4.3 HAEMOPHILUS INFLUENZAE TYPE B

4.3.1 Bacteriology

*Haemophilus influenzae* is a Gram-negative coccobacillus that is a normal part of upper respiratory tract flora. It can be isolated in two forms: capsular and non-capsular. 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-typeable *Haemophilus influenzae* (NTHi). 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.

4.3.2 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. The case-fatality rate for Hib meningitis in developed countries is at least 3% even with treatment, and 15 to 30% of survivors have permanent neurological sequelae. There are no specific clinical features of any of the focal infections due to Hib that 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. Non-typeable *Haemophilus influenzae* strains may occasionally cause invasive disease, but are a common cause of otitis media in children and bronchitis in adults. Hib vaccines are not effective in preventing NTHi infections.

4.3.3 Epidemiology

Since Hib vaccines were included in the routine vaccination schedule in 1993, there has been a reduction of more than 95% in notified cases of Hib disease. In 1992 alone, 549 Hib cases were reported; in contrast, during the 2 years from January 2006 to December 2007, a total of 39 Hib infections were notified in Australia, giving an average annual notification rate of 0.09 per 100 000 population. The reduction in the incidence of Hib disease following routine vaccination has been particularly marked in Indigenous children, although absolute rates remain substantially higher than those in the non-Indigenous population. Similar impressive reductions in Hib disease have been seen in other countries with routine childhood vaccination. 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.

4.3.4 Vaccines

Four types of conjugate Hib vaccines have been developed, each containing the Hib capsular polysaccharide polyribosylribitol phosphate (PRP) conjugated to a different carrier protein. Of these, PRP-OMP (conjugated to the outer membrane protein of *Neisseria meningitidis*), PRP-T (conjugated to tetanus toxoid) and HbOC (conjugated to a mutant diphtheria toxoid) elicit antibody responses associated with protection of children against Hib. The fourth vaccine type, PRP-D (conjugated to diphtheria toxoid), was less immunogenic and found to be poorly protective in high-risk populations, such as Indigenous children. PRP-T has subsequently been included in a number of combination vaccines including DTPa-hepB-IPV-Hib and Hib-MenCCV. Hib-MenCCV (which contains meningococcal serogroup C and *Haemophilus influenzae* type b antigens) has been used under the NIP since July 2013. The Hib PRP-T component in Hib-MenCCV has similar immunogenicity and safety to monovalent PRP-T Hib vaccine. PRP-OMP vaccines have not been used routinely in Australia since 2009 and were discontinued in 2017.

In Australia, the differing epidemiology of invasive Hib disease by ethnicity and region has determined the recommendations for Hib vaccine choice (refer to 3.1 Vaccination for Aboriginal and Torres Strait Islander people). There have been four distinct eras of implementation of the Hib vaccination program for Australian children, which are described in detail elsewhere.

Some Hib combination vaccines containing acelluar pertussis are known to produce lower Hib antibody responses than similar formulations containing whole-cell pertussis. 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. In other European countries that routinely give a 4th dose around the time of the 1st birthday, as Australia does, no loss of effectiveness has been observed.
Monovalent Hib vaccines

- **Act-HIB** – Sanofi-Aventis Australia Pty Ltd (PRP-T). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains 10 µg Hib capsular polysaccharide (polyribosyl-ribitol-phosphate [PRP]) conjugated to 18–30 µg tetanus protein.

- **Hiberix** – GlaxoSmithKline Australia Pty Ltd (PRP-T). Lyophilised pellet in a monodose vial with separate diluent. Each 0.5 mL reconstituted dose contains 10 µg Hib capsular polysaccharide (PRP) conjugated to 30 µg tetanus toxoid; lactose.

Combination vaccines that contain Hib

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

- **Infanrix hexa** – GlaxoSmithKline Australia Pty Ltd (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b [PRP-T]). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polysorbate 20, polymyxin and neomycin; *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. May contain yeast proteins.

- **Menitorix** – GlaxoSmithKline Australia Pty Ltd (Hib-MenCCV; *Haemophilus influenzae* type b [PRP-T]-meningococcal serogroup C–tetanus toxoid conjugate). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains 5 µg Hib capsular polysaccharide (PRP) conjugated to 12.5 µg tetanus toxoid, and 5 µg *Neisseria meningitidis* serogroup C polysaccharide conjugated to 5 µg tetanus toxoid; traces of treptomamol and sucrose.

4.3.5 Transport, storage and handling

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

Act-HIB *must be reconstituted* by adding the entire contents of the diluent syringe to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine must be used immediately.

Hiberix *must be reconstituted* by adding the entire contents of the diluent container to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 24 hours.

Infanrix hexa *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at room temperature for not more than 8 hours.

Menitorix *must be reconstituted* by adding the entire contents of the diluent syringe to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 24 hours.

4.3.6 Dosage and administration

The dose of all Hib-containing vaccines is 0.5 mL to be given by IM injection.

Co-administration with other vaccines

All Hib-containing vaccines may be administered in separate sites on the same day as any of the other childhood vaccines, such as pneumococcal conjugate, hepatitis B, DTPa-containing, inactivated poliomyelitis (IPV or IPV-containing) and monovalent meningococcal C (MenCCV) vaccines. General catch-up vaccination principles outlined in 2.1.5 *Catch-up* should be followed when planning catch-up schedules for Hib that require the use of Hib-MenCCV.
No or minimal immunologic interference has been observed when children are vaccinated with pneumococcal conjugate vaccines (7vPCV – Prevenar; 13vPCV – Prevenar 13; or 10vPCV – Synflorix) and PRP-T-containing hexavalent vaccine (Infanrix hexa) at the same immunisation visit.27–30

**Interchangeability of Hib vaccines**

Where possible, the same brand of Hib-containing vaccine should be used for all primary doses. If different Hib-containing vaccines (i.e. PRP-OMP and PRP-T vaccines) are used in the primary series, for example, in a child born overseas, then 3 doses (of any Hib-containing vaccine) are required at 2, 4 and 6 months of age, with a booster of a Hib-containing vaccine at 12 months of age. For booster doses and in children >15 months of age, regardless of previous Hib vaccinations, a single dose of any Hib-containing vaccine is sufficient for protection.

**4.3.7 Recommendations**

**Infants**

A Hib-containing vaccine is recommended in a 3-dose primary schedule for infants at 2, 4 and 6 months of age, followed by a booster dose at 12 months of age (refer to ‘Booster doses’ below).

The 1st dose of a Hib-containing vaccine can be given as early as 6 weeks of age. If the 1st dose is given at 6 weeks of age, the next scheduled doses should still be given at 4 months and 6 months of age.

**Booster doses**

A single booster dose of Hib-containing vaccine is recommended at 12 months of age (refer to ‘Infants’ above). This can be provided as either the monovalent Hib vaccine or the combination vaccine Hib-MenCCV (refer to 4.10 *Meningococcal disease*).

Children aged >15 months and up to 59 months of age at presentation who have not received a primary course of a Hib or Hib-containing vaccine will only require 1 dose of vaccine as catch-up, irrespective of the number of previous doses administered. There should be a minimum 2-month interval between their last dose and the catch-up dose. Catch-up for Hib vaccination for children up to 59 months of age is outlined in Table 2.1.8 *Catch-up schedule for Hib vaccination for children <5 years of age* in 2.1.5 *Catch-up*.

**Preterm infants**

Preterm infants can be immunised according to their chronological age, without correction for prematurity (refer to 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*). For PRP-T-containing Hib vaccines, including Infanrix hexa, no change in the usual schedule is required. Preterm infants 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 full-term infants.31

If a PRP-OMP-containing Hib vaccine is used for the primary doses in an extremely preterm and/or low-birth-weight baby (<28 weeks gestation or <1500 g birth weight), an additional dose should be given at 6 months of age; that is, doses should be given at 2, 4, 6 and 12 months of age.

**Persons with functional or anatomical asplenia**

Hib is an uncommon cause of post-splenectomy sepsis in adults and children. A single dose of Hib vaccine is recommended for persons with functional or anatomical asplenia who were not fully vaccinated in early childhood according to the recommendations above and Table 2.1.8 *Catch-up schedule for Hib vaccination for children <5 years of age*. If vaccination is required, the dose should, where possible, be given 2 weeks before a planned splenectomy or at approximately 1 week following an emergency splenectomy. Subsequent booster doses of Hib vaccine are not required.32 For all recommendations for persons with functional or anatomical asplenia, refer to 3.3.3 *Vaccination of immunocompromised persons*, Table 3.3.5 *Recommendations for vaccination in persons with functional or anatomical asplenia*.

**Allogeneic and autologous haematopoietic stem cell transplant recipients**

Allogeneic and autologous haematopoietic stem cell transplant (HSCT) recipients should also be given Hib vaccine post transplant. Three doses of Hib conjugate vaccine should be administered to HSCT recipients at 6, 8 and 12 months after transplant. Refer to 3.3.3 *Vaccination of immunocompromised persons*, Table 3.3.3 *Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history*.

**4.3.8 Pregnancy and breastfeeding**

Hib vaccine is not routinely recommended for pregnant or breastfeeding women. However, for women who have functional or anatomical asplenia refer to ‘Persons with functional or anatomical asplenia’ above.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.
4.3.9 Contraindications
The only absolute contraindications to Hib-containing vaccines are:
- anaphylaxis following a previous dose of any Hib-containing vaccine
- anaphylaxis following any vaccine component.

4.3.10 Adverse events
Swelling and redness at the injection site after the 1st dose are common and have been reported in up to 5% of vaccinated children. Fever in up to 2% has also been reported. These adverse events usually appear within 3 to 4 hours of vaccination 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.

4.3.11 Public health management of invasive Hib disease
_Haemophilus influenzae_ type b is a notifiable disease in all states and territories in Australia.

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

4.3.12 Variations from product information
The product information for Infanrix hexa states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks and as a booster dose for children 18 months of age if boosting is required for all antigens. The ATAGI recommends that this vaccine may also be used for catch-up of the primary schedule in children <10 years of age.

The product information for Infanrix hexa states that this vaccine is contraindicated in children with encephalopathy of unknown aetiology or with neurologic complications occurring within 7 days following a vaccine dose. The ATAGI recommends instead that the only contraindication is a history of anaphylaxis to a previous dose or to any of the vaccine components.

The product information for Act-HIB and Hiberix states that these vaccines are indicated for use in children aged 2 months to 5 years. The ATAGI also recommends administration of Hib vaccine to older people with asplenia or following either allogeneic or autologous haematopoietic stem cell transplantation.

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


Haemophilus influenzae type b when given concomitantly with 13-valent pneumococcal conjugate vaccine. 


32. Davies JM, Barnes R, Milligan D. Update of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. 