2012 Antigen Review for the New Zealand National Immunisation Schedule: *Haemophilus influenza* type b

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Prepared for:
New Zealand Ministry of Health

Prepared by a scientific team incorporating the
Immunisation Advisory Centre, The University of Auckland
Institute of Environmental Science and Research Ltd.

February 2013

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Executive summary

Haemophilus influenzae is responsible for a number of diseases including meningitis, pneumonia and epiglottitis. It is a human pathogen and spreads via the transfer of respiratory secretions. Carriage of *H. influenzae* in the nasopharynx is intermittent and varies with age, which peaks in preschool children. The polysaccharide capsule is the most important virulence factor and *H. influenzae* with the serotype b capsule cause the vast majority of human disease. Vaccines against *H. influenzae* serogroup b (Hib) have been developed using the polyribosylribitol (PRP) capsule polysaccharide as the immunogen. Conjugation of the polysaccharide to a protein carrier has provided an effective vaccine that can be administered to infants and elicits a protective immune response. The vaccine reduces carriage of Hib by interrupting the spread of the organism to non-vaccinated populations, the herd effect.

This report summarises research on Hib vaccines and vaccination published during 2009 – 2012. A full review of data and vaccination schedules was not conducted during an edit in 2014.

The number of cases of invasive Hib disease in New Zealand (NZ) has fallen dramatically since the introduction of the Hib conjugate vaccine in 1994. In 2011, there were only eight cases of invasive Hib disease, three of whom were in the under-five year old age group and two of whom were in the under-one year old age group. In 2012, provisional data indicated there was only one case of Hib invasive disease in the under-five year old age group who had been fully immunised. There were no cases in the under-one year old age group. The current immunisation schedule has maintained control of invasive Hib disease in NZ.

There are a number of vaccines available for the control of invasive Hib disease. The monovalent Hib conjugate vaccines have the PRP polysaccharide conjugated to tetanus toxoid (Hib-T), diphtheria cross-reactive material (Hib-CRM197), or meningococcal outer membrane protein (Hib-OMP). The monovalent Hib conjugate vaccines have been used as primary or booster doses in different immunisation schedules. In NZ, the monovalent Hib-T (Act-HIB) is used as the booster dose. All have an excellent safety record and no safety concerns were identified in the current literature search.

To minimise the number of injections in the immunisation schedule and reduce the number of visits to healthcare facilities, a number of vaccines have been combined. This includes vaccines containing Hib conjugate and there is a range of different Hib conjugate-containing vaccines. Most contain the diphtheria, tetanus and acellular pertussis (DTaP) antigens plus Hib-T and may contain inactivated polio virus and hepatitis B antigen. These vaccines are generally used in the primary vaccination schedule. NZ currently uses a DTaP-HepB-IPV/Hib vaccine (Infanrix-hexa®) in a three dose primary schedule. All these multivalent combinations have been shown to have an excellent safety record and no safety issues were identified in the literature search. Other multivalent vaccines are available including HibMenC, HibMenCY and HibHBV conjugate vaccines.

Carriage of Hib is age related and is most common in preschool children. Vaccination with Hib conjugate vaccine reduces carriage of the organism preventing spread to vulnerable groups. Reducing the spread of the organism protects both vaccinated and unvaccinated populations against invasive Hib disease, the herd effect. This plays a critical role in the control of Hib invasive disease.

Monovalent and multivalent vaccines all induce protective levels of antibody. Levels of protective antibody decline, but protective levels have been seen following booster doses of the vaccine up to the age of five years. This indicates that the current NZ schedule should provide adequate protective levels of antibody throughout the most vulnerable period for Hib disease.

The Hib conjugate vaccines have been shown to have high efficacy and effectiveness in the control of Hib invasive disease. This has been established in both developed and developing countries. Estimates of the effectiveness of 100%, and dose specific estimates of 69% for one dose and 92% for two doses have been reported.

There have been no issues regarding implementation of the Hib conjugate vaccines either in the monovalent or multivalent form. No evidence of serotype switching has been reported, but the incidence of invasive non-typeable *H. influenzae* is higher than that of Hib. Serotypes e and f are the most common serotypes reported for *H. influenzae* invasive disease. The case fatality rate is higher for non-typeable *H. influenzae* than for Hib.

The under-five year olds and the under-one year olds remain the most vulnerable population. The current NZ immunisation schedule has successfully controlled the disease in these age groups. Consideration might be given to using a combined Hib-MenC conjugate vaccine as the booster dose and whether two or three doses should be used in the primary schedule. Both would require a cost benefit analysis.

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Prepared as part of a Ministry of Health contract

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This review is one of a series of 18 antigen reviews presented in 15 individual reports.

February 2013 (edited December 2014)

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Abbreviations

ACIP	Advisory Committee on Immunisation Practices
AEFI	Adverse Event Following Immunisation
CFR	Case Fatality Rate
DTaP	Diphtheria, Tetanus and acellular Pertussis
GAVI	Global Alliance for Vaccines and Immunization
GMT	Geometric mean titres
H. influenzae	*Haemophilus influenzae*
Hib	*Haemophilus influenzae* serotype b
Hib-OMP	meningococcal outer membrane protein
Hib-T	monovalent Hib conjugate vaccines have the PRP polysaccharide conjugated to tetanus toxoid
NZ	New Zealand
PRP	Polyribosylribitol phosphate
SAE	Serious Adverse Event
UK	United Kingdom
US	United States
WHO	World Health Organization

Acknowledgements

The Immunisation Advisory Centre (IMAC) and the University of Auckland appreciates the opportunity to undertake literature reviews of the specific vaccines under consideration for, or currently in use for the NZ national immunisation programme. This work was commissioned by the Ministry of Health, to inform decision-making for changes to the schedule and to enable up-to-date clinical guidelines to be incorporated into the NZ Immunisation Handbook 2014. These documents were prepared by IMAC, in collaboration with Environmental Science and Research (ESR), under contract to the Ministry of Health, and were reviewed by members of the Prescription and Therapeutics Advisory Committee (PTAC) immunisation subcommittee 2013 to Pharmac. The authors would also like to acknowledge Val Grey, Graphic Designer, Faculty of Medical and Health Sciences, The University of Auckland, for her assistance with design and layout of these documents.

1. Background – *Haemophilus influenzae* and vaccination

Haemophilus influenzae is a leading cause of morbidity and mortality worldwide in children under five years of age. The organism is a non-spore forming Gram-negative coccobacillus and was first described by Kock in 1883 and isolated from post-mortem cultures by Pfeiffer in 1889. There are two forms of the bacterium, encapsulated and non-encapsulated. Encapsulated strains produce a polysaccharide capsule which is a major virulence factor. The capsule can be distinguished antigenically into six serotypes, a-f. Prior to the introduction of a vaccine the majority of *H. influenzae* infections were due to strains producing the serotype b polysaccharide. These are commonly referred to as Hib. Non-encapsulated strains lack the genes to produce the polysaccharide capsule and are non-typeable. Strains which have the capsule genes may stop producing the polysaccharide under certain conditions but can be typed by detection of the capsular genes. The Hib polysaccharide is composed of polyribosylribitol phosphate (PRP) and this is believed to be very effective in preventing recognition and elimination of the pathogen by the host defence mechanisms

Hib is a human pathogen and spreads via the transfer of respiratory secretions. Before the introduction of a vaccine, 95% of *H. influenzae* disease in infants and children was caused by Hib. Hib colonises the nasopharynx and carriage of the organism varies with age. Prior to vaccine use, 3-5% of pre-school children carried the organism; carriage rates were low in infants under six months old and peaking in pre-school children before gradually declining in adulthood. Carriage rates in different ethnic groups vary considerably (1).

Hib can cause a number of diseases of the respiratory tract including otitis media, sinusitis and bronchitis. Invasive diseases caused by Hib include meningitis, epiglottitis, pneumonia and septicaemia. The annual incidence of Hib invasive disease in the US prior to vaccine use was 20-88 per 100,000 in the under five year olds (2). Hib was responsible for the majority of epiglottitis cases prior to the Hib vaccine with rates as high as 32 per 100,000 populations (3). Case fatality rates from Hib meningitis are high and sequelae following infection include deafness and cerebral palsy.

The major risk factors for infection include age, race, household crowding, day-care attendance and medical conditions (asplenia, complement/antibody deficiencies, and HIV infection). Children under one years of age are at highest risk of disease followed by children under five years of age and interventions are primarily aimed at reducing the burden of disease in these age groups.

The polysaccharide capsule of Hib is the major antigen used in Hib vaccines. Vaccines using the PRP polysaccharide alone have been developed but are poorly immunogenic in children under two and do not generate immune memory. Conjugate vaccines are more effective and can elicit antibody responses in infants. A range of Hib PRP conjugate vaccines are available but at present six are licensed for use in New Zealand (NZ). Infanrix-hexa® (GSK) is a hexavalent vaccine containing a Hib PRP conjugate component; Act-HIB® (Sanofi-Aventis) and Hiberix® (GSK) are monovalent Hib conjugate vaccines; Comvax (Merck) is a combined Hib and HepB vaccine; Infanrix-Hib (GSK) is a combined DTaP Hib vaccine; Infanrix-IPV-Hib (GSK) is a combined DTap Hib and polio vaccine.

Hib conjugate vaccines have been very effective in reducing the rates of disease in both developed and developing countries. Declines in invasive Hib disease of 90-98% have been recorded. Initiatives such as the Global Alliance for Vaccines and Immunisation to aid introduction of Hib vaccine into the immunisation schedule of developing countries have been successful in helping reduce the burden of disease in infants (4, 5).

2. Methodology for review

2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2012 NZ antigen review and the specific specifications for *H. influenzae* type b pertussis vaccines. These are listed below. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around Hib vaccines for NZ.

- General specifications
  - Safety
  - Effectiveness
  - Implementation issues (practicality and possible impact on uptake)
  - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination
  - Different options of placement on the schedule, based on international findings and best practice
  - Different vaccine options and comparisons between the options

2.2 New Zealand epidemiology

In NZ, Hib is an infectious disease notifiable to Medical Officers of Health. The NZ epidemiological information presented is based on national notification and laboratory-based surveillance summarised in the Notifiable and Other Diseases in NZ, 2011.

2.3 Literature search strategy

The points below have formed the focus of the literature search:

- Safety
- Effectiveness in disease control
  - Effect on
    - Indirect effects/herd immunity
    - Duration of protection
  - Immunogenicity
- Implementation issues (practicality of and possible impact on uptake)
- Differences that need to be considered for each age group, and groups with particular needs
  - Age
  - High-risk groups – definition of which groups most likely to benefit and which vaccines/s
- Different option for placement on the schedule, based on international findings and best practice
- Different vaccine options and comparison between the options
- Current international research and evidence around use of vaccines

2.3.1 Medline search terms and strategy

MeSH term: Haemophilus influenza type b Vaccin*, focus, subgroups Haemophilus influenza type b, Haemophilus influenza vaccines

2150

Limit to Humans, English, 2009 – current

293

NOT Cost* Attitud*Survey Qualitative Parents Interview

245

Remove duplicates

245 (keep and view)

2.3.2 Cochrane Library search terms and strategy

Search term HiB Vaccin*

4 results (keep and view)

2.3.3 Scopus search terms and strategy

Haemophilus influenza type b Vaccin* Published 2011 – present

217

Limit to: Medicine English

175

Exclude Letter, Short survey, editorial

152

Reject social science, Arts and Humanities, Veterinary articles.

60 (keep and view)

Delete duplicates

Final EndNote library after literature search and revisions 264

2.3.4 Grey literature

Conference abstracts were sought to include data that has not yet been published, particularly from the key infectious diseases conferences for 2011 and 2012 – there were no abstracts or posters accessed. One book chapter was added.

2.3.5 Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. A further 14 articles were accessed.

2.3.6 Final library

The final library includes 279 references. Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.

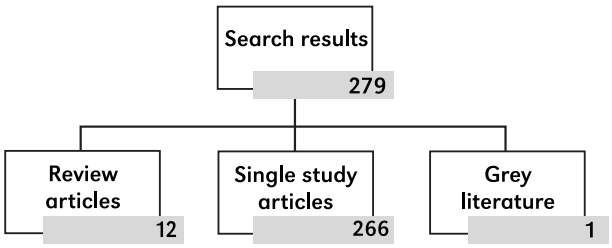

Figure 1. Flow of selection of articles for review

2.4 Participants/populations

The populations considered here are infants eligible for universal vaccination.

2.5 The interventions included are:

2.5.1 Infanrix®-IPV+Hib

Infanrix®-IPV+Hib (GlaxoSmithKline) contains diphtheria toxoid, tetanus toxoid, three purified pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN/69 kD outer membrane protein)] adsorbed on aluminium salts. It contains three types of inactivated polio viruses (type 1: Mahoney strain; type 2: MEF-1 strain; type 3: Saukett strain) and contains purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b (Hib), covalently bound to tetanus toxoid.

A 0.5ml dose of vaccine contains not less than 25Lf (≈ min. 30IU) of adsorbed diphtheria toxoid, not less than 10Lf (≈ min. 40IU) of adsorbed tetanus toxoid, 25µg of PT, 25µg of FHA, 8µg of pertactin, 40D antigen units of type 1 (Mahoney), 8D antigen units of type 2 (MEF-1) and 32D antigen units of type 3 (Saukett) of the polio virus. It also contains 10µg of purified capsular polysaccharide of Hib covalently bound to approximately 30µg tetanus toxoid.

2.5.2 Act-HIB ™

Act-HIB™ (sanofi-aventis), contains the capsular polysaccharide of the *H. influenzae* type b bacterial strain conjugated to tetanus protein. The polysaccharide consists of polyribosyl ribitol phosphate (PRP).

2.5.3 Hiberix®

Hiberix® (GlaxoSmithKline) is a lyophilised vaccine of purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of Hib, covalently bound to tetanus toxoid. Each single dose of vaccine is formulated to contain 10µg of purified capsular polysaccharide covalently bound to approximately 30µg tetanus toxoid.

2.5.4 Menitorix®

Menitorix® (GlaxoSmithKline) *H. influenzae* type b and *Neisseria meningitidis* group C conjugate vaccine. Each 0.5ml dose of the reconstituted vaccine contains 5µg of *H. influenzae* type b polysaccharide (polyribosylribitol phosphate) conjugated to 12.5µg of tetanus toxoid as a carrier protein and 5µg of *Neisseria meningitidis* serogroup C (strain C11) polysaccharide conjugated to 5µg of tetanus toxoid as a carrier protein.

2.6 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching.

3. Recent New Zealand epidemiology

A vaccine for the control of Hib disease was introduced into the NZ immunisation schedule in 1994. In the years prior to this, the rates of disease were approximately 150 per 100,000 population with the infant population bearing the burden of disease. Following introduction of the vaccine rates have fallen to approximately 0.2 per 100,000.

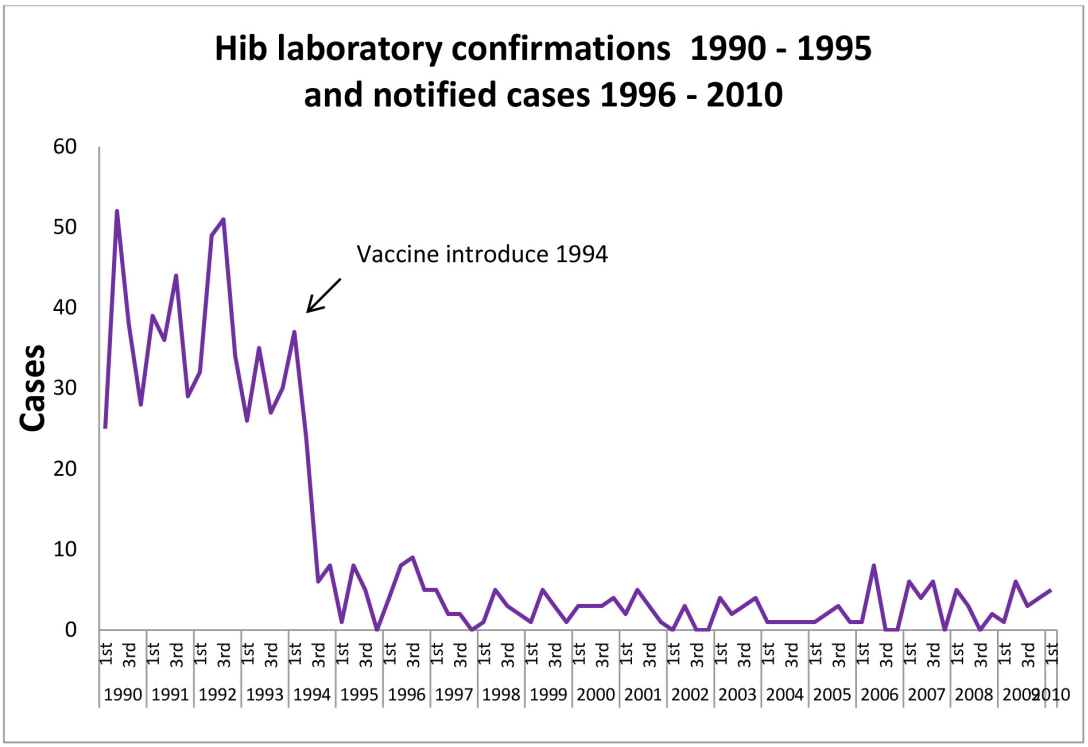

Figure 2. Hib laboratory confirmations and notified cases in NZ during 1990-2010 (ESR).

In 2011, eight cases of Hib disease were notified, a rate of 0.2 per100 000 population. All cases were laboratory-confirmed. Three of the laboratory-confirmed cases were aged <5 years (compared with five in 2010 and four in 2009). The cases were from Northland, Auckland and Capital and Coast DHBs (1 case each DHB). Two were male and one was female and the cases were distributed by ethnic group as follows: Māori, Pacific Peoples and European or Other (6).

The vaccination history was recorded for all three Hib cases aged less than five years. Only one of these cases was immunised with three doses. All three cases were hospitalised: one with meningitis, septicaemia and pneumonia, one with septicaemia and pneumonia, and one with pneumonia (6).

In 2012, there were four laboratory confirmed cases of Hib in NZ, one case in a four year old and the others in adults. The four year old had been fully immunised. The adult cases were an unvaccinated 36 year old, a 48 year old with unknown vaccination status and an unvaccinated 81 year old (7).

Table 1. Number and rate of Hib notifications in New Zealand 1997-2012.

Year	Number	Rate per 100 000	Number in < 1 year olds	Rate per 100 000
1997	9	0.2	3	5.5
1998	11	0.3	3	7.3
1999	10	0.3	2	3.1
2000	13	0.3	5	9.1
2001	11	0.3	2	3.7
2002	3		0	
2003	12	0.3	5	9.1
2004	4		0	
2005	7	0.2	1	1.8
2006	9	0.2	1	1.8
2007	15	0.4	6	10.6
2008	9	0.2	1	1.8
2009	10	0.2	4	7.1
2010	8	0.2	4	7.1
2011	8	0.2	2	3.5
2012	4	0.1	0	

3.1 Summary of NZ epidemiology

The incidence of Hib disease in NZ remains low since the introduction of the vaccine. In 2012, there were four cases and three of these were in adults.

4. Safety

4.1 Objective

The objective of this section is to review the most recent safety data for currently licensed Hib conjugate vaccines. The focus is on studies on the conjugate vaccines. No data is reviewed regarding polysaccharide vaccines as these are not in usage in NZ. Consideration is given to vaccines undergoing clinical trials and vaccines not currently licensed in NZ but have been approved in countries of similar stature. These include the combination Hib plus group C conjugate vaccine, multivalent conjugate vaccines using alternative protein carriers, alternative formulations of conjugate vaccines.

4.2 Outcomes

Outcomes are vaccine safety including adverse events following immunisation (AEFI) and serious adverse events (SAE). Excluded is reactogenicity - injection site reactions and minor systemic reactions - as these are considered as part of the licensure studies.

4.3 Review

There are a wide range of Hib vaccine conjugate formulations currently in use or in development.

The safety of the majority of these vaccines has been addressed in the pre-licensure studies and considered via licensure procedures in the countries in which the vaccines are used. The review below focuses on any more recent data published during 2009-2012.

4.3.1 Multicomponent vaccines

The safety of the investigational hexavalent vaccine $DTaP_2$-IPV-HBV-Hib-T (Hexaxim®) has been assessed in a number of studies. This vaccine is in a fully liquid form and contains the PRP-T (tetanus toxoid) conjugate, but also has a new hepatitis B component derived from the yeast *Hansenula polymorpha* (8). It contains two-component pertussis. Safety data have been described in three studies (8-10).

A South African randomised trial with the investigational vaccine compared three groups: in group 1, 286 infants were given DTaP-IPV-HepB-HibT at six, ten and 14 weeks; group 3, 143 infants were given hepatitis B vaccine at birth and DTaP-IPV-HepB-HibT at six, ten and 14 weeks; as a comparator, in Group 2, 296 infants given DTwP-Hib with hepatitis B and OPV at six, ten and 14 weeks. Of the total, 243, 137 and 242 infants, respectively, completed diary cards for seven days after each vaccination event and serious adverse event reports were collected until six months after the last vaccination. The incidence of injection site and systemic reactions was similar in groups 1 and 3 and lower than group two, as would be expected with group 2 containing a whole cell pertussis vaccine. A total of 80 SAE were reported in the study across experimental and control groups. The incidence of SAE was similar across all study groups and none were considered vaccine related. Four subjects experience fatal SAE - one described as 'death of natural causes during sleep before the first primary series', bronchitis one month after the third vaccination, pneumonia one month after the third vaccination and a RTI and suspected TB with HIV positivity (9).

Similarly in a study 412 Thai infants compared immunisation with $DTaP_2$-IPV-HBV-Hib-T (group 1 n=206) to a control vaccine, $DTaP_3$-IPV-HBV/Hib-T (Infanrix-hexa®) (group 2, n=206), which were given in an infant course at two, four and six months of age. Of the total enrolled, 197 of group one and 196 of group two completed the study. Parents of infants completed diary cards for seven days post each vaccination event and serious adverse event reports were collected until six months after the last vaccination. The frequency of solicited and unsolicited events were similar between both groups, except pyrexia was more frequent in group one (10.5%), although following a post hoc analysis, this was not considered significant. There were six SAE in group 1 and eight in group 2, which were all considered to be common childhood symptoms and not related to vaccination (10).

In an Argentinian study, 624 infants were randomised equally to receive $DTaP_2$-IPV-HBV-Hib-T (Hexaxim®) or $DTaP_2$-IPV/Hib-T (Pentaxim®) plus the HepB vaccine Engerix-B® at two, four and six months of age. The incidence of SAE was similar across both groups and none were considered vaccine related (8).

Another investigational vaccine containing the tetanus toxoid Hib PRP conjugate is the HibMenCY-TT vaccine. This vaccine has been assessed for safety in a number of studies. At total of 352 SAE were recorded, out of the 5893 infants in the three studies, who received either the experimental or control vaccines (monovalent Hib-TT conjugate or MenC-CRM_{197} and Hib-TT), as a primary infant course at two, four and six months of age and a booster at 12-15 months; of the reported SAE, 245 were in the HibMenCY-TT

vaccine group. Only three of these were considered HibMenCY-TT vaccine-related: one case of a hypotonic hyporesponsive episode and two cases of fever (11-13).

The literature search did not identify any recent publications addressing the safety of the other Hib conjugate vaccines listed above when used in a primary course of vaccinations or a booster dose (14-29).

4.3.2 Concomitant use

Co-administration of the Hib conjugate vaccine either in the monovalent or multivalent form with other routine vaccines used in the immunisation schedule has not raised any safety concerns based on the publications identified by the literature search (10, 20, 21, 25, 27, 30-33).

4.4 Summary vaccine safety

There have been no concerns raised in publications identified by the literature search regarding either monovalent or multivalent Hib conjugate vaccines. Co-administration with other routine vaccines has not identified any safety concerns.

5. Immunogenicity, efficacy, effectiveness and vaccine impact

5.1 Objective

The objective of this section is to review the most recent performance data for currently licensed Hib vaccines and those undergoing clinical trials. Consideration is given to relevant immunogenicity data, efficacy and effectiveness studies that contribute to the current understanding of the effectiveness of Hib vaccines and evidence of their impact in populations.

5.2 Outcomes

The outcomes considered for this review are:

- Meningitis
- Pneumonia
- Epiglottitis
- Immunogenicity
- Nasopharyngeal carriage
- Indirect effect/herd immunity
- Duration of protection

5.3 Review

The capsule of *H. influenzae* is the major virulence factor. It is thought that the presence of the capsule allows the pathogen to survive in the blood of the host by preventing bactericidal attack by the complement system and opsonisation. The Hib capsule is very effective in shielding the organisms from the innate defences of the host. The non-encapsulated *H. influenzae* can colonise and spread from the nasopharynx to adjacent areas such as the middle ear, sinuses and respiratory tract, but are significantly less effective at causing disease. The non-Hib encapsulated strains are also capable of causing disease. The genes encoding capsule production in Hib have been identified and most invasive Hib isolates have a duplication of the capsulation b locus with some having up to five copies. It has been found that strains isolated from children with Hib conjugate vaccine failure were more likely to contain multiple copies of the locus suggesting that amplification of the locus may play a part in the vaccine failure (34).

5.3.1 Carriage

Hib, like meningococci, only colonises humans and therefore, the source of any invasive isolate must be in contact with a carrier of that isolate. The majority of studies looking at carriage of Hib were conducted before the introduction of the Hib vaccine. Carriage rates were highest in children under five years old and increased with increasing number of siblings, attendance at day-care and contact with an index case of Hib disease (35). Following the introduction of the conjugate vaccine, rates of carriage fell significantly in both vaccinated and unvaccinated populations. The persistence of Hib carriage in fully vaccinated populations has been seen especially in ethnic populations, such as Native Alaskans, American Indians and Australian Aboriginal peoples.

It has been suggested that monitoring of Hib carriage may provide an early warning system for invasive disease and allow interventions to be implemented (36). An upsurge in Hib carriage in the UK in 2005 was thought to be due to the waning of antibody levels in the absence of a booster dose and that Hib continued to circulate among school-aged children serving as a reservoir for the organism (37).

Recent studies have examined the carriage of Hib in Brazilian, Australian, South American and Nepalese children (1, 36, 38, 39). In Nepalese children, a carriage rate of 5% was determined prior to the introduction of the Hib vaccine (40).

Brazil introduced a Hib vaccine into the immunisation programme in 1999 and rates of disease fell significantly. A recent survey of day-care centres showed that the rate of Hib carriage was 0.7% (38). In another study, carriage rates were determined in two South American countries: Argentina, which has a booster dose, and Colombia that only uses a primary vaccination series. The Hib carriage rates were too low for any meaningful distinction between the two schedules to be determined (39).

In a study looking at children in the Northern Territories of Australia, carriage was significantly higher in the indigenous (3.4%) than in the non-indigenous (0.2%) population despite a high vaccine uptake (1). Reasons for this appear to be a younger age of colonisation (median age 3.5 months in indigenous versus 6.9 months in non-indigenous) with

an inadequate vaccine response or waning antibody levels low enough to permit colonization. Furthermore, a highly vaccinated population means a decrease in natural boosting. The younger age of Hib colonization in Australian indigenous children living in communities with high vaccine uptake is similar to the age of Hib colonisation seen in developing countries. The authors commented that lower serologic responses to Hib-OMP vaccines by rural indigenous children compared to non-indigenous has already been shown previously, and therefore, the accepted level of antibody concentration for protection against Hib carriage may need to be higher than the currently accepted level, and they suggest a level of ≥5µg/mL.

The Hib conjugate vaccine has clearly had a role in reducing the carriage of the organism, and therefore, in the persistence and spread of invasive disease. On occasions, the supply of Hib vaccine has been limited and has led to a modification of the schedule. This occurred most notably in the US in December 2007. Specific batches of both Pedvax® and Comvax® were recalled and the Hib booster dose at 12-15 months was deferred. Two studies looked at the effect of the deferred booster on carriage rates in children under five or six years old. No change in the carriage rates was observed and the rate of carriage remained low (41, 42).

5.3.2 Immunogenicity

The Hib conjugate vaccines are able to induce antibodies that prevent Hib infection and the universally accepted correlate of protection is 0.15 µg/ml of anti-PRP antibody. A level of 1.0 µg/ml is thought necessary for long term protection and these values have been used in all studies on the immunogenicity of PRP-containing vaccines.

All licensed vaccines have the ability to induce anti-PRP antibody levels of 0.15 µg/ml or greater using the recommended dose schedules. However, individual vaccines using different conjugates may differ in the dose to achieve this level. For instance, it was recognised that Hib-OMP vaccine induced a high level of antibody (>1 µg/ml) after the first dose at two months of age making it the preferred vaccine for the immunisation of high risk populations. However, the peak antibody titre after a booster of this vaccine at 12-15 months was lower than for other vaccines. Similarly, it was found that Hib-CRM_{197} vaccine did not induce protective anti-PRP antibody levels until after the third dose. The licensed vaccines, however, all provide sufficient antibody levels for protection against Hib disease based on currently accepted antibody-titre levels. Note, however, the Australian experiences with indigenous populations where higher immunogenicity titres may be necessary to obtain more effective herd immunity (1). It is unknown if the same effect is seen in the NZ indigenous population.

The immunogenicity of NZ licensed vaccine Infanrix-hexa® has recently been reviewed for schedule at three, five and 11 months, which differs from the NZ schedule. The studies reviewed showed that this schedule produced protective levels of antibody of >0.15µg/ml after the third dose in 99.7% of participants (43).

The immunogenicity of investigational vaccines that include a conjugated PRP component has also been reported. The $DTaP_2$-IPV-HBV-Hib vaccine, Hexaxim®, was shown to induce antibody levels of >1 µg/ml in 85% of participants measured one month after the third dose of a two, four and six month schedule. This was similar to the control group using DTaP-IPV/PRP-T and hepatitis B vaccine (83.7%) and therefore, non-inferior in terms of immunogenicity (8). A similar study in Thai children with the same schedule showed that 97.9% of participants had protective levels of antibody and the vaccine was non-inferior to the control vaccine DTaP-IPV-HepB//PRP-T Infanrix-hexa® (10). South African infants on an Expanded Programme on Immunisation (EPI) schedule (six, ten and 14 weeks of age) also showed that Hexaxim® was non-inferior for protective levels of antibody when compared with DTwP-Hib, hepatitis B and OPV vaccines (9).

Data was recently published from a phase II trial of a vaccine in which the type (PRP-OMP or PRP-T) and quantity (3µg or 6µg PRP-OMP, 12µg PRP-T) of PRP conjugate in a fully liquid hexavalent vaccine ($DTaP_5$-HBV-IPV-Hib) were varied. Infants were vaccinated at two, three, four and 12 months and the immunogenicity of each formulation was measured after each dose. Differences between each formulation were observed. After the third dose, the antibody levels of the PRP-OMP containing vaccines were four to five-fold higher than the PRP-T vaccine. However, the post-dose four antibody levels in the PRP-T vaccine were twice those of the PRP-OMP vaccine formulations. These results were consistent with previous observations (44).

The combination of Hib and meningococcal polysaccharides in a conjugate vaccine has been examined in immunogenicity studies. The HibMenCY-TT vaccine was non-inferior in terms of antibody response at levels >1 µg/ml when compared to ActHib in infants vaccinated at 2, 4, 6 and 12 -15 months (13). A similar study examined the antibody response one month after the third dose of HibMenCY-TT given at 2, 4, and 6 months compared to a control group given Hib-TT. Significantly more of the participants who received the HibMenCY-TT (93.5%) had anti-PRP antibody levels of >1 µg/ml than those who received the Hib-TT (85.8%) (11).

The combination of different components in a multivalent vaccine may affect the antibody response to any of the individual component when compared to the individual vaccine. This has been reported previously for the Hib response when combined with DTaP in the primary vaccinations. The antibody levels for Hib are significantly reduced when the conjugated polysaccharide is combined with DTaP reducing vaccine effectiveness in the under-five year olds (45-47). However, the clinical significance of these reduced antibody responses is unknown. The successful elimination of Hib in countries using multivalent vaccines is testament to the effectiveness of the vaccines despite the reduced antibody response.

5.3.3 Efficacy and effectiveness

A recent systematic review and meta-analysis of controlled clinical trials looked at the dose-specific efficacy of Hib conjugate vaccines. It was found that the pooled vaccine efficacy against Hib invasive disease was 59%, 92% and 93% after one, two and three doses, respectively, in a primary course. Efficacies against meningitis for one, two and three doses were 62%, 92% and 88% (lower than two doses due to one trial only estimating one and two dose efficacy). The efficacy of Hib vaccines against confirmed Hib pneumonia for one dose was 67%, and 91% for two and three doses (mid-point estimate). All the studies included in the meta-analysis demonstrated very high vaccine efficacy even at one, and particularly, two doses suggesting that all dosing regimens used currently are robust (48). A systematic review of studies examining Hib conjugate vaccines estimated effectiveness of 95% after three doses of vaccine. The authors questioned the need for further Hib vaccine effectiveness studies given the high number of studies already done (49). Studies examining the effectiveness of hexavalent vaccines used in Germany showed them to have an effectiveness of 100% (50).

5.3.4 Herd immunity

The ability of a vaccine to provide protection through the reduction in carriage and transmission of a pathogen is known as herd immunity. This has previously been identified as an important consequence of introducing the Hib conjugate vaccines. In 1992, the UK introduced the Hib conjugate vaccine in a primary series at two, three and four months with a catch-up campaign for the under four-year olds. This led to a dramatic fall in the invasive Hib disease, not only in this age group, but also in unvaccinated older children and adults - a herd effect. A study in India found that, although only 35% of children under two received three doses of Hib conjugate vaccine, there was a 65% fall in the number of Hib cases (51). The herd effect has been observed in other populations (2, 52, 53).

In 1998, the UK observed an increase in Hib invasive disease in children under four, six years after the introduction of the vaccine. This increase was thought to be due in part to a change in vaccine (DTwP plus Hib to DTaP plus Hib), but also to the fact that no booster was included in the immunisation schedule. It was reasoned that immunity to Hib waned in the cohort of children who received the primary vaccination but no booster, such that they were susceptible to colonisation with the organisms (37). This provided a reservoir for the spread of Hib and an increase in the number of cases. It appears that herd immunity plays a critical role in the control of Hib disease (54, 55). A booster dose was introduced in the UK immunisation schedule in 2006, which has led to the re-establishment of herd immunity (56).

5.3.5 Duration of protection

Antibody levels against PRP are known to decline between the primary series of vaccinations and the booster dose (55). Recent publications have shown that the percentage of infants aged 12 – 15 months with protective levels of antibody prior to a booster is between 65% and 82% (22, 57-59). Measurement of anti-PRP antibody levels, two years following a booster dose of HibMenC-TT, showed nearly all participants (98.7%) maintained protective levels of anti-PRP antibody. Long term persistence of anti-PRP antibodies was measured in infants who have received a booster dose of HibMenC-TT vaccine. All participants who received the booster vaccine had protective levels of antibody at five years of age (22). A similar study measuring the antibody levels following a booster dose of HibMenC-TT at 12 – 15 months of age showed 98% of participants had protective antibody levels two years following the booster dose (59). These results

indicate that a primary series followed by a booster dose in the second year of life should provide sufficient antibody levels to protect the under-five year olds from invasive Hib disease.

5.3.6 Vaccine impact

The impact of a vaccine is its ability to reduce the burden of disease within a population in a cost effective manner. The major age group affected by Hib disease are the under-five year olds and especially the under-one year olds. All Hib vaccine campaigns have been aimed at reducing the incidence of disease in these age groups.

When introduced, the impact of Hib conjugate vaccines has been seen in both developed and developing countries. In NZ, the addition of the conjugate vaccine to the schedule in 1994 reduced the rate of disease in the under five-year olds from 36.4 per 100,000 in 1993 to 1.7 per 100,000 in 1999.

In the UK, the incidence of invasive Hib incidence in children aged under five years fell from 21/100,000 - 44/100,000 in the pre-vaccine period to 0.63/100,000 in 1998, six years after the introduction of the vaccine with an estimated vaccine failure rate of 2.2/100,000 vaccinees. However, invasive Hib disease increased after 1999, particularly in toddlers, and peaked in 2003. This was attributed to an earlier than expected decline in Hib antibodies after primary immunisation, waning of herd immunity offered by the initial catch-up campaign and use of a less immunogenic vaccine in 2000–2001. In response to the resurgence, a Hib vaccine containing whole-cell pertussis was reintroduced in 2002, followed by a childhood Hib booster campaign in 2003. In 2004, a different combination vaccine was introduced with a superior Hib response (and less reactogenicity). A routine 12-month Hib booster was added to the schedule in 2006 (37). The pattern of Hib disease in the UK is illustrated in Figure 3 using number of laboratory reports.

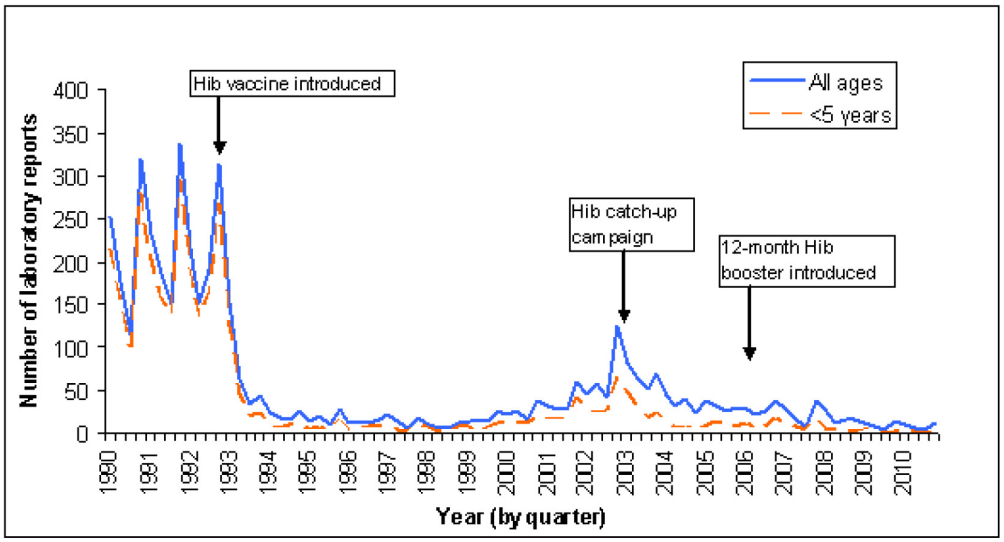

Figure 3. Laboratory reports of *Haemophilus influenzae* type b in the UK 1990-2010 (60)

In the US, rates have decreased 99% to less than 1 per 100,000 population in the under-five year olds following vaccine introduction (61, 62).

Following the introduction of Hib vaccines in Canada in 1988, the incidence of reported Hib disease decreased by 94% from an average of 1.51 cases per 100,000 population during the period 1981 to 1985 (385 cases per year) to an average of 0.09 cases per 100,000 for the 2006 to 2010 period (31 cases per year) (Figure 4). Between 2006 and 2010, the greatest numbers of cases were in infants less than one year of age (2.08 cases per 100,000) and children aged one to four years (0.22 cases per 100,000). Most paediatric cases occurred in unimmunised children, children too young to have received their primary series, or those with either an immunodeficiency or other chronic illness (63).

The impact of the vaccine on Hib disease is clearly evident.

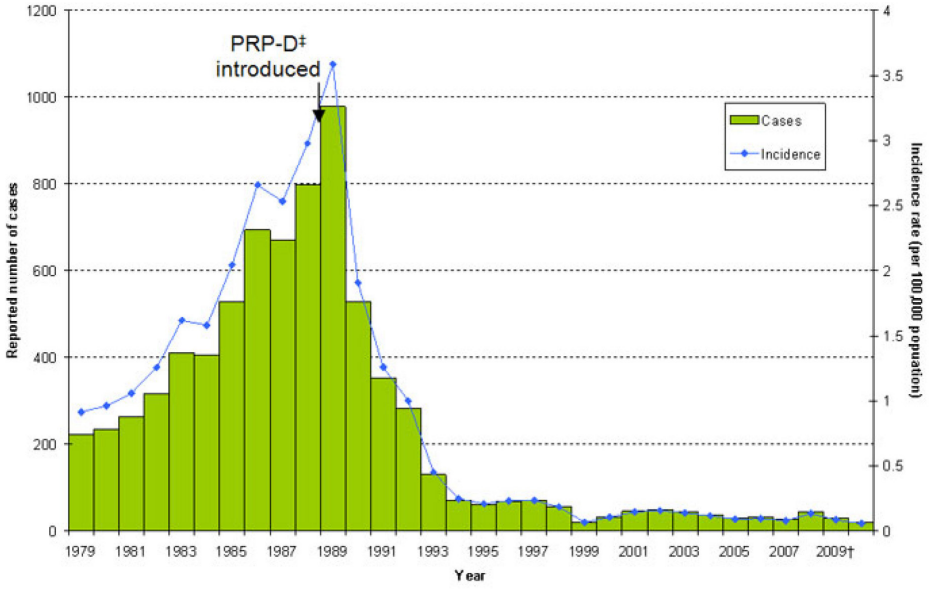

Figure 4. Reported cases and incidence (per 100,000 population) of *Haemophilus influenzae* type b (Hib) in Canada by year, 1979 to 2010 (63)

5.3.7 Serotype Replacement

One potential effect of vaccine introduction and the reduction in carriage of Hib is the emergence of non-type b and non-typeable *H. influenzae* in invasive disease, known as serotype replacement. Initial surveillance following vaccine introduction led to reports of serotype replacement, but this has not been confirmed (55, 64-69). One Canadian study showed an increase in the risk of non-Hib invasive disease in children under five years of age which was suggestive of serotype replacement (2). Surveillance has identified non-typeable and *H. influenzae* type f as the most common cause of *H. influenzae* invasive disease in Canada and Europe (2, 66). In the US, non-typeable *H. influenzae* causes 62.5% of invasive disease in children under five years of age (70). Continuing surveillance of *H. influenzae* serotypes is important even after the successful reduction of Hib disease.

5.4 Summary of effectiveness

Carriage rates, which are highest in children under five years of age, have dramatically reduced since the introduction of national vaccination programmes. However, carriage rates in some populations may increase with the risk of the return of invasive disease. This may be due to waning antibody level from factors such as a national programme without a booster dose, different immunogenicity responses by some communities, such as indigenous populations, and different types of conjugate. Reduced carriage in the community may lead to reduced boosting in the community and resurgence in older disease, although, this has not been demonstrated.

All Hib conjugate vaccines on the international market, both monovalent and in combinations, produce antibody titre levels that meet the currently acceptable definitions of protection. However, immunogenicity titres may need to be higher in some communities to obtain more effective herd immunity, such as with indigenous Australians. Different immunogenicity levels are seen with different vaccine formulations. The PRP-OMP vaccines consistently induce higher initial antibody levels than PRP-T vaccines following a primary course, but lower antibody levels following the booster dose in the second year of life. Multivalent vaccines can reduce the Hib response when combined with DTaP vaccines; however the clinical significance of this is unknown.

The high efficacy and effectiveness of Hib vaccines have been clearly demonstrated by the virtual elimination of Hib disease in countries implementing the vaccine. These vaccines are highly effective after a primary course of two or three doses.

H. influenzae conjugate vaccines show very strong herd immunity effects. Boosters in the second year of life appear important for herd immunity and add to longevity of effectiveness. Vaccination schedules with a primary course of two or three doses and a booster in the second year of life have been shown to give good protective antibody levels to five years of age.

As of early 2013, serotype replacement has not been shown to be a problem for disease, but on-going surveillance remains important.

6. Age-specific issues

6.1 Objective

This section considers the differences that need to be considered for various age groups. Literature for morbidity and mortality is included. Issues around the use of vaccines in age groups other than infants and children are also considered.

62 Review

6.2.1 Burden of disease by age

The burden of Hib disease falls mainly in the under-five years old, and especially, in the under-one year olds; all vaccination strategies are aimed at reducing disease in this age group. Where Hib vaccination has been introduced, it has successfully reduced the incidence of Hib disease in this age group. For NZ, the number of invasive Hib infections in the under-one year olds has been less than ten since 1997. A shift in the distribution of serotype has been seen in invasive isolates with non-typeable strains replacing Hib as the most common isolates and this is occurring in older adults (71). In infants, non-Hib infection occurs at an earlier age than Hib infection (66).

The case fatality rate (CFR) for invasive Hib disease is approximately 3% and this has not changed from the pre-vaccine era (66). The CFR for non-typeable *H. influenzae* are much higher and have been estimated at 13-20% in adults (55). CFR for infants with non-typeable *H. influenzae* are approximately 17% (66). Thus the incidence of non-type b *H. influenzae* is now higher than that of Hib and has a higher CFR.

Adult vaccination with Hib conjugate vaccine is not part of the NZ immunisation schedule, except for pre and post splenectomy. The currently available Hib conjugate vaccine is not licensed for use in the adult population, but it is unlikely its use in adults will present any safety or immunogenicity issues. Should the number of cases of Hib disease in the adult and elderly population rise due to waning antibody levels and lack of natural boosting, vaccination in this population will need to be considered.

6.3 Summary of age-specific issues

The burden of disease is the under-five year olds and the under-one year olds. The current vaccination schedule for Hib has successfully controlled the disease in this age group. Monitoring of the disease in the older age groups and determination of the type to identify any serotype switching should continue.

7. Vaccine options

7.1 Objective

The objectives of this review are to consider the vaccine options available to NZ for *H. influenzae* type b in terms of available vaccines and schedules. Consideration is given to the effect of these vaccines the *H. influenzae* populations in NZ, their pathogenicity and the implications for herd immunity.

7.2 Review

There are a number of options for Hib conjugate vaccines, ranging from monovalent to multivalent. The vaccination schedule reduces the carriage of Hib, decreasing the spread of the organism, thereby, reducing exposure of vulnerable populations.

There are a wide range of Hib vaccine formulations that are currently in use or are in development. Monovalent Hib conjugates and multivalent vaccines containing the Hib PRP conjugate are available. The demand for multivalent vaccines is driven by the desire to minimise the number of injections required to attain full immunisation and also to improve the rate of coverage by vaccination by reducing the number of health visits needed.

Most of the multivalent vaccines require re-suspension of the PRP component in the liquid form of the other components. Four of the multivalent vaccines, Hib-OMP-HBV, DTwP-Hib, $DTaP_5$-IPV-Hib and $DTaP_2$-IPV-Hib come in liquid form.

7.2.1 Types of Vaccines

The range of international vaccines which include a Hib conjugate component is given in table 2.

Table 2. International vaccines with Hib conjugate component

Hib conjugate vaccine	Trade name	Hib conjugate vaccine	Trade name
Hib-T	Act-HIB Hiberix	$DTaP_5$-IPV-Hib-T	Pediacel
Hib_{syn}-T*	Quimi-Hib	$DTaP_5$-IPV/Hib-T	Pentacel
Hib-CRM	HibTITER Vaxem HIB	DTwP-IPV/Hib-T	Pentact-Hib
Hib-OMP	Pedvax HIB	$DTaP_3$-Hib-T	Infanrix- Hib
Hib-OMP-HBV	Comvax	$DTaP_3$-IPV/Hib-T	Infanrix-IPV-Hib
$DTaP_2$/Hib-T	TriHIBit	$DTaP_2$-IPV-HBV-Hib-T	Hexaxim
$DTaP_5$/Hib-T	Actacel	$DTaP_2$-IPV/Hib-T	Pentaxim
DTwP-Hib-T	Quadrovax	$DTaP_3$-IPV-HBV/Hib-T	Infanrix-hexa
DTwP/Hib-T	TetrAct-Hib	Hib-MenC-TT	Menatorix
		Hib-MenCY-TT	
*Hib_{syn} indicates the PRP component is synthetic			

7.2.2 Types of Conjugates

There are three main conjugates in use with Hib vaccines:

- Hib-T indicates PRP is conjugated to tetanus toxoid,
- Hib-CRM indicates PRP is conjugated to the mutated diphtheria toxoid CRM_{197}
- Hib-OMP indicates PRP is conjugated to *Neisseria meningitidis* group b outer membrane protein complex.

7.2.3 Monovalent vaccines

Five monovalent Hib conjugate vaccines are available and differ in their conjugate or manufacturing company. PRP can be conjugated to tetanus toxoid (as used in Act-HIB™ 10 µg of PRP to 24 µg toxoid, Hiberix® 10 µg of PRP to 25 µg toxoid), CRM, a mutant form of diphtheria toxin known as cross-reacting material CRM_{197} (10 µg of PRP to 25 µg CRM_{197}), or OMP (7.5 µg of PRP to 125 µg of *Neisseria meningitis* group b outer membrane protein complex). A Hib conjugate vaccine containing synthetic PRP conjugated to tetanus toxoid (Quimi-Hib) has been used in Cuba as part of their immunisation schedule (72). All are effective at inducing protective levels of anti-PRP antibody following one, two or three doses depending on the vaccine (see above). In NZ, monovalent Hib conjugate vaccine is used as the booster dose for vaccination against Hib. Provision of the booster dose provides long term protection against Hib disease and helps maintain herd immunity.

7.2.4 Multivalent vaccine

Multivalent vaccines are the preferred option for use in the primary immunisation schedule as they reduce the number of visits to healthcare centres and the number of injection required while improving compliance. In NZ, a minimum of eleven individual injections are received by infants before the age of five. As more vaccines are developed and become available, it will be important to minimise the health visits and injections by combining vaccines. For Hib conjugate vaccines, there are a range of multivalent vaccine options which differ in the components other than the PRP conjugate. These vaccines are listed in table 2. The majority of multivalent vaccines have the PRP conjugated to the tetanus toxoid. The use of the tetanus toxoid to conjugate a number of vaccine components in multivalent vaccines can have a negative and positive effect. The administration of DTaP-HBV-IPV/Hib-T concomitantly with MenC-T led to a reduced level of anti-MenC antibodies, but significantly higher anti-PRP antibodies (73). The effect of the carrier protein on the immune response is unpredictable and it is difficult to compare carrier protein efficacies among multivalent vaccines (74). The most notable effect of the multivalent vaccine on immunogenicity is the combination of DTaP with Hib conjugate vaccine (45, 46). All multivalent vaccines available are safe, immunogenic and control Hib disease in the under-five year olds.

7.3 Summary for vaccine options

A number of monovalent and multivalent Hib vaccines are available, all of which induce protective levels of antibody when used as either primary or booster doses. The effect of combining vaccines which use the same conjugate is unpredictable in terms of the antibody response, but as yet, has not appeared to alter the effectiveness of Hib vaccines for controlling invasive disease.

8. Options for scheduling

8.1 Objective

This section reviews the evidence for different options for placement of Hib conjugate vaccines on the childhood immunisation schedule.

8.2 Outcomes

The outcomes for which different schedules are compared are Hib invasive disease and protective antibody titres.

8.3 Review

8.3.1 Primary doses

There is a range of scheduling options, and a recent WHO report identified 43 different vaccination schedules around the world (75). The most frequently used schedule is the two, four and six month schedule used in 43 countries. The EPI schedule (six, ten and fourteen weeks) is used in 31 countries. There appears to be a certain amount of flexibility as to the timing of the primary doses with both developed and developing countries implementing a range of schedules, but all being effective in reducing Hib disease (76). The time between doses is not less than four weeks, and generally in the two dose primary schedule, there is a two month gap between the doses. It is clear that better immune responses are seen if vaccination occurs at an older age and the herd effect is important for the reduction of Hib invasive disease.

8.3.2 Booster doses

Booster doses of Hib conjugate vaccine are offered in 61 countries, this is given between ten months and four years of age with the majority boosting in the second year of life. Evidence for the need for a booster dose comes primarily from the UK experience described previously. The upsurge in Hib disease cases starting around 1999 was seen in all age groups, in older vaccinated children and unvaccinated populations, suggesting waning immunity and a reduction in the herd effect. The implementation of a booster dose saw a reduction in Hib cases. Other countries not using a booster dose also experienced the upsurge in invasive Hib disease (42). Given that most developing countries do not offer a booster dose, it will be important for continued surveillance to occur to identify any change in the incidence of Hib disease in these countries.

A primary series of doses followed by a booster dose in the second year of life is required to maintain the low level of disease in NZ. The only other consideration is whether there is a need for a two or three dose primary schedule. The two dose schedule has been implemented in a number of developed countries and has been successful in maintaining control of Hib disease. In countries where the burden of disease is high, the type of conjugate vaccine used will influence whether a two or three dose schedule is implemented based on the levels of protective antibody elicited by the vaccine. The Hib-OMP vaccine can elicit protective levels of antibody after one dose, but the Hib-CRM requires three doses. In NZ, where the burden of invasive Hib disease is low, a cost-benefit analysis of the two versus three dose schedule may be warranted.

8.4 Summary of schedule options

The primary vaccination series can be either two or three doses given in a variety of different scheduling options, all of which have successfully reduced the burden of Hib disease. Booster doses are given in those countries using a two dose primary schedule and in many developed countries using a three dose primary schedule. The booster dose is important to maintain control of the disease.

9. Implementation issues

9.1 Objective

The objective of this section is to review the most recent data for the currently licensed vaccines with respect to potential implementation issues in the NZ context. This includes the effect of vaccines on serotype switching, types and timing of schedules, co-administration, and specific vulnerable population groups.

The current NZ schedule provides for routine Hib vaccination at six weeks, three months and five months with a combination vaccine, which is currently Infanrix-hexa®, and a booster dose of monovalent conjugate Hib, currently ActHIB, at 15 months. Monovalent Hib vaccine is funded for pre and post-splenectomy patients in older children and adults.

9.2 Review

There have been no recent publications regarding implementation issues of the Hib conjugate vaccines. Multicomponent vaccines are safe and effective in the control of Hib disease.

9.2.1 Serotype replacement

There has been no clear evidence of serotype switching in the H. influenzae population causing invasive disease. Interestingly, in Ontario, Canada the largest proportion of invasive H. influenzae disease occurred in older adults and was due to non-typeable *H. influenzae* (2). A similar trend has been seen in the US (70). In Denmark, non-Hib was the primary cause of meningitis in adults but less so in children (67). It has also been observed that the type of invasive disease has switched from meningitis to bacteraemia associated with a shift in invasive disease from infants and children to older adults following implementation of the Hib vaccine (2).

9.2.2 Hib/MenC combination

One possible point to consider is the use of a multivalent HibMenC conjugate vaccine as the booster dose rather than the monovalent Hib conjugate vaccine. This would require a cost-benefit analysis based on the NZ epidemiology of group C meningococcal disease. As of early 2013, only the UK has the combined HibMenC combined vaccine in its immunisation schedule, introduced to control the large number of group C meningococci cases. A cost-benefit analysis would be required in NZ.

9.2.3 Two + one schedule (primary schedule + booster)

Another point to consider is the use of a two dose primary immunisation schedule. This has been used in a number of European countries, including Sweden, Denmark, Finland, Iceland, Italy and Norway. The immunisation schedule has two doses at three and five months with a booster dose at 12 months in these countries (77). The two dose primary schedules all have a booster dose at 10-15 months (76). All countries implementing a Hib vaccination schedule whether two dose plus booster or three dose primary plus or minus booster have effectively reduced Hib invasive disease in infants and children. However, the concerns as described in Australia, with earlier onset of carriage of disease for indigenous populations, suggest that local epidemiology always needs to be taken into consideration with a primary course and the type of conjugate used (1). With the current NZ approach to use a combination hexavalent for all doses in the primary schedule, there is less need to consider the question of the benefit of a primary schedule of two doses.

9.2.4 Co-administration

There has been no recent data suggesting any implementation issues around co-administration of Hib conjugate vaccines with other vaccines (10, 20, 25-27, 29, 31-33, 39, 78-81).

9.2.5 At-risk populations

At-risk populations include under-five year olds, particularly infants and premature infants, HIV infected patients and those with serious medical conditions (asplenic patients, those with complement deficiencies or antibody deficiencies). Ethnicity is also a high risk factor, with higher rates of Hib disease reported in Native American populations, Inuit and Australian Aboriginal peoples. Socio-economic factors, such as household over-crowding and low household income, have been identified as risks for Hib invasive disease.

Infection with HIV is associated with an increased risk of invasive Hib disease and higher morbidity and mortality rates. A recent review on the disease epidemiology and effectiveness of Hib conjugate vaccines in HIV-infected children found that HIV infection was associated with a six-fold higher risk of invasive Hib infection (82). The Hib vaccine also

has a lower effectiveness in this population. The immunogenicity of the vaccine in HIV-infected children was also estimated to be lower. In countries where HIV is prevalent, thought should be given to the schedule of Hib vaccination and the use of a booster dose. A study on Hib infection in adults with secondary immunodeficiency, such as COPD and myeloma, showed that the anti-PRP antibody levels were not protective in up to 55% of patients and concluded that vaccination of these patients may be beneficial (83).

Preterm infants have higher rates of infectious disease morbidity and mortality due, primarily, to the impaired functioning of barriers and immune system; this includes vaccine-preventable diseases. A UK study showed that, although preterm infants can mount non-inferior antibody responses to some vaccine components, only two-thirds of infants born <32 weeks gestational age had protective levels of anti-PRP antibody and only one-third having long term protective levels after the third vaccine dose (84). A Spanish study however, found that all preterm infants (<31 weeks and 31-36 weeks gestational age) had protective levels of antibody after the third dose (26). A Japanese study found that preterm infants had significantly lower geometric mean titres of anti-PRP antibody, but that 85.2% had long term protection levels (85). It has been shown that the transplacental transfer of anti-Hib polysaccharide antibody is lower in preterm infants (86, 87).

Patients with congenital or acquired asplenia are at high risk of infection from encapsulated pathogens, including *H. influenzae*, and vaccination of this group is highly recommended. Measurement of the antibody response to a single dose of Hib conjugate vaccine in asplenic children and young adults showed that there was a modest increase in antibody levels, but these were above that required for protection (88). Eighty-five per cent of the patients achieved long term protection levels of antibody after vaccination.

9.2.6 Outbreak control

There have been no recent reports regarding outbreaks of Hib disease. Updated recommendations for the prevention of secondary cases have been published (35). Close contacts of index cases, either in households or day-care centres, have an increased risk of infection with Hib than the general population, especially the under-one year olds. In the advent of Hib immunisation, it may well be older populations who are more at risk due to waning antibody titres and no natural boosting of immunity. Chemoprophylaxis is recommended for the index case and close contacts of the index case. Vaccination is strongly recommended for index cases under ten years of age who are unimmunised or partially immunised. All household contacts of the index are recommended to have chemoprophylaxis if there is a vulnerable individual in the household, and vaccination of partially or unimmunised children under ten years old.

9.3 Summary for implementation issues

No concerns were identified in the literature search regarding implementation of either monovalent or multivalent vaccines containing the Hib conjugate vaccine. Serotype replacement has not been shown to date to be a significant issue, but on-going surveillance remains important. If meningococcal C is to be considered on the national schedule, a combined Hib and meningococcal group C vaccine could be considered as a booster in the second year of life. A two dose primary schedule with a booster is effective in some international schedules and could be considered if NZ moved away from a hexavalent in the primary course. However, particular awareness of epidemiology for high risk groups such as indigenous people may require caution here. HIV infected patients have reduced antibody responses to Hib conjugate vaccines and may require additional vaccination. Preterm infants should be vaccinated at their chronological age, but may have reduced antibody responses

10. International policy and practice

10.1 Objective

The objective to this section is to summarise international practice with regard to the use of HiB vaccines.

10.2 Review

10.2.1 Global use of Hib vaccines

According to the WHO, 165/191 member states had introduced Hib vaccination to their routine programmes (75).

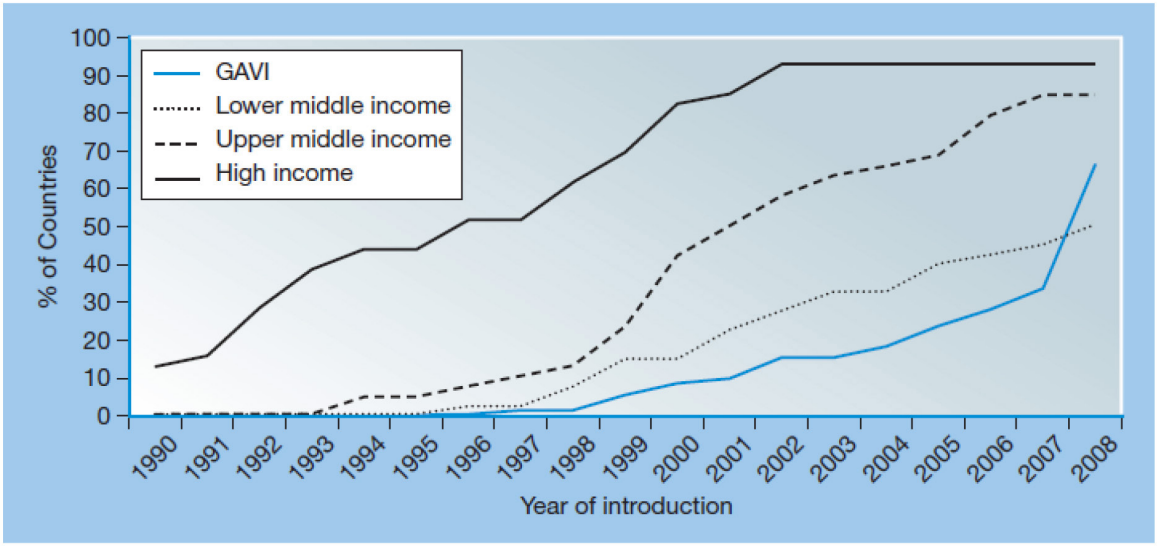

Figure 5. Proportion of countries that have introduced Hib conjugate vaccines, by gross national income grouping. Global Alliance for Vaccines and Immunizations.

10.2.2 United States

In October 2012, the Advisory Committee on Immunization Practices (ACIP) voted to recommend vaccination against meningococcal serogroups C and Y for children aged six weeks through 18 months at increased risk for meningococcal disease. They recommend using a combination vaccine that includes Hib.

Meningococcal groups C and Y and *Haemophilus* b-tetanus toxoid conjugate vaccine, Hib-MenCY-TT (MenHibrix, GlaxoSmithKline Biologicals), is licensed for active immunisation for prevention of invasive disease caused by *Haemophilus influenzae* type b (Hib) and meningococcal serogroups C and Y. Hib-MenCY-TT is not indicated for prevention of disease caused by meningococcal serogroup B, the most common serogroup causing disease in infants, or serogroups W135 or A, which are represented in quadrivalent meningococcal vaccines. These vaccines are recommended for routine use in adolescents aged 11-18 years, and for people with increased risk of meningococcal disease aged two-55 years (89).

10.2.3 UK

The Hib vaccine is offered to children at two, three and four months of age as part of the combined DTaP/IPV/Hib 5-in-1 vaccination. A booster dose is offered at 12 months as part of the combined Hib/MenC booster, to provide longer-term protection.

10.2.4 Australia

Aboriginal and Torres Strait Islander children in the Northern Territory, Queensland, South Australia and Western Australia jurisdictions, where different patterns of Hib disease remain evident, continue to receive PRP-OMP. This is due to the early antibody response seen with this vaccine, as described in Alaskan natives, who experienced similar pre-vaccination attack rate profiles, re-emergence of Hib disease was observed when the Hib vaccine in use was changed from PRP-OMP to HbOC (90).

Non-Indigenous children and Indigenous children living in Australian Capital Territory, New South Wales, Tasmania and Victoria receive any licensed Hib vaccine as the period of significant risk does not begin until after six months of age.

10.3 Summary of international policy and practice

Hib vaccination is delivered in many counties as part of the hexavalent vaccine. There were no new issues for international policy and practice identified in the literature.

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