

# 6 *Haemophilus influenzae* type b (Hib) disease

## Key information

Mode of transmission	By inhalation of respiratory tract droplets or by direct contact with respiratory tract secretions.
Incubation period	Unknown, but probably 2–4 days.
Period of communicability	May be prolonged. Non-communicable within 24–48 hours after starting effective antimicrobial therapy.
Burden of disease	Children aged under 5 years, particularly those aged under 1 year: meningitis, epiglottitis, pneumonia and bacteraemia.
Funded vaccines	DTaP-IPV-HepB/Hib (Infanrix-hexa). Hib-PRP-T (Hiberix).
Dose, presentation, route	DTaP-IPV-HepB/Hib and Hib-PRP-T: <ul style="list-style-type: none"><li>• 0.5 mL per dose after reconstitution</li><li>• pre-filled syringe and glass vial – the vaccines must be reconstituted prior to injection</li><li>• intramuscular injection (Hib-PRP-T can also be administered subcutaneously).</li></ul>
Funded vaccine indications and schedule	Usual childhood schedule: <ul style="list-style-type: none"><li>• at ages 6 weeks, 3 months and 5 months: DTaP-IPV-HepB/Hib</li><li>• at age 15 months: Hib-PRP-T.</li></ul> For (re)vaccination of eligible patients: <ul style="list-style-type: none"><li>• up to 4 additional doses of DTaP-IPV-HepB/Hib (for eligible children &lt;10 years); or</li><li>• 1 additional dose of Hib-PRP-T.</li></ul> For children <10 years receiving solid organ transplantation: up to 5 doses of DTaP-IPV-HepB/Hib. For testing for primary immune deficiencies: Hib-PRP-T.
Vaccine effectiveness	Hib disease has been almost eliminated in countries where Hib vaccine is used.
Public health measures	All cases of Hib disease be notified immediately on suspicion. All contacts should have their immunisation status assessed and updated as appropriate.
Post exposure prophylaxis	Rifampicin prophylaxis should be administered to contacts as appropriate.

## 6.1 Bacteriology

*Haemophilus influenzae* is a gram-negative coccobacillus, which occurs in typeable and non-typeable (NTHi) forms. There are six antigenically distinct capsular types (a–f), of which type b is the most important. Before the introduction of the vaccine, *H. influenzae* type b (Hib) caused 95 percent of *H. influenzae* invasive disease in infants and children.

## 6.2 Clinical features

Transmission is by inhalation of respiratory tract droplets or by direct contact with respiratory tract secretions. Hib causes meningitis and other focal infections (such as pneumonia, septic arthritis and cellulitis) in children, primarily those aged under 2 years, while epiglottitis was more common in children over 2 years. Invasive Hib disease was rare over the age of 5 years, but could occur in adults. In the absence of vaccination these presentations may still occur. There have always been a small number of cases of *H. influenzae* invasive disease in adults, and these continue to occur. The incubation period of the disease is unknown, but is probably from two to four days.

Immunisation against Hib does not protect against infections due to other *H. influenzae* types or NTHi strains. Non-typeable *H. influenzae* (NTHi) organisms usually cause non-invasive mucosal infections, such as otitis media, sinusitis and bronchitis, but can occasionally cause bloodstream infection, especially in neonates. They are frequently present (60–90 percent) in the normal upper respiratory tract flora.

Young infants (aged under 2 years) do not produce an antibody response following Hib invasive disease, so a course of Hib-PRP vaccine is recommended when they have recovered (see section 6.5.3).

Hib and NTHi strains also cause diseases (including pneumonia and septicaemia) in the elderly.

## 6.3 Epidemiology

### 6.3.1 Global burden of disease

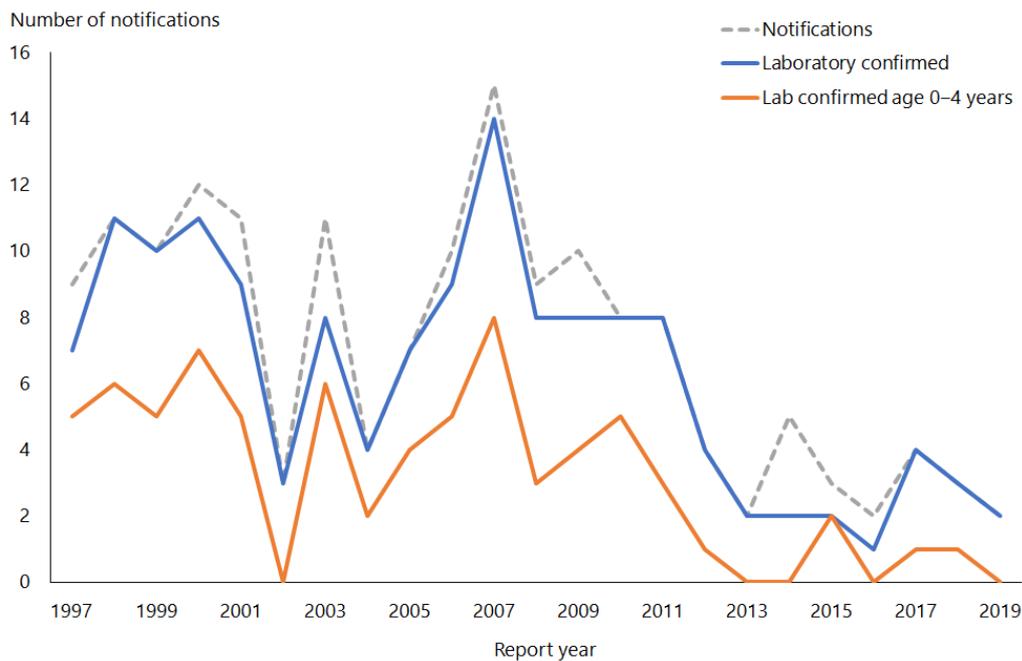
The source of the organism is the upper respiratory tract. Immunisation with a protein conjugate vaccine reduces the frequency of asymptomatic colonisation by Hib. Before the introduction of the vaccine, Hib was the most common cause of bacterial meningitis in children. Worldwide immunisation coverage is increasing, with approximately 194 countries having fully or partially introduced Hib onto their schedules by July 2019 (98 percent of all WHO member states).<sup>1</sup> The estimated global coverage for three doses of Hib is 72 percent as of July 2019.<sup>2</sup>

## 6.3.2 New Zealand epidemiology

Hib-PRP was introduced in 1994 (see Appendix 1). In 1993, 101 children aged under 5 years had laboratory-confirmed invasive Hib disease (an age-specific rate of 36.4 per 100,000 population). By 1999 only five children in this age group had laboratory-confirmed disease (1.7 per 100,000) (Figure 6.1).

Two cases of Hib were notified and laboratory confirmed in 2019 (ESR, 8 June 2020). The cases were aged 50–59 and 60–69 years, both were unvaccinated. There were seven deaths from Hib between 1997 and 2019 (ESR, 8 June 2020), the most recent was in 2012 in an adult over 70 years of age.<sup>3</sup>

**Figure 6.1: Number of notifications and culture-positive cases of *Haemophilus influenzae* type b invasive disease, 1997–2019**



Source: ESR

For details of Hib notifications, refer to the most recent ESR notifiable disease annual tables and reports (available at [surv.esr.cri.nz/surveillance/surveillance.php](http://surv.esr.cri.nz/surveillance/surveillance.php)).

## 6.4 Vaccines

Antibodies to PRP, a component of the polysaccharide cell capsule of Hib, are protective against invasive Hib disease. To induce a T-cell dependent immune response, the polyribosylribitol phosphate (PRP) polysaccharide has been linked (conjugated) to a variety of protein carriers. These conjugate Hib vaccines are immunogenic and effective in young infants (see also section 1.4.3). The protein carriers used are either an outer membrane protein of *Neisseria meningitidis* (Hib-PRP-OMP vaccine), or a tetanus toxoid (Hib-PRP-T vaccine).

Note that the protein conjugates used in Hib vaccines are not themselves expected to be immunogenic and do not give protection against *N. meningitidis* or tetanus.

## 6.4.1 Available vaccines

### Funded vaccines

The Hib vaccines funded as part of the Schedule are:

- Hib-PRP-T, given as the hexavalent vaccine DTaP-IPV-HepB/Hib (Infanrix-hexa, GSK). It contains diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B and Haemophilus influenzae type b vaccine (see section 5.4 for more information)
- Hib-PRP-T given as monovalent Hib vaccine (Hiberix, GSK). It contains 10 µg of purified Hib capsular PRP polysaccharide conjugated to 25 µg of inactivated tetanus toxoid. Other components (excipients) include lactose in the vaccine and sterile saline solution in the diluent.

### Other vaccines

No other Hib vaccines are available currently. Hib-PRP-T (Act-HIB, Sanofi) was the funded vaccine prior to the 1 July 2017 Schedule change.

## 6.4.2 Efficacy and effectiveness

The high efficacy and effectiveness of Hib-PRP vaccines have been clearly demonstrated by the virtual elimination of Hib in countries implementing the vaccine,<sup>4, 5, 6</sup> including New Zealand. Hib-PRP vaccines are highly effective after a primary course of two or three doses.<sup>7, 8, 9</sup> Disease following a full course of Hib-PRP is rare.

Conjugate vaccines reduce carriage in immunised children and as a result also decrease carriage and disease in unimmunised people (herd immunity). These vaccines will not protect against infection with NTHi strains, and therefore do not prevent the great majority of otitis media, recurrent upper respiratory tract infections, sinusitis or bronchitis.

(See also section 14.4.2 for information about the DTaP-IPV-HepB/Hib vaccine.)

### Duration of immunity

A primary series followed by a booster dose in the second year of life should provide sufficient antibody levels to protect against invasive Hib disease to at least the age of 5 years.<sup>10</sup>

## 6.4.3 Transport, storage and handling

Transport according to the *National Standards for Vaccine Storage and Transportation for Immunisation Providers 2017 (2nd edition)* (available at [www.health.govt.nz/publication/national-standards-vaccine-storage-and-transportation-immunisation-providers-2017](http://www.health.govt.nz/publication/national-standards-vaccine-storage-and-transportation-immunisation-providers-2017)).

Store at +2°C to +8°C. Do not freeze. DTaP-IPV-HepB/Hib should be stored in the dark.

DTaP-IPV-HepB/Hib vaccine (Infanrix-hexa) must be reconstituted by adding the entire contents of the pre-filled syringe containing DTaP-IPV-HepB vaccine to the vial containing the Hib powder. After adding the vaccine to the powder, the mixture should be shaken until the powder is completely dissolved. Use the reconstituted vaccine as soon as possible. If storage is necessary, the reconstituted vaccine may be kept for up to eight hours at 21°C.

Hib-PRP-T vaccine (Hiberix) must be reconstituted with the supplied diluent and used immediately after reconstitution.

## 6.4.4 Dosage and administration

The dose of DTaP-IPV-HepB/Hib and Hib-PRP-T vaccines is 0.5 mL administered by intramuscular injection. Hib-PRP-T can also be administered subcutaneously if indicated (see section 2.2.3).

### Co-administration

DTaP-IPV-HepB/Hib and Hib-PRP-T vaccines can be co-administered with other routine vaccines on the Schedule, in separate syringes and at separate sites.

# 6.5 Recommended immunisation schedule

## 6.5.1 Usual childhood schedule

Hib vaccine is funded for all children aged under 5 years. Three doses of DTaP-IPV-HepB/Hib (Infanrix-hexa) vaccine are given as the primary course, with a booster of Hib-PRP-T (Hiberix) at age 15 months (see Table 6.1).

**Table 6.1: Usual childhood Hib schedule (excluding catch-up)**

Age	Vaccine	Comment
6 weeks	DTaP-IPV-HepB/Hib	Primary series
3 months	DTaP-IPV-HepB/Hib	Primary series
5 months	DTaP-IPV-HepB/Hib	Primary series
15 months	Hib-PRP-T	Booster

For children aged under 5 years who, for whatever reason, have missed out on Hib vaccine in infancy, a catch-up schedule is recommended. The total number of doses of Hib vaccine required is determined by the age at which Hib immunisation commences. Where possible, the combined available vaccines should be used, but individual immunisation schedules based on the recommended national schedule may be required for children who have missed some immunisations (see Appendix 2).

## 6.5.2 Special groups

### Children

Because of an increased risk of infection, it is particularly important that the following groups of children, whatever their age, receive the Hib vaccine as early as possible (see also sections 4.2 and 4.3):

- children with anatomical or functional asplenia, or who are suffering from sickle cell disease (if possible, it is recommended that children be immunised prior to splenectomy)
- children with partial immunoglobulin deficiency, Hodgkin's disease or following chemotherapy (note, however, that response to the vaccine in these children is likely to be suboptimal)
- children with nephrotic syndrome
- HIV-positive children.

### Recommendations for Hib vaccine for older children and adults with asplenia

Although there is no strong evidence of an increased risk of invasive Hib disease in asplenic older children and adults, some authorities recommend Hib immunisation for these individuals.<sup>11, 12</sup> The Hib PRP-T vaccine has been shown to be immunogenic in adults.

- Hib-PRP-T vaccine (Hiberix) is funded for older children and adults pre- or post-splenectomy or with functional asplenia; one dose of vaccine is recommended (see also section 4.3.4) if childhood vaccine schedule is incomplete or unknown.

Note: Pneumococcal, meningococcal, influenza, varicella and pertussis-containing vaccines are also recommended for these individuals; see section 4.3 and the relevant disease chapters.

## 6.5.3 Children who have recovered from invasive Hib disease

Children aged under 2 years with Hib disease do not reliably produce protective antibodies and need to receive a complete course of Hib-PRP-T. The number of doses required will depend on the age at which the first dose after the illness is given, **ignoring** any doses given before the illness (follow the age-appropriate catch-up schedules in Appendix 2).

Commence immunisation approximately four weeks after the onset of disease.

Any immunised child who develops Hib disease or who experiences recurrent episodes of Hib invasive disease requires immunological investigation by a paediatrician.

## 6.5.4 (Re)vaccination

Hib-PRP-containing vaccines are funded for vaccination and revaccination of eligible patients, as follows. See also section 4.3.

### DTaP-IPV-HepB/Hib (Infanrix-hexa)

Up to an additional four doses (as appropriate) of DTaP-IPV-HepB/Hib are funded for vaccination or revaccination of children aged under 10 years:

- post-HSCT or chemotherapy
- pre- or post-splenectomy
- pre- or post-solid organ transplant
- undergoing renal dialysis
- prior to planned or following other severely immunosuppressive regimens.

Up to five doses of DTaP-IPV-HepB/Hib are funded for children aged under 10 years receiving solid organ transplantation.

### Hib-PRP-T (Hiberix)

One additional dose of Hib-PRP-T (Hiberix) is funded for vaccination or revaccination of patients:

- post-HSCT or chemotherapy
- pre- or post-splenectomy or with functional asplenia
- pre- or post-solid organ transplant
- pre- or post-cochlear implants
- undergoing renal dialysis
- prior to planned or after other severely immunosuppressive regimens.

## 6.5.5 Pregnancy and breastfeeding

Hib-PRP is not routinely recommended for pregnant or breastfeeding women. However, for women with asplenia see the 'Recommendations for Hib vaccine for older children and adults with asplenia' in section 6.5.2.

## 6.6 Contraindications and precautions

See also section 2.1.3 for pre-vaccination screening guidelines and section 2.1.4 for general vaccine contraindications. Anaphylaxis to a previous vaccine dose or any component of the vaccine is an absolute contraindication to further vaccination with that vaccine.

See section 14.6 for contraindications and precautions to DTaP-IPV-HepB/Hib vaccine.

Hib-PRP-T vaccines should not be administered to people with a history of an anaphylactic reaction to a prior dose of Hib vaccine or to a vaccine component. Significant hypersensitivity reactions to Hib vaccines appear to be extremely rare.

## 6.7 Potential responses and AEFIs

See section 14.7.1 for potential responses and AEFIs with DTaP-IPV-HepB/Hib vaccine.

### 6.7.1 Potential responses

Adverse reactions to Hib-PRP conjugate vaccines are uncommon. Pain, redness and swelling at the injection site occur in approximately 25 percent of recipients, but these symptoms typically are mild and last less than 24 hours.<sup>13</sup>

### 6.7.2 AEFIs

A meta-analysis of trials of Hib-PRP vaccination from 1990 to 1997 found that serious adverse events were rare.<sup>14</sup> No serious vaccine-related adverse experiences were observed during clinical trials of Hib vaccine alone. There have been rare reports, not proven to be causally related to Hib vaccine, of transverse myelitis, thrombocytopenia and Guillain-Barré syndrome (GBS).<sup>15</sup>

## 6.8 Public health measures

It is a legal requirement that all cases of Hib disease be notified immediately on suspicion to the local medical officer of health, who will arrange for contact tracing, immunisation and administration of prophylactic rifampicin, where appropriate.

For further information see the *Communicable Disease Control Manual*.<sup>16</sup>

### 6.8.1 Management of contacts

All child contacts should have their immunisation status assessed and updated, as appropriate.

Immunisation reduces – but does not necessarily prevent – the acquisition and carriage of Hib. Therefore, immunised children still need rifampicin prophylaxis, when indicated, to prevent them transmitting infection to their contacts. Careful observation of exposed household and early childhood service contacts is essential. Exposed children who develop a febrile illness should receive prompt medical evaluation.

#### Rifampicin chemoprophylaxis

To eradicate the carrier state and protect susceptible children, antimicrobial prophylaxis should be given to contacts as soon as possible, and ideally within seven days of the index case developing the disease, irrespective of their own immunisation status. Prophylaxis started after seven days may still be of benefit and is recommended. Note that the prophylaxis for Hib is different from that for meningococcal disease (see chapter 12).

#### Rifampicin recommendations

Chemoprophylaxis with rifampicin is recommended for the following contacts of an index case of Hib:

- all members of the case's household (including adults) where there is at least one contact aged under 4 years who is either unimmunised or partially immunised
- all members of a household where there is a child aged under 12 months, even if the child has had three doses (primary series) of the Hib-PRP vaccine
- all members of a household where there is an immunosuppressed person
- all staff and children at an early childhood service where two or more cases of Hib have occurred within 60 days.

Use oral rifampicin 20 mg/kg (maximum 600 mg) daily for four days. The dose for infants aged under 4 weeks has not been established, but a dose of 10 mg/kg per day is recommended. This is a different regimen to that recommended for prophylaxis from meningococcal disease (see chapter 12).

The index case should also receive rifampicin unless treated with cefotaxime or ceftriaxone.

Rifampicin is not recommended for:

- occupants of households where there are no children aged under 4 years, other than the index case
- occupants of households where all contacts aged 12 months to under 4 years have completed their immunisation series, including the second-year-of-life dose
- pregnant women – rifampicin is contraindicated in pregnant women; pregnant women who are a household contact of an index case should receive ceftriaxone.

For more details on control measures, refer to the 'Haemophilus influenzae type b invasive disease (Hib)' chapter of the *Communicable Disease Control Manual* (available at [www.health.govt.nz/publication/communicable-disease-control-manual-2012](http://www.health.govt.nz/publication/communicable-disease-control-manual-2012)).<sup>16</sup>

## 6.9 Variations from the vaccine data sheets

The Hib-PRP-T (Hiberix) data sheet states that the vaccine is not intended for use in adults. However, the Ministry of Health recommends that asplenic adults (see section 6.5.2) or adults with specified immunocompromised conditions (see section 6.5.4) receive Hib-PRP-T vaccine.<sup>11, 17</sup> There are not expected to be any safety concerns in regard to use in older age groups.

See section 14.9 for variations from the DTaP-IPV-HepB/Hib (Infanrix-hexa) data sheet.

## References

1. World Health Organization, UNICEF. 2019. *Progress and challenges with achieving universal immunisation coverage: 2018 WHO/UNICEF Estimates of National Immunization Coverage*. Monitoring and Surveillance, July. URL: [https://www.who.int/immunization/monitoring\\_surveillance/who-immuniz.pdf?ua=1](https://www.who.int/immunization/monitoring_surveillance/who-immuniz.pdf?ua=1) (accessed 3 July 2020).
2. World Health Organization, UNICEF. 2019. *Global and Regional Immunization Profile*. URL: [https://www.who.int/immunization/monitoring\\_surveillance/data/gloprofile.pdf?ua=1](https://www.who.int/immunization/monitoring_surveillance/data/gloprofile.pdf?ua=1) (accessed 3 July 2020).

3. Institute of Environmental Science and Research Ltd. 2013. *Notifiable and Other Diseases in New Zealand: Annual Report 2012* (ed). Porirua: Institute of Environmental Science and Research Ltd. URL: [https://surv.esr.cri.nz/PDF\\_surveillance/AnnualRpt/AnnualSurv/2012/2012AnnualSurvRpt.pdf](https://surv.esr.cri.nz/PDF_surveillance/AnnualRpt/AnnualSurv/2012/2012AnnualSurvRpt.pdf) (accessed 3 July 2020).
4. Ladhani SN. 2012. Two decades of experience with the Haemophilus influenzae serotype b conjugate vaccine in the United Kingdom. *Clinical Therapeutics* 34(2): 385–99.
5. Bisgard KM, Kao A, Leake J, et al. 1998. Haemophilus influenzae invasive disease in the United States, 1994–1995: near disappearance of a vaccine-preventable childhood disease. *Emerging Infectious Diseases* 4(2): 229–37.
6. MacNeil JR, Cohn AC, Farley M, et al. 2011. Current epidemiology and trends in invasive Haemophilus influenzae disease – United States, 1989–2008. *Clinical Infectious Diseases* 53(12): 1230–6.
7. Griffiths UK, Clark A, Gessner B, et al. 2012. Dose-specific efficacy of Haemophilus influenzae type b conjugate vaccines: a systematic review and meta-analysis of controlled clinical trials. *Epidemiology and Infection* 140(8): 1343–55.
8. O’Loughlin RE, Edmond K, Mangtani P, et al. 2010. Methodology and measurement of the effectiveness of Haemophilus influenzae type b vaccine: systematic review. *Vaccine* 28(38): 6128–36.
9. Kalies H, Grote V, Siedler A, et al. 2008. Effectiveness of hexavalent vaccines against invasive Haemophilus influenzae type b disease: Germany’s experience after 5 years of licensure. *Vaccine* 26(20): 2545–52.
10. Khatami A, Snape MD, John TM, et al. 2011. Persistence of immunity following a booster dose of Haemophilus influenzae type B-meningococcal serogroup C glycoconjugate vaccine: follow-up of a randomized controlled trial. *Pediatric Infectious Disease Journal* 30(3): 197–202.
11. Centers for Disease Control and Prevention. 2014. Prevention and control of Haemophilus influenzae type b disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report: Recommendations and Reports* 63(RR-1): 1–14. URL: <https://www.cdc.gov/mmwr/pdf/rr/rr6301.pdf> (accessed 3 July 2020).
12. Australian Technical Advisory Group on Immunisation (ATAGI). 2018. Haemophilus influenzae type b (Hib). In *Australian Immunisation Handbook*. Canberra. URL: <https://immunisationhandbook.health.gov.au/vaccine-preventable-diseases/haemophilus-influenzae-type-b-hib> (accessed 6 July 2020).
13. American Academy of Pediatrics. 2018. Haemophilus influenzae infections. In Kimberlin D, Brady M, Jackson M, et al (eds). *Red Book: 2018 Report of the Committee on Infectious Diseases*. URL: <https://redbook.solutions.aap.org/redbook.aspx> (accessed 3 July 2020).
14. Obonyo CO, Lau J. 2006. Efficacy of haemophilus influenzae type b vaccination of children: a meta-analysis. *European Journal of Clinical Microbiology and Infectious Diseases* 25(2): 90–7.
15. Nanduri S, Sutherland A, Gordon L, et al. 2018. Haemophilus influenzae type b vaccines. In Plotkin S, Orenstein W, Offit P, et al (eds) *Plotkin’s Vaccines (7th edition)*. Elsevier: Philadelphia, US.
16. Ministry of Health. 2012. *Communicable Disease Control Manual* (ed). Wellington: Ministry of Health. URL: <http://www.health.govt.nz/publication/communicable-disease-control-manual-2012> (accessed 3 July 2020).
17. Public Health England. 2016. Immunisation of individuals with underlying medical conditions. In *The Green Book*. URL: [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/566853/Green\\_Book\\_Chapter7.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/566853/Green_Book_Chapter7.pdf) (accessed 1 April 2017).