

# 7 *Haemophilus influenzae* type b (Hib)

## 7.1 Introduction

*Haemophilus influenzae*, first described by Pfeiffer in 1889, is a gram negative coccobacillus, which occurs in encapsulated (typeable) and non-encapsulated (untypeable) forms. There are six antigenically distinct capsular types (a–f), type b being the most important.

## 7.2 The illness

Before the introduction of the vaccine, *H. influenzae* type b (Hib) caused 95 percent of *H. influenzae* invasive disease in infants and children. Hib causes meningitis, pneumonia, epiglottitis, septic arthritis, bacteraemia, cellulitis, and empyema in infants and young children, particularly under the age of two years but up to four years. The incubation period of the disease is unknown, probably from two to four days.

Prior to immunisation, the two most common presentations of Hib invasive disease in New Zealand were meningitis and epiglottitis. Meningitis tends to occur in younger children between three months and three years of age, while epiglottitis usually occurs in children between two and four years of age. The common signs of meningitis include fever, irritability or lethargy, refusing feeds and neck stiffness, although in the young child the signs can be very vague and non-specific. The strongest lead to the diagnosis of Hib invasive disease may be an ominous deterioration in a child who has been a little unwell with a respiratory tract infection for a day or two.

The onset of epiglottitis is rapid, with initial features of fever and dyspnoea, progressing to dysphagia, pooling of oral secretions and drooling of saliva. The child characteristically adopts a sitting posture with the neck extended and the tongue protruding to reduce airway obstruction.

Non-encapsulated *H. influenzae* organisms usually cause mucosal non-invasive infections, such as otitis media, sinusitis and bronchitis, and occasionally are the cause of neonatal infections. Non-encapsulated strains are frequently present (60–90 percent) in the normal upper respiratory tract flora. In contrast, Hib was found in 2–5 percent of asymptomatic children in the pre-vaccine era. Immunisation against Hib will not protect against infections due to other *H. influenzae* types or untypeable strains.

Young infants (under two years of age) with Hib invasive disease do not produce an antibody response and are therefore still susceptible. They should be given a course of Hib vaccine when recovered (see section 7.5).

*H. influenzae* type b and untypeable strains also cause diseases, including pneumonia and septicaemia, in the elderly.

## 7.3 Epidemiology

The source of the organism is the upper respiratory tract, and transmission is by direct contact and by respiratory spread from secretions containing the Hib organism. 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.

Hib vaccine is now on the schedule in most developed countries, but is not yet routinely on the World Health Organization (WHO) Expanded Programme of Immunization. Hib vaccine is not on the immunisation schedule in most Pacific Islands, but Tokelau started Hib immunisation in 2005.

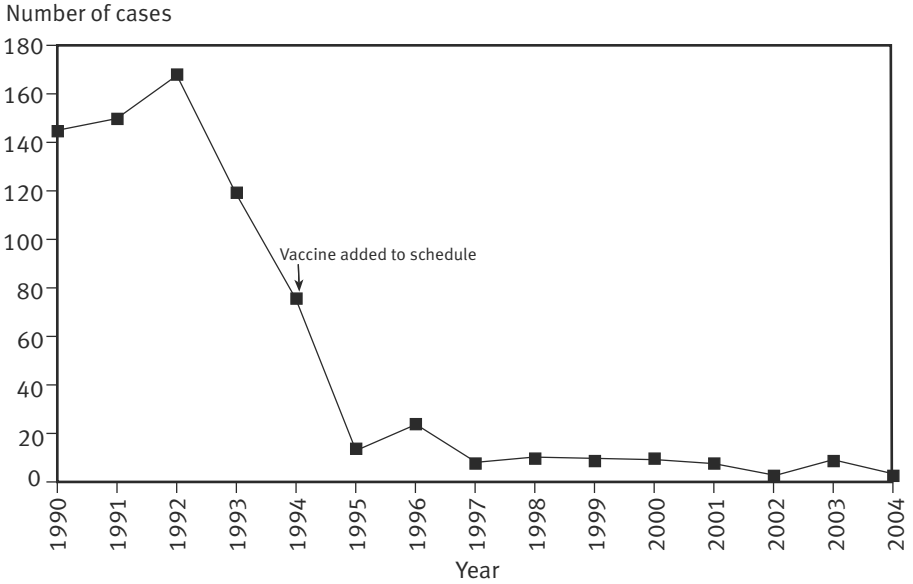
In the United Kingdom (UK), Hib immunisation started in 1992 for infants, plus a catch-up for older children. Hib vaccine was given at two, three and four months of age, with no booster in the second year. In 2002 there was an increase in Hib cases reported in children born in 2000 to 2001 compared with children born during 1992–1999. Investigation showed that cases were more frequent, and the risk increased after each dose, in infants who had received DTaP-Hib vaccine (diphtheria, tetanus, acellular pertussis and Hib) instead of the usual DTwP-Hib vaccine (diphtheria, tetanus, whole cell pertussis, and Hib) following a vaccine shortage.<sup>1</sup>

A national catch-up of a fourth dose of Hib was given to all UK children aged six months to four years in 2003. Results of Hib surveillance following the catch-up showed there were six reported cases of Hib disease in 2004 in children aged one to four years, compared with 46 cases in 2003.<sup>2</sup> Surveillance will continue and further consideration will be given to a booster dose. It was thought the increase in cases was the result of giving the Hib vaccine schedule at two, three and four months without a booster, and the change of vaccine to DTaP-Hib, which induces lower antibody titres than the whole cell DTwP-Hib.

### New Zealand epidemiology

In 1993, 101 isolates of Hib from children under five years of age with invasive disease were referred to the Institute of Environmental Science and Research (ESR). This equates to an age specific rate of 36.4 per 100,000, which can be compared with five isolates referred in 1999 for a rate of 1.7 per 100,000 (see Figure 7.1). Since the introduction of Hib vaccine in January 1994 there has been a greater than 90 percent reduction in the incidence of Hib disease in children less than five years of age. However, the reduction of Hib incidence in New Zealand has not been as great as in those countries where immunisation coverage is higher.

**Figure 7.1: Number of culture positive cases of *Haemophilus influenzae* type b invasive disease, 1990–2004**



Hib

Before immunisation was available in New Zealand, Hib was the commonest cause of life threatening bacterial infection, usually meningitis, in children under five years of age.<sup>3</sup> Approximately one in every 350 New Zealand children developed an invasive Hib infection by that age. The peak occurrence of invasive disease in New Zealand was between six and 11 months of age. Despite the availability of antibiotics and medical care, the case fatality rate remains up to 5 percent, and survivors of Hib meningitis have a 30–40 percent risk of long term neurological developmental impairment. In the pre-vaccine era, Māori and Pacific children had higher rates of Hib infection, especially meningitis, and presented at a younger age. More than 25 percent of Hib meningitis in Māori and Pacific children occurred before the age of six months, and 80 percent by 18 months. Overcrowding and early exposure to the disease were seen as contributing factors. European children were more likely to be affected at an older age and to suffer from epiglottitis.

The conjugate Hib vaccine protects against disease and reduces nasopharyngeal carriage. Vaccinating around 80 percent of children under five years of age results in the virtual disappearance of the disease. Analysis of the cases of invasive Hib disease from 1995 to 1999 showed that 43 cases were in children less than five years of age, and that of these, 12 cases were babies under five and a half months of age; 14 children were not fully vaccinated for their age, and nine cases occurred in children who were fully immunised.<sup>4</sup> The New Zealand epidemiology suggested that early protection was important and supported the change to a Hib-OMP (outer

membrane protein) vaccine, which provides protection after one dose (see also the discussion in section 7.4).

In 2000 there were seven laboratory confirmed cases of Hib reported in children under the age of five years, followed by six cases in 2001 and zero cases in 2002. Of the cases in 2000 and 2001, 11 out of 13 children had either received no Hib immunisation or were incompletely immunised for their age. The other two children, aged four months and four years, had both received Hib immunisation appropriate for their age.

In 2003 there were seven laboratory confirmed cases of Hib in children under the age of five years. The children's ages ranged from two to 14 months. Four infants were of European ethnicity, one was Māori, one Pacific and the ethnicity of one child was not reported. Three of the four infants with Hib infection under the age of one year were not up to date with their immunisations, one baby of two months had not received Hib vaccine, and two infants aged five to 11 months had both received only one dose of Hib vaccine. The immunisation history on the fourth infant under one year of age was not known. There were two infants aged 12 months who had both received the scheduled two doses of vaccine, and one child aged 14 months whose immunisation history was uncertain. In 2004 there were two laboratory confirmed cases of Hib in children, both over the age of one year. One child had received no Hib vaccine and the other the first two doses.

**Of the small numbers of children who have developed Hib infection in New Zealand since the change in schedule in 2000, most were incompletely vaccinated for their age.**

It is important to continue to monitor the epidemiology of Hib to provide the optimum schedule for protecting children. However, at the present time improving coverage and providing immunisation on time are the most important factors.

### **History of the New Zealand Immunisation Schedule**

Hib vaccine was added to the National Immunisation Schedule in January 1994, with diphtheria, tetanus, whole cell pertussis and Hib (DTwPH) vaccine replacing the diphtheria, tetanus and whole cell pertussis (DTwP) vaccine given at six weeks, three months and five months of age. A monovalent Hib vaccine was given at 18 months of age, and a catch-up programme of a single dose of monovalent Hib vaccine was recommended for all children under the age of five years (ie, those born from January 1989).

From February 1996 the fourth dose was changed to 15 months of age and given as DTwPH to reduce the two immunisation events in the second year to one at 15 months of age.

In August 2000, because of the unavailability of DTwPH, the planned change to acellular pertussis vaccine was brought forward. The vaccines introduced were

diphtheria, tetanus, and acellular pertussis vaccine (DTaP) at six weeks, three months and five months, plus the combination vaccine Hib and hepatitis B (Hib-Hepatitis B) at six weeks and three months and the monovalent hepatitis B vaccine at five months. DTaP/Hib vaccine replaced the DTwPH at 15 months. The PRP-OMP (polyribosylribitol phosphate outer membrane protein) component of the Hib-Hepatitis B combined vaccine requires only two doses in the first six months of life followed by a booster in the second year. PRP-OMP induces a significant immune response and protection after a single dose as early as six weeks.<sup>4</sup>

In 2006 the Hib schedule continues as two doses of Hib-Hepatitis B at the age of six weeks and three months, and a booster of Hib vaccine at age 15 months. There is no longer a dose of DTaP given at age 15 months, and therefore the Hib vaccine given at age 15 months is a single antigen Hib-PRP-T vaccine (see below).

## 7.4 Vaccines

The best way to control Hib disease, with the aim of elimination, is immunisation because of the increasing resistance to antimicrobial agents and continuing morbidity and mortality despite treatment.

Antibodies to PRP (polyribosylribitol phosphate), a component of the polysaccharide cell capsule of Hib, are protective against invasive Hib disease. The first generation Hib vaccine was an unconjugated vaccine and was not used in New Zealand. This polysaccharide Hib-PRP vaccine was poorly immunogenic in children under two years of age, who do not mount a T-cell dependent immune response to polysaccharides. The T-cell dependent antibody response is poor until about two years of age and does not induce immunological memory. To induce a T-cell dependent immune response, the PRP polysaccharide has been linked to a variety of protein carriers. These conjugate Hib vaccines are more immunogenic and effective in young infants. The protein carriers used are either a mutant diphtheria toxin (Hb-OC Hib vaccine), or an outer membrane protein of *Neisseria meningitidis* (PRP-OMP Hib vaccine) or tetanus toxoid (PRP-T Hib vaccine). It should be noted that the protein conjugates used in Hib vaccines are not themselves immunogenic and do not give protection against diphtheria, tetanus or *N. meningitidis*.

The current vaccines available for use in New Zealand are as follows.

- 1 PRP-OMP (given as the combination vaccine Hib-Hepatitis B, COMVAX<sup>®</sup>, MSD) – two doses are given, at six weeks and three months of age. This vaccine has been found to be protective, with good immunogenicity when two doses are given to infants from two months of age with a booster at 12 months. One dose of this vaccine offers protection to a substantial percentage of infants at risk of Hib invasive disease.
- 2 PRP-T – one booster dose is given at 15 months. The vaccine is the monovalent Hib vaccine (Hib-PRP-T, Hiberix<sup>™</sup>, GSK).

The other protein conjugate Hib vaccine licensed for distribution, but not marketed, in New Zealand is Hb-OC (HibTITER, Wyeth). HbOC has been found to be protective with good immunogenicity when three doses are given in the first six months of life and a booster at 15 months of age. This vaccine had an efficacy of 100 percent in one study, with no Hib disease in those who had received at least two doses.<sup>6</sup> The vaccine was mostly given as the combination vaccine DTwPH (TETRAMUNE®), which is no longer available.

With all of these vaccines, it is recommended that a booster dose be given in the second year of life. All these vaccines can be given as a single dose for children 15 months of age and over.

### **Efficacy**

A primary course of Hib-OMP at two and four months of age and a booster dose at 12 months, had an efficacy of 100 percent in 2588 Navajo children less than 15 months of age, who had received either one or two doses.<sup>7</sup> The trial had a single failure, with a case at 15.5 months, but this was in the context of continuous exposure to the organism, as only a minority of infants were enrolled in the trial and received vaccine.<sup>8</sup>

A study of three doses of Hib PRP-T given in the first 12 months of life to Gambian children found an efficacy of 95 percent protection against invasive Hib disease.<sup>9</sup> Disease following a full course of Hib vaccine is rare. In the United States (US), 15 cases per year are expected in children who have completed their Hib immunisation.<sup>10</sup>

### **Dosage**

The dose of either Hib-Hepatitis B (COMVAX®, MSD) or Hib (Hiberix™, GSK) is 0.5 mL, given by intramuscular injection. (See section 2.3 for needle sites and sizes.)

## **7.5 Recommended immunisation schedule**

Hib vaccine is publicly funded, as part of the National Immunisation Schedule, to all children under five years of age. Hib-OMP as Hib-Hepatitis B (COMVAX®, MSD) is given at six weeks and three months of age, and a booster of Hib (Hiberix™, GSK) is given at 15 months of age. The number of doses of Hib vaccine needed is age dependent, as described above.

For children up to the age of five years who, for whatever reason, have missed out on Hib vaccine alone in infancy, a catch-up schedule should be instituted (see Appendix 2: Immunisation Catch-up Schedules). 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 for details.)

## Preterm babies

All preterm babies should be given immunisation at the usual chronological age. Because it is uncertain whether very low birthweight preterm babies are able to mount an adequate response to the Hib vaccine, it is recommended that babies whose birthweight is under 1000 g or gestation is less than 29 weeks should be given Hib-Hepatitis B instead of hepatitis B vaccine, at five months of age, as well as routinely at six weeks and three months. The usual booster of Hib vaccine is given at 15 months of age. (See also section 1.8 for general recommendations, and section 3.5 on hepatitis B.)

## Special groups

Because of an increased risk of infection, it is particularly important that the following groups of children, whatever their age, receive the Hib vaccine schedule as per the National Immunisation Schedule:

- children with anatomic or functional asplenia, or who are suffering from sickle cell disease (if possible, children should be immunised prior to splenectomy, see section 1.8)
- children with partial immunoglobulin deficiency, Hodgkin's disease or following chemotherapy (note, however, that responsiveness to the vaccine in these children has not been confirmed and is likely to be sub-optimal)
- children with nephrotic syndrome
- HIV (human immunodeficiency virus) positive children.

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

Although there is no strong evidence to support immunisation with Hib vaccine for asplenic older children and adults, and the vaccine dosage is not defined, some authorities recommend Hib immunisation for these individuals. The Hib PRP-T vaccine has been shown to be immunogenic in adults.

From 2006, Hib vaccine (Hiberix™) and administration is funded for older children and adults pre- or post-splenectomy; one dose of vaccine is recommended. (See also the vaccine recommendations in sections 15.5 A and C, and 16.5 A and B for information on pre- and post-splenectomy recommendations).

## Children who have suffered invasive Hib disease

As described above, children under two years of age with Hib disease do not reliably produce antibodies, so these children need to receive a complete course of Hib vaccine. 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 (see Appendix 2). Reimmunisation should be initiated approximately one month after the onset of disease.

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

## 7.6 Expected responses and adverse events following immunisation (AEFI)

### Expected responses following Hib-Hepatitis B (COMVAX®)

Clinical trials involving the administration of COMVAX® to healthy infants between six weeks and 15 months of age have shown that adverse experiences observed within a five-day period following each dose of COMVAX® were generally similar in type and frequency to those observed in infants who received concurrent injections of PRP-OMP (Hib vaccine) and H-B-Vax II® (hepatitis B vaccine) at separate sites. Other studies have also shown that rates of local injection site reactions and systemic adverse experiences in vaccinees given COMVAX® were similar to those in vaccinees given separate but concurrent injections of PRP-OMP and H-B-Vax II®. The most frequently cited events were mild, transient signs and symptoms of inflammation at the injection site, sleepiness and irritability (see manufacturer's data sheet).

### Expected responses following Hib (Hiberix™)

The most frequently reported reactions following Hib vaccine are local reactions in up to 32 percent of children, and a fever higher than 38°C in 5 to 10 percent.

### Adverse events following immunisation with Hib-Hepatitis B or Hib vaccine

No serious vaccine related adverse experiences were observed during clinical trials of Hib-Hepatitis B vaccine or Hib vaccine alone. There have been rare reports, not proven to be causally related to Hib vaccine, of erythema multiforme, urticaria, seizures, and Guillain-Barré Syndrome following Hib vaccine.

Any severe or unexpected reactions should be reported to CARM, PO Box 913, Dunedin, using the prepaid postcard HP3442 (see section 2.4) or via online reporting at <http://carm.otago.ac.nz>. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

## 7.7 Contraindications

In any child with a suspected contraindication to the Hib vaccine, the circumstances should be discussed with a paediatrician. (See also section 1.9 for general contraindications for all vaccines, and section 3.7 for contraindications to hepatitis B.)

Hib-Hepatitis B (COMVAX®) or Hib (Hiberix™) should not be administered to individuals:

- with known hypersensitivity or anaphylaxis to any component of the vaccine
- who develop symptoms of hypersensitivity after a previous Hib injection.

Significant hypersensitivity reactions to Hib vaccines appear to be extremely rare.

These vaccines will not protect against infection with non-encapsulated strains of *H. influenzae*, and therefore do not prevent otitis media, recurrent upper respiratory tract infections, sinusitis or bronchitis.

## 7.8 Control measures

All cases of Hib disease should be notified immediately to the local medical officer of health, who will arrange for contact tracing, immunisation and administration of prophylactic rifampicin where appropriate. All contacts should have their immunisation status assessed and updated as appropriate. Note that the prophylaxis for Hib is different from that for meningococcal disease (see chapter 15).

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

The risk of invasive Hib disease among household contacts increases in those under four years of age. Asymptomatic colonisation with Hib is more frequent in household contacts of all ages than in the general population. Secondary cases are more common in the first week after diagnosis of the index case, although prophylaxis started after seven days may still be of benefit. Family members should receive prophylaxis as soon as possible, because 54 percent of secondary cases occur within one week of the index case.

Rifampicin is thought to be 95 percent efficient in clearing the carrier state. Reinfection can occur, and secondary cases have been reported in spite of prophylaxis.

#### *Household contacts*

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

- all household contacts, regardless of age, who live in a home where there is one or more children below four years of age who are either unimmunised or partially immunised
- all members of a household where there is a child younger than 12 months of age, even if the child has had two doses (primary series) of the Hib vaccine
- all members of a household where there is a child with immune suppression, regardless of whether the child is fully immunised against Hib or not.

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

### *Early childhood services*

The administration of rifampicin to children in early childhood services is controversial. The risk of infection is greatest if the facility caters for children less than two years of age. It is therefore recommended that chemoprophylaxis should be offered to all early childhood service people (children and teachers), regardless of the age of the children, when two or more cases of Hib invasive disease have occurred within 60 days. When a single case has occurred in an early childhood service, chemoprophylaxis is no longer recommended to attendees.

Parents of children attending an early childhood service should be advised the child should see their family doctor in the event of any febrile illness occurring within 60 days of the onset of the index case of Hib. Unimmunised or incompletely immunised children should receive Hib vaccine and have arrangements made for them to complete the course of vaccine. When rifampicin prophylaxis is given (after two cases in 60 days), children and staff should be excluded from the early childhood service until rifampicin therapy has been initiated. Children entering the group while prophylaxis is being given should also receive it.

The efficiency of rifampicin prophylaxis in early childhood services is dependent on prompt initiation of treatment and strict compliance by the children and parents/ caregivers. This is best achieved through the medical officer of health, who should be notified on suspicion of any case of invasive Hib disease. It is the responsibility of the treating doctor to initiate prophylaxis in the primary case, although in practical terms the household contacts of the index case may also be treated.

### *Recommendations for other groups*

Chemoprophylaxis is not recommended for:

- pregnant women
- occupants of households where there are no children under four years of age other than the index case
- occupants of households where all contacts younger than four years have completed their immunisation series.

### *Dosage*

Rifampicin prophylaxis for Hib disease is given orally once daily in a dose of 20 mg/kg per day to a maximum of *600 mg per day for four days*. The dose for infants less than one month old 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 15). The medical officer of health will advise on the availability of rifampicin supplies.

### Side effects

Rifampicin causes orange discoloration of urine, sputum and tears, and staining of soft contact lenses. The colour change in body secretions is harmless, but patients should be warned and advised not to wear soft contact lenses. Rifampicin increases the hepatic metabolism of oral contraceptives, and women on these should be reminded of the seven-day rule: to use extra contraceptive precautions during antibiotic therapy and following completion of the course of antibiotics use extra contraceptive precautions until after seven consecutive days on the active pills (hormone containing, not sugar pills) of oral contraceptive.

For more details on control measures, refer to *Control of Communicable Diseases Manual*.<sup>11</sup>

## References

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