

Haemophilus influenzae type b

HAEMOPHILUS INFLUENZAE TYPE B (HIB) VACCINES FOR AUSTRALIAN CHILDREN: INFORMATION FOR IMMUNISATION PROVIDERS

Disease and epidemiology

- *Haemophilus influenzae* type b (Hib) is a bacterium that causes a range of clinical syndromes such as meningitis, pneumonia and epiglottitis, particularly among young children.
- Introduction of Hib conjugate vaccines into routine vaccination programs has led to a dramatic decline in the incidence of Hib disease in many regions of the world.
- In Australia, Hib conjugate vaccines were first introduced into the routine vaccination schedule in 1993, leading to a more than 95% reduction in the reported incidence of Hib disease.

Who should be vaccinated

- Hib vaccination is recommended for all infants from 2 months of age and also for those persons with special vaccination requirements, such as splenectomised patients and haematopoietic stem cell transplant recipients.
- Hib vaccination of infants using PRP-OMP requires 2 primary doses at 2 and 4 months of age and a booster at 12 months of age. Schedules using PRP-T require 3 primary doses at 2, 4 and 6 months of age and a booster at 12 months of age. For those persons with medical risk conditions, a single dose of either Hib vaccine is recommended.

Vaccines

- There are two types of Hib conjugate vaccines currently used in the National Immunisation Program in Australia – PRP-OMP and PRP-T. Both vaccines contain the capsular polysaccharide of Hib, polyribosyl-ribitol phosphate (PRP), linked to a carrier protein.
- PRP-OMP vaccines (e.g. Liquid PedvaxHIB) have the outer membrane protein of *Neisseria meningitidis* as the carrier protein. PRP-T vaccines (e.g. Infanrix hexa, Hiberix) have tetanus toxoid as the carrier protein. The combined PRP-OMP Hib and hepatitis B vaccine (COMVAX) is currently unavailable.

The disease

Causative agent

Haemophilus influenzae is a bacterium that exists in two forms: capsular and non-capsular. Capsular (typable) forms have a polysaccharide covering that is responsible for the organism's virulence and stimulation of immunity. Six distinct capsular serotypes have been described; they are designated types 'a' through 'f'. Of these, type 'b' is

almost always responsible for serious disease in children, such as meningitis, pneumonia and septicaemia (i.e. invasive Hib disease). Non-capsular (non-typable) forms of *Haemophilus influenzae* mostly colonise the upper respiratory tract without causing illness. However, non-typable *Haemophilus influenzae* (NTHi) can also cause middle ear infection (otitis media) in young children.

Haemophilus influenzae vaccines provide protection specifically against infection by the 'b' capsular type (Hib).¹⁻³

Clinical features

There is a range of clinical syndromes caused by Hib. The most common manifestation of Hib disease is meningitis (52%) followed by pneumonia (12%) and epiglottitis (10%).⁴ Most cases of Hib-related mortality and morbidity occur due to meningitis and pneumonia. Hib can also infect other organ systems and cause septic arthritis, pericarditis, osteomyelitis, bacteraemia or septicæmia, and cellulitis. Many other organisms can also cause these infections and there are no specific signs that indicate infection by Hib.

The classic clinical features of meningitis are fever, neck stiffness and photophobia. However, young infants with meningitis may present with vague and non-specific symptoms such as lethargy, poor feeding and irritability. Even with appropriate antibiotic treatment, Hib meningitis can be fatal. Long-term complications, such as mental retardation, cerebral palsy, hearing loss and seizure disorders, are often reported in children with Hib meningitis following the acute illness.

Epiglottitis is the inflammation of the epiglottis and the surrounding structures. Patients with epiglottitis present with soft stridor, high fever, dysphagia and drooling. If appropriate treatment, including antibiotic therapy and airway management, is not instituted, the swollen epiglottis can rapidly cause respiratory obstruction leading to death. Hib was responsible for over 95% of cases of epiglottitis in the pre-vaccination era.

Transmission

The only reservoir of Hib is humans and the organism is mostly carried as a commensal (present without causing symptoms) in the nasopharynx of healthy individuals. Many children will come into contact with Hib at some time in the first 2 years of life, mostly by being around asymptomatic children or adults who have the organism (carriers). Hib enters the body through the upper respiratory tract via droplets, after direct contact with either asymptomatic carriers or patients with Hib disease. When the organism enters the bloodstream or the lungs it causes serious disease. The incubation period of the disease is short, around 2–4 days.

Immunity to Hib

Age-dependent susceptibility is an important feature of Hib disease. Most newborns initially have passive protection from Hib disease due to antibodies transferred from their mother. When maternal antibody levels decline

in the first few months of life, children become susceptible to Hib infection until they acquire their own immunity. As a result, peak Hib disease attack rates occur at 6–7 months of age. Children start to progressively acquire immunity through natural exposure to Hib from about 2 years of age. Older children have adequately mature immune systems and develop immunity to Hib infection when nasopharyngeal colonisation with Hib or similar (cross-reacting) organisms occurs. Due to naturally acquired immunity, Hib disease was not common beyond 5 years of age even prior to the introduction of effective Hib vaccines. Hib vaccination programs mainly target infants and children up to 5 years of age, the group at highest risk of Hib disease.

Epidemiology

Hib is predominantly a childhood disease with over 80% of cases worldwide occurring in children aged <5 years. Before the commencement of vaccination, Hib was one of the commonest bacterial causes of pneumonia and meningitis in children aged between 4 and 18 months, with a high case fatality rate the world over.^{4,5}

Hib was previously the commonest cause of bacterial meningitis in Australian children. Aboriginal and Torres Strait Islander children, especially in remote and rural areas, had a much higher incidence of Hib infection and presented at a younger age than non-Indigenous children.^{6,7} Hib epiglottitis was particularly rare among Indigenous children. A similar pattern is described among other indigenous populations, such as American Indians and Alaskan Natives in the USA and Maori and Pacific children in New Zealand.^{8,9} In the pre-vaccination era, Indigenous Australian children in the Northern Territory had one of the highest documented incidence rates of invasive Hib disease in the world.^{10,11}

Introduction of Hib vaccine led to a remarkable decrease in the incidence of Hib disease in Australia and other countries with vaccine programs.⁴ Hib vaccine was first added to the National Immunisation Program in Australia in 1993.¹² The sharp decline in Hib disease incidence since then is seen both among the Indigenous and non-Indigenous populations. In the pre-vaccination era, there were at least 500 cases of Hib disease and 10–15 deaths annually among Australian children aged <6 years. At present, the number of cases reported in Australia for all ages is around 20 per year, a reduction of over 95% from the pre-vaccination period.

Who should be vaccinated

National Immunisation Program (NIP)

Routine Hib vaccination is recommended for all infants from 2 months of age.¹³

Others recommended for vaccination

Hib vaccination is also recommended for persons who have undergone splenectomy and recipients of haematopoietic stem cell transplants (HSCT).¹³

Vaccines

Vaccine types

Protection against Hib disease is provided by antibodies produced against polyribosyl-ribitol phosphate (PRP), the polysaccharide capsule of *Haemophilus influenzae* type b. The first generation of Hib vaccines consisted of purified PRP.¹⁴ These purified PRP vaccines failed to induce an adequate immune response in children younger than 18 months, the age group most susceptible to Hib disease. Combining the PRP with a 'carrier' protein (conjugation) enhanced the immunogenicity of the vaccine and generated a protective response to Hib disease in young infants as well.¹⁵

Four different carrier proteins have been used to develop conjugated Hib vaccines. They are all conjugated to PRP: diphtheria toxoid (PRP-D), tetanus toxoid (PRP-T), a mutant diphtheria toxin (HbOC), and an outer membrane protein of meningococcus (PRP-OMP).⁴ PRP-OMP gives a protective antibody response after the 1st dose and requires only 2 doses to complete the primary course. Therefore, PRP-OMP is the best to be used in populations with a high incidence of early onset disease.¹⁶⁻¹⁸ In comparison, PRP-T (and HbOC) conjugates achieve protective antibody levels only after the administration of the 2nd dose of the vaccine.^{19,20}

The Hib-containing vaccines that are currently used in the Australian National Immunisation Program are Infanrix hexa, Hiberix, Liquid PedvaxHIB and COMVAX.

Infanrix hexa (DTPa-HepB-IPV-Hib) contains Hib PRP-T in combination with diphtheria and tetanus toxoids and acellular pertussis (DTPa), hepatitis B (HepB), and inactivated poliomyelitis (IPV) antigens.

Hiberix contains monovalent Hib PRP-T.

Liquid PedvaxHIB is a monovalent Hib vaccine containing PRP-OMP.

COMVAX contains PRP-OMP in combination with the hepatitis B antigen. This vaccine is currently unavailable.

Administration

Routine

Hib vaccine is recommended in Australia for all infants from 2 months of age in either a 3- or 4-dose schedule. Hib vaccines are given by intramuscular injection. The schedule for PRP-OMP Hib conjugate vaccines (COMVAX or Liquid PedvaxHIB) is 2 primary doses at 2 and 4 months of age and a booster dose at 12 months of age. The schedule for PRP-T vaccines (Infanrix hexa or Hiberix) is 3 primary doses at 2, 4 and 6 months of age and a booster at 12 months of age.

PRP-OMP conjugate Hib vaccine that elicited a protective immune response following a single dose at 2 months of age was recommended for all Indigenous children from the inception of the national program. PRP-OMP Hib vaccine is recommended for Indigenous children living in the Northern Territory, Queensland, South Australia and Western Australia. As a response to a disruption to the supply of PRP-OMP that began in December 2007, it was recommended that administration of PRP-OMP be limited to all children in the Northern Territory and those children who have already received primary dose(s) of PRP-OMP to complete their course. Both Indigenous and non-Indigenous children living in other jurisdictions were recommended PRP-T Hib-containing vaccines (Infanrix hexa or Hiberix). However, due to the continued shortage of PRP-OMP, as of 1 October 2009, all children in all jurisdictions, including the Northern Territory, now receive a primary course of 3 doses of PRP-T Hib-containing Infanrix hexa and a booster dose of monovalent PRP-T Hib vaccine (Hiberix).

If extremely pre-term infants (<28 weeks gestation or <1500 g birth weight) receive PRP-OMP-containing Hib vaccines, they require an extra dose at 6 months of age, resulting in a 4-dose schedule at 2, 4 and 6 months of age with a booster at 12 months of age.

High-risk patients

Hib is not a common cause of sepsis among patients who have undergone a splenectomy. Children >2 years old who have completed their Hib vaccination do not require a further booster dose after splenectomy. For those splenectomised individuals who have not been vaccinated in infancy or are incompletely vaccinated, a single dose of Hib vaccine is recommended. In these patients, Hib vaccine should preferably be administered 2 weeks prior to the planned splenectomy. If not given then, Hib vaccine should be given 2 weeks post splenectomy. No further booster doses of Hib vaccine are required in these patients.

Allogenic and autologous HSCT recipients should receive 3 doses of Hib conjugate vaccine at 12, 14 and 24 months post transplant. All solid organ transplantation recipients should receive Hib vaccination at least 6 weeks prior to their procedure or, if that is not possible, within 6–12 months post transplantation.

Interchangeability

Ideally the same Hib conjugate vaccine type should be used for all doses of the complete schedule. However, studies have shown that schedules combining different types of Hib conjugate vaccines are safe and provide adequate protection against Hib disease.^{16,21,22} Therefore, it is recommended that, after the 1st dose, any Hib conjugate vaccine may be used to complete the primary course. PRP-OMP requires 2 doses in the primary sequence, whereas PRP-T requires 3. Therefore, when completing a primary sequence, when the previous vaccine type is unknown for any dose or the same vaccine type is not available, administering a total of 3 doses of any registered Hib conjugate vaccine is safe and will result in adequate protection against the disease with antibody levels similar to a sequence using a single type of the vaccine.

For the booster dose, a single dose of any registered Hib conjugate vaccine is recommended, regardless of previous Hib vaccine type given.

For further information on the use of Hib vaccines, please see the 9th edition of *The Australian Immunisation Handbook* (2008).¹³

Vaccine efficacy/effectiveness

Several prospective randomised studies have reported a protective efficacy of over 90% for Hib conjugate vaccine following the primary vaccine schedule. In Australia, vaccine effectiveness was estimated to be between 83% and 90% when adjusted for under-reporting.⁵ Hib conjugate vaccines have been shown to not only reduce the rate of disease in vaccinees, but also reduce the prevalence of Hib carriage. Due to this effect on the 'reservoir of infection', Hib vaccines cause a reduction in disease incidence even among the non-vaccinated (herd immunity).²³⁻²⁵

Since 2000, every state and territory in Australia has achieved Hib vaccine coverage rates of over 90% for the primary series by 12 months of age in Indigenous as well as non-Indigenous children. Hib vaccine coverage among children at 24 months of age for the primary series plus the booster is slightly lower than at 12 months of age but still over 90%.^{12,26}

Vaccine safety

Hib is not a live vaccine and, therefore, there is no risk of the vaccine causing Hib disease. Adverse reactions that have been reported following Hib vaccination have been mild and transient. One in 10 children may have local reactions such as pain, swelling or redness at the injection site. These reactions generally appear within 3–4 hours of injection and do not last longer than 24 hours. A slightly raised temperature that is short-lived has been reported as well.

Anaphylaxis is a rare possibility following Hib vaccination as with all other vaccines. However, anaphylaxis following Hib vaccination is exceptionally rare in comparison to most other vaccines.

Concomitant administration

Children can be safely vaccinated with Infanrix hexa, 7-valent pneumococcal conjugate vaccine, oral rotavirus vaccines, and other inactivated and live attenuated vaccines at the same visit.

Contraindications/precautions

The only contraindications to any of the Hib vaccines are a history of anaphylaxis following a previous dose of Hib vaccine or anaphylaxis following any component of the vaccine.

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