FactSheet

Haemophilus influenzae type b

NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

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

This fact sheet provides information on Hib disease and the available vaccines to assist immunisation providers in the delivery of Hib vaccinations to children.

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-containing vaccine is recommended for all infants from 2 months of age and also for people with special vaccination requirements, such as people with asplenia and people who have received haematopoietic stem cell transplants.
- Infants should be given 3 primary doses of Hib vaccine at 2, 4 and 6 months of age and a booster at 18 months of age.

Vaccines

- The current Hib conjugate and monovalent vaccines used in the National Immunisation Program are PRP-T vaccines. These vaccines contain the capsular polysaccharide of Hib, polyribosyl-ribitol phosphate (PRP), linked to a tetanus toxoid carrier protein.
- Previously used PRP-OMP vaccines are no longer available and have been discontinued for use in Australia since 2017.

The disease

Causative agent

Haemophilus influenzae is a bacterium that has 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. There are 6 distinct capsular serotypes: a to 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] Meningitis and pneumonia are responsible for most cases of Hib-related mortality and morbidity. Hib can also infect other organ systems and cause septic arthritis, pericarditis, osteomyelitis, bacteraemia or septicaemia, 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 after 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 started, 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. 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.

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).

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. Because of naturally acquired immunity, Hib disease was not common beyond 5 years of age even before the introduction of 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 mainly a childhood disease with over 80% of cases worldwide occurring in children aged <5 years. Before Hib vaccination started, Hib was one of the most common 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]

Before Hib vaccines were introduced, Hib was the most common 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.[6-9] 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.[10,11]

Introduction of Hib vaccines 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 among both Aboriginal and Torres Strait Islander 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.[5,13]

Who should be vaccinated?

National Immunisation Program

Hib-containing vaccine is recommended for all infants from 2 months of age under the National Immunisation Program. The recommended schedule is 3 primary doses at 2, 4 and 6 months of age and a booster at 18 months of age. For the booster dose, a single dose of any registered Hib monovalent vaccine is recommended, regardless of previous Hib vaccine type given.

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.

Children aged >18 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.

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. A single dose of Hib vaccine is recommended for those splenectomised patients who have not been vaccinated in infancy or are incompletely vaccinated. These patients should preferably receive the vaccine 2 weeks before the planned splenectomy. If not received then, they should receive the Hib vaccine 2 weeks after the splenectomy. No further booster doses of Hib vaccine are required in these patients.

Functional and autologous HSCT recipients should receive 3 doses of Hib conjugate vaccine at 6, 8 and 12 months post-transplant. All solid organ transplantation recipients should receive Hib vaccination at least 6 weeks before their procedure or, if that is not possible, within 6–12 months post transplantation.

Women who are pregnant or breastfeeding

Women who are pregnant or breastfeeding are not routinely recommended to receive Hib vaccine. However, for women who have functional or anatomical asplenia, refer to *High-risk patients* above.

Vaccines

Vaccine types

Protection against Hib disease is provided by antibodies produced against Hib polysaccharide capsule polyribosyl-ribitol phosphate (PRP). The first generation of Hib vaccines had 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-T conjugates achieve protective antibody levels only after the administration of the 2nd dose of the vaccine.[16,17]

The Hib-containing vaccines that are currently used in the National Immunisation Program (NIP) are: Act-Hib and Infanrix hexa.

Act-Hib is a monovalent Hib PRP-T vaccine.

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.

Hib-containing vaccines registered for use in Australia but not currently used in the NIP:

Hexaxim (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.

Menitorix (Hib-MenC) contains Hib PRP-T in combination with meningococcal serogroup C – tetanus toxoid conjugate.

Hiberix is a monovalent Hib PRP-T vaccine.

Dose and route

The dose of all Hib-containing vaccines is 0.5 mL given by intramuscular injection.

Vaccine efficacy and effectiveness

Several prospective randomised studies have reported a protective efficacy of over 94% for Hib conjugate vaccine following the primary vaccine schedule.[18] 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 people who have been vaccinated but also reduce the prevalence of Hib carriage. Because of this effect on the 'reservoir of infection', Hib vaccines reduce disease incidence even among the non-vaccinated people (herd immunity).[19-21]

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 Aboriginal and Torres Strait Islander 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 is still over 90%.[12,22]

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. 5%-30% of children may have local reactions such as pain, swelling or redness at the injection site, most commonly presenting after the 1st dose. These reactions generally appear within 3–4 hours of injection and resolve completely within 24 hours. A slightly raised temperature that is short-lived in 2% of vaccinated children 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.

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.[23-25]

Concomitant administration

Children can be safely vaccinated with pneumococcal conjugate vaccines, hepatitis B vaccines, DTPa-containing vaccines, inactivated poliomyelitis (IPV or IPV-containing) vaccines, and monovalent meningococcal C vaccine in separate sites at the same visit.

Contraindications and 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.

References

1. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC). *Haemophilus influenzae* type b. In: Hamborsky J, Kroger A, Wolfe C (editors). *Epidemiology and prevention of vaccine-preventable diseases*. 13th. Washington DC: Public Health Foundation; 2015. p. 119-32. Available from: https://www.cdc.gov/vaccines/pubs/pinkbook/hib.html.
2. Nanduri SA, Sutherland AR, Gordon LK, Santosham M. *Haemophilus influenzae* type b vaccines. In: Plotkin SA, Orenstein WA, Offit PA (editors). *Plotkin's vaccines*. 7th. Philadelphia, PA: Elsevier; 2018.
3. Haggard M. Otitis media: prospects for prevention. *Vaccine* 2008;26 Suppl 7:G20-G4.
4. Peltola H. Worldwide Haemophilus influenzae type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. *Clinical Microbiology Reviews* 2000;13:302-17.
5. Horby P, Gilmour R, Wang H, McIntyre P. Progress towards eliminating Hib in Australia: an evaluation of *Haemophilus influenzae* type b prevention in Australia, 1 July 1993 to 30 June 2000. *Communicable Diseases Intelligence* 2003;27:324-41.
6. Hanna JN, Wild BE. Bacterial meningitis in children under five years of age in Western Australia. *Medical Journal of Australia* 1991;155:160-4.
7. McIntyre PB, Leeder SR, Irwig LM. Invasive Haemophilus influenzae type b disease in Sydney children 1985-1987: a population-based study. *Medical Journal of Australia* 1991;154:832-7.
8. Bower C, Condon R, Payne J, et al. Measuring the impact of conjugate vaccines on invasive Haemophilus influenzae type b infection in Western

Australia. *Australian and New Zealand Journal of Public Health* 1998;22:67-72.

9. Markey P, Krause V, Boslego JW, et al. The effectiveness of Haemophilus influenzae type b conjugate vaccines in a high risk population measured using immunization register data. *Epidemiology and Infection* 2001;126:31-6.
10. Coulehan JL, Michaels RH, Hallowell C, et al. Epidemiology of Haemophilus influenzae type b disease among Navajo Indians. *Public Health Reports* 1984;99:404-9.
11. Ward JI, Lum MK, Hall DB, Silimperi DR, Bender TR. Invasive Haemophilus influenzae type b disease in Alaska: background epidemiology for a vaccine efficacy trial. *Journal of Infectious Diseases* 1986;153:17-26.
12. Wang H, Deeks S, Glasswell A, McIntyre P. Trends in invasive Haemophilus influenzae type b disease in Australia, 1995-2005. *Communicable Diseases Intelligence* 2008;32:316-25.
13. Chiu C, Dey A, Wang H, et al. Vaccine preventable diseases in Australia, 2005 to 2007. *Communicable Diseases Intelligence* 2010;34 Suppl:ix-S167.
14. Swingler GH, Michaels D, Hussey GG. Conjugate vaccines for preventing Haemophilus influenzae type b infections. [update of Cochrane Database Syst Rev. 2003;(4):CD001729; PMID: 14583937]. *Cochrane Database of Systematic Reviews* 2007;(2):CD001729. DOI: 10.1002/14651858.CD001729.pub2.
15. Morris SK, Moss WJ, Halsey N. Haemophilus influenzae type b conjugate vaccine use and effectiveness. *The Lancet Infectious Diseases* 2008;8:435-43.
16. GuimarÆes T, Cereda RF, Bianchin PJ, et al. Antibody response to Haemophilus influenzae type b tetanus conjugate vaccine with two doses given at 3 and 5 months of age. *International Journal of Infectious Diseases* 2002;6:113-7.
17. Kurikka S, Käyhty H, Saarinen L, et al. Comparison of five different vaccination schedules with Haemophilus influenzae type b-tetanus toxoid conjugate vaccine. *Journal of Pediatrics* 1996;128:524-30.
18. Jackson C, Mann A, Mangtani P, Fine P. Effectiveness of Haemophilus influenzae type b vaccines administered according to various schedules: systematic review and meta-analysis of observational data. *The Pediatric Infectious Disease Journal* 2013;32:1261-9.
19. Fry AM, Lurie P, Gidley M, et al. Haemophilus influenzae type b disease among Amish children in Pennsylvania: reasons for persistent disease. *Pediatrics* 2001;108:E60.
20. Heath PT, McVernon J. The UK Hib vaccine experience. *Archives of Disease in Childhood* 2002;86:396-9.
21. Trotter CL, McVernon J, Ramsay ME, et al. Optimising the use of conjugate vaccines to prevent disease caused by Haemophilus influenzae type b, Neisseria meningitidis and Streptococcus pneumoniae *Vaccine* 2008;26:4434-45.
22. Brotherton J, Wang H, Schaffer A, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2003 to 2005. *Communicable Diseases Intelligence* 2007;31(Suppl):S1-152.
23. Decker MD, Edwards KM, Bradley R, Palmer P. Responses of children to booster immunization with their primary conjugate Haemophilus influenzae type b vaccine or with polyribosylribitol phosphate conjugated with diphtheria toxoid. *Journal of Pediatrics* 1993;122:410-3.
24. Greenberg DP, Wong VK, Partridge S, et al. Immunogenicity of a Haemophilus influenzae type b-tetanus toxoid conjugate vaccine when mixed with a diphtheria-tetanus-acellular pertussis-hepatitis B combination vaccine. *Pediatric Infectious Disease Journal* 2000;19:1135-40.
25. Scheifele D, Law B, Mitchell L, Ochnio J. Study of booster doses of two Haemophilus influenzae type b conjugate vaccines including their interchangeability. *Vaccine* 1996;14:1399-406.