Recommendations

(i) Hib vaccine is recommended for all infants from 2 months of age

Immunisation using PRP-OMP (COMVAX or Liquid PedvaxHIB) requires 2 primary doses at 2 and 4 months, followed by a booster at 12 months of age. If PRP-T (Infanrix hexa or Hiberix) is used, 3 primary doses at 2, 4 and 6 months are needed, with a booster at 12 months of age.

(ii) Indigenous children living in the Northern Territory, Queensland, South Australia and Western Australia

Many Indigenous populations experienced high Hib attack rates associated with early peak disease onset before the introduction of Hib immunisation. While vaccination has reduced the overall incidence of invasive Hib infection in these vulnerable groups, increased disease risk during the first year of life remains. It is therefore important that Aboriginal and Torres Strait Islander children in jurisdictions (the Northern Territory, Queensland, South Australia and Western Australia) where such different patterns of Hib disease remain evident continue to receive PRP-OMP, because of the early antibody response seen with this vaccine.⁷ In Alaskan natives, who experienced similar pre-vaccination attack rate profiles, re-emergence of Hib disease was observed when the Hib vaccine in use was changed from PRP-OMP to HbOC.²¹

(iii) Non-Indigenous children and Indigenous children living in Australian Capital Territory, New South Wales, Tasmania and Victoria

Any licensed Hib vaccine may be used in these children as the period of significant risk does not begin until after 6 months of age. Although there are limited data on the epidemiology of Hib disease before vaccination in Indigenous children in south-eastern Australia, available data since vaccination commenced in 1993 suggest that the epidemiology in these children does not differ substantially from that in non-Indigenous children living in these areas (NCIRS data, unpublished).

(iv) Interchangeability of Hib vaccines

It is recommended that the same conjugate vaccine be used for all doses. However, if necessary, after the first dose, any Hib vaccine may be used to complete the primary course.²² For primary vaccination, only 2 doses of PRP-OMP are required, but if any other Hib vaccine is given, a total of 3 doses is required to complete the primary course.²³ This means that if the previous Hib vaccine type is unknown for any doses, or the same vaccine type is unavailable, the primary course can be completed with a total of 3 doses of any combination of registered Hib vaccines. For booster doses and in children >15 months of age, regardless of previous Hib vaccinations, a single dose of any registered Hib vaccine is sufficient for protection. Details of catch-up vaccination schedules are given in Section 1.3.5, *Catch-up*.

(v) Vaccine failures

Children who have developed confirmed Hib disease after 2 or more doses of PRP-OMP or 3 or more doses of PRP-T may warrant immunological investigation. Consultation with an immunologist with paediatric expertise is recommended.

(vi) Preterm babies

Preterm babies can be immunised at the normal age, without correction for prematurity²⁴ (see Section 2.3.2, *Vaccination of women planning pregnancy, pregnant or breastfeeding women, and preterm infants*). Extremely preterm babies (<28 weeks' gestation or <1500 g birth weight) who are vaccinated with PRP-OMP should be given an extra dose at 6 months of age, resulting in a 4-dose schedule at 2, 4, 6 and 12 months of age.²⁵ When other Hib vaccines, including Infanrix hexa, are used, no change in the usual schedule is required. Preterm babies have been shown to produce good antibody responses to all the antigens in Infanrix hexa following administration at 2, 4 and 6 months of age, although the responses to hepatitis B and Hib are not quite as high as in term babies.

(vii) Splenectomy

Hib is an uncommon cause of post-splenectomy sepsis in adults and children. Children >2 years of age who have received all scheduled doses of Hib vaccine do not require a booster dose after splenectomy. A single dose of Hib vaccine is recommended for other splenectomised individuals who were not vaccinated in infancy or are incompletely vaccinated. The vaccine should be given 2 weeks before a planned splenectomy. Subsequent booster doses of Hib vaccine are not required.²⁶ For other recommendations for asplenic or splenectomised individuals, see Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*.

(viii) Allogeneic and autologous haematopoietic stem cell transplant (HSCT) recipients

These patients should also be considered for Hib vaccination post transplant. The Hib conjugate vaccine should be administered to recipients at 12, 14, and 24 months after HSCT. See Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*.

Contraindications

The only contraindications to any of the Hib vaccines are:

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

Adverse events

Swelling and redness at the injection site after the first dose are common and have been reported in up to 5% of vaccinated children. Fever in up to 2% (common) has also been reported. These adverse events usually appear within 3 to 4 hours and resolve completely within 24 hours. The incidence of these adverse events declines with subsequent doses, so it is recommended that the course of vaccination be completed regardless.

The public health management of contacts of a child with invasive Hib disease

Healthcare workers should be guided by public health authorities in the public health management of cases of invasive Hib disease.

Household

As the incidence of invasive Hib disease is now very low, rifampicin chemoprophylaxis is no longer routinely indicated *unless* the household contains either:

- an infant <7 months of age (regardless of vaccination status), or
- a child aged 7 months to 5 years who is inadequately vaccinated according to the Hib schedule.

In this case, *everybody in the household* should receive rifampicin prophylaxis after a case of invasive Hib disease in any household member, with the exception of pregnant women for whom ceftriaxone may be used. The recommended dose of rifampicin is 20 mg/kg as a single daily dose (maximum daily dose 600 mg) for 4 days. Neonates (<1 month of age) should receive 10 mg/kg daily for 4 days.

Childcare facilities

Similarly, if the index case attends a child day-care facility for more than 18 hours a week, rifampicin should be given to all children and staff who were in the same room group (as the case) in the 7 days preceding the case's onset, provided that at least one of these close contacts is a child <24 months of age who is inadequately vaccinated. Although there may have been some intermingling of all the children at the facility at the beginning and end of the day, this is usually of a short duration only and not enough to justify extending the use of rifampicin. Rifampicin prophylaxis is of no value more than 30 days after initial contact with a case.

Use in pregnancy

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

Variations from product information

The product information for Hib vaccines recommends the vaccine for use in children aged 2 months to 5 years. NHMRC recommends administration of Hib vaccine to older people with asplenia or following either allogeneic or autologous haematopoietic stem cell transplantation.

With the exception of PRP-OMP, the product information for Hib vaccines recommends use as a booster at 18 months, but the NHMRC regards a booster at 12 months of age as likely to result in an equivalent immune response.

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

References

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