Review of evidence to inform the New Zealand National Immunisation Programme, 2025: *Haemophilus influenzae* type B

Prepared by Dr Mary Nowlan, on behalf of the Immunisation Advisory Centre for the National Immunisation Programme at Health New Zealand | Te Whatu Ora

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Immunisation Advisory Centre

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Prepared by: Dr Mary Nowlan, Senior Advisor
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Abbreviations

AE	Adverse events
AEFI	Adverse events following immunisation
ATSI	Aboriginal Torres Strait Islander (indigenous Australians)
95% CI	95% confidence interval
CDC	Centers for Disease Control and Prevention
CRM_{197}	non-toxic *Corynebacterium diphtheriae* toxin protein
DT	diphtheria toxoid
DTaP-IPV/Hib	combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus and *H. influenzae* type b vaccine
DTaP-IPV-HepB/Hib	combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B and *H. influenzae* type b vaccine
GISN	Global Invasive Bacterial Vaccine Preventable Disease Surveillance
Hi	*Haemophilus influenzae*
Hib	*Haemophilus influenzae* type b
MenACWY	meningococcal conjugate vaccine groups A, C, W, Y
MMRV	combined measles mumps rubella and varicella vaccine
NTHi	Non-typeable *Haemophilus influenzae*
PCV (10 / 13)	pneumococcal conjugated vaccine (10 or 13-valent)
PHF Science	New Zealand Institute of Public Health and Forensic Science
PRP	polyribosylribitol phosphate
PRP-OMP	*Neisseria meningitidis* outer membrane protein conjugated polyribosylribitol phosphate
PRP-T	tetanus toxoid conjugated polyribosylribitol phosphate
RCT	randomised controlled trial
US	United States of America
UK	United Kingdom
VAERS	Vaccine adverse events reporting system (US)
VE	vaccine efficacy / effectiveness
VF	vaccine failure
vs	versus
WHO	World Health Organization

Executive Summary

This review aims to present evidence published between 2018 and 2025 around immunisation against *Haemophilus influenzae* type b (Hib) with relevance to the New Zealand National Immunisation Programme and the Immunisation Handbook. It is not a systematic review and cost-benefit analysis is not included. The opinions and interpretations of the literature presented are solely those of the author.

Burden of disease

Prior to the introduction of a conjugated vaccine, invasive *H. influenzae* type b (Hib) disease was the leading cause of death in children aged under 5 years, globally. As seen elsewhere, in New Zealand the incidence of invasive Hib declined rapidly with the introduction of Hib-PRP conjugate vaccines in 1994 (by 80% within two years). Hib remains a cause of invasive bacterial disease in young unvaccinated children and some adults, but notified cases are rare. Since Hib remains in circulation, there is a risk that declines in immunisation coverage will both directly affect children and, through loss of herd immunity, increase the risk of Hib in high-risk individuals.

Haemophilus influenzae has two forms – non-encapsulated and encapsulated with six polysaccharide capsule serotypes (a to f). Currently, non-typeable *H. influenzae* (NTHi) and other non-type b strains account for the majority of invasive infections, particularly in adults. No vaccines have been developed against these types.

Immunisation and vaccines

Hib vaccines used in New Zealand are composed of the Hib capsule polysaccharide, polyribosylribitol phosphate, conjugated to tetanus toxoid (PRP-T). Two formulations are available, currently:

- a single component (monovalent) vaccine: Act-HIB (Sanofi)
- a hexavalent combination vaccine, DTaP-IPV-HepB/Hib: Infanrix-Hexa® (GSK).

These are funded routinely as part of the National Immunisation Schedule for infants and children and as additional doses for certain special groups at increased risk of Hib disease.

Neisseria meningitidis outer membrane proteins (OMP) are also used to conjugate Hib-PRP in Hib vaccine formulations, used elsewhere, and have been included in this review.

Vaccine safety

The safety of DTaP-IPV-HepB/Hib is very well characterised following almost 20 years of use, globally. No recent studies have investigated the safety of single component Hib-PRP-T or Hib-PRP-OMP vaccines as they also have a very well characterised safety profile after three decades of use and no safety concerns have arisen through routine safety surveillance.

Immunogenicity

Combined Hib-PRP vaccines (DTaP-IPV-HepB/Hib) have slightly reduced immunogenicity compared with monovalent Hib-PRP. Despite this, they achieve clinically protective antibody levels in infants,

including when co-administered with other vaccines and paracetamol, or following antenatal Tdap vaccination. PRP-OMP conjugates offer early protection to high-risk infants, while PRP-T provides better long-term immunity. A three-dose primary plus booster (3+1) schedule induces stronger seroprotection than 2+1, particularly at age 2 years. Hib vaccination is beneficial in complement-deficient individuals by enhancing bactericidal function.

Efficacy, effectiveness and impact

Despite high vaccination coverage and stable vaccine effectiveness, recent European data show a rise in invasive Hib cases and vaccine failures, especially in young children. Waning immunity, potential changes in bacterial carriage and slight declines in coverage may contribute to this rise, but no clear risk factors were identified. Studies from Australia and the Netherlands confirm that vaccine schedule changes, with immunisation coverage of over 90%, have not reduced effectiveness of Hib immunisation. Ongoing surveillance remains essential.

Special groups

This review identified no additional special groups for which Hib-PRP could be considered. However, it is important that all children are fully immunised as soon as possible – ensuring that those at high risk are vaccinated on time or as soon as possible as appropriate to special medical considerations. Immunisation of children provides herd immunity to other groups by reducing nasopharyngeal carriage of Hib and transmission.

A review of Hib vaccination in children and adults who have received cochlear implants could be undertaken. No additional Hib vaccinations are recommended by the American Academy of Pediatrics following cochlear implants, since most cases of bacterial meningitis occurred following acute otitis media due to pneumococcal or NTHi infection. In New Zealand, timely immunisation is suboptimal for this group.

Conclusions

Hib-PRP conjugate vaccines remain safe and highly effective at providing direct and indirect protection against invasive *H. influenzae* type b. It is important that children are fully immunised according to the Schedule to maintain immunity and disease control. Surveillance for Hib infections is essential, especially for emerging vaccine-resistant clonal complexes. Other invasive *H. influenzae* types are of concern, particularly in adults.

Key points and recommendations

It is important to:

- maintain surveillance for invasive Hib disease, monitoring for vaccine-resistant clonal expansion
- achieve and maintain high immunisation coverage and timeliness, for infants and young children
- continue to provide a booster dose in the second year of life for longer-lasting protection
- ensure siblings and household members of young infants and individuals with immunocompromise are up to date with immunisations to reduce risk of transmission through carriage.

Recommendations for special groups

- Encourage providers to take all opportunities to ensure high-risk infants are vaccinated
    - Rare Hib cases occur mostly in under-immunised children, rather than as result of needing to change Schedule.
- Consideration of the current epidemiology and immunisation coverage is required when making changes to at risk groups.
    - High childhood immunisation coverage required to protect adults from Hib
    - Consequently, Hib is a very rare condition in adults, who are at higher risk from invasive NTHi and other Hi infections.
- No additional adult groups stood out as requiring Hib boosters.
- NZ could consider reducing the number of adult special groups funded this vaccine.
    - Some countries only recommended additional Hib-PRP for adults with functional or anatomical asplenia or pre or post splenectomy and revaccination post-haematopoietic stem cell transplant.
    - Evidence suggests a benefit to individuals with complement deficiency (primary immunodeficiency is not listed on the Pharmac Schedule for Hib-PRP vaccine).

Updates to Immunisation Handbook

- Clinical features – Hib remains rare, noting that other *H. influenzae* types are not vaccine preventable.
- Epidemiology and global vaccine coverage rates
- Efficacy and effectiveness - review current data on duration of immunity and efficacy
- Add newer AEFI references for DTaP-IPV-HepB/Hib

Introduction

This review aims to present evidence published between 2018 and 2025 around immunisation against *Haemophilus influenzae* type b with relevance to the New Zealand National Immunisation Programme and the Immunisation Handbook. It is not a systematic review and cost-benefit analysis is not included. The opinions and interpretations of the literature presented are solely those of the author.

Background

The bacterium, *Haemophilus influenzae* was first identified in 1883 and then further recognised in 1930s as having two forms – non-encapsulated and encapsulated with six polysaccharide capsule serotypes (a to f).[1] Prior to the introduction of a conjugated vaccine, invasive *H. influenzae* type b (Hib) disease was the leading cause of death in children aged under 5 years, globally. Hib meningitis occurred in around one third of cases and was associated with severe morbidity due to neurological sequalae. Other clinical conditions associated with Hib included pneumonia, epiglottitis, otitis media and sinusitis, septic arthritis and osteomyelitis, and facial and orbital cellulitis. The polyribosylribitol phosphate (PRP) capsular polysaccharide of Hib allows it to effectively evade complement-mediated killing and splenic clearance. It is also thought to give Hib greater pathogenic potential than other encapsulated *H. influenzae* strains. Other non-capsule virulence factors also contribute to the pathogenesis of Hib, which are toxic to epithelial cells in the upper respiratory tract and alter host defences to enable the bacteria to replicate in macrophage cells.

Pre-vaccine era, Hib was carried asymptomatically by around 3% – 5% of preschoolers and spread within crowded households and daycare settings, increasing the risk for invasive disease in young infants. Damage to the respiratory epithelium, by respiratory virus infections or smoke exposure, facilitates invasive infection. Haemoglobinopathies (eg sickle cell disease), complement or antibody deficiencies, and anatomical or functional asplenia increase the risk of Hib disease.

Available vaccines

Haemophilus influenzae type b (Hib) vaccines used in New Zealand are composed of Hib capsular polysaccharide, polyribosylribitol phosphate, conjugated to tetanus toxoid (PRP-T). Two formulations are available, currently:

- a single component (monovalent) vaccine: Act-HIB (Sanofi)
- a hexavalent combination vaccine, DTaP-IPV-HepB/Hib: Infanrix-Hexa® (GSK).

To ensure lot-to-lot consistency and improved shelf-life, the Hib component of DTaP-IPV-HepB/Hib is reconstituted from a lyophilised powered before adding to the vaccine.[2, 3]

Tetanus toxoid is a commonly used as the protein carrier for PRP, worldwide. A fully liquid hexavalent DTaP2-IPV-HepB-Hib (PRP-T) vaccine (Hexyon® or Hexaxim, Sanofi) is available in Europe, which has demonstrated non-inferiority to Infanrix-Hexa.[4]

Other Hib conjugate vaccines use the outer membrane protein (OMP) complex of *Neisseria meningitidis* as the PRP protein carrier. These include:

- monovalent Hib: PedvaxHIB® (Merck)
- a hexavalent DTaP5-IPV-HepB-Hib vaccine: Vaxelis® (MCM Vaccine) is approved for use in the US for primary course only and Europe and Australia for infants and toddler booster.[5]
- pentavalent DTaP-IPV/Hib vaccine: Pentacel® (Sanofi) is available in the US, given as a two-dose primary course.

For further details on international Hib vaccine recommendations see *International immunisation schedules*.

Now discontinued formulations used either diphtheria toxoid (Hib-DT) or the non-toxic *Corynebacterium diphtheriae* toxin protein (Hib-CRM_{197}) conjugates.[6, 7]

The New Zealand National Immunisation Schedule

Hib-PRP vaccines are funded by Pharmac as part of the National Immunisation Schedule for:

- Infants: DTaP-IPV-HepB/Hib at ages 6 week, 3 months, 5 months; Act-HIB at age 15 months.
- For children and adults at increased risk: Act-HIB – one dose

Extended immunisation schedule for special groups at increased risk (see below):

- for immunisation or re-immunisation of individuals at increased risk
- testing for primary immunodeficiency, as recommended by a specialist or paediatrician.

Vaccination of special groups

An additional dose of Hib vaccine is recommended and funded in New Zealand for all children and certain adults who are:

- post-HSCT (one dose funded, three-doses required for revaccination)
- post-chemotherapy
- functional asplenia
- pre/post splenectomy
- post-solid organ transplant
- pre/post cochlear implants
- on renal dialysis
- pre/post other severely immunosuppressive regimens.

Children with cochlear implants

Children who have received cochlear implants are recommended vaccines against invasive bacterial infections. In New Zealand, children who have received cochlear implants are funded additional pneumococcal, Hib and meningococcal vaccinations, and seasonal influenza vaccine. A retrospective study reviewed vaccine coverage in 203 children who received cochlear implants between 2005 – 2019 in New Zealand.[8] Hib vaccination was documented for 94.1% of this cohort (higher than the average immunisation coverage across those years), but only 21.2% had received influenza vaccine. Hib is given routinely as part of the childhood immunisation schedule– unfortunately, immunisation coverage has declined since this study, therefore it is likely that not all children with cochlear implants have been fully immunised.[8]

The US Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics state, however, that there is no evidence for an increased risk of meningitis due to Hib disease or meningococcal bacteria in people with cochlear implants and recommend only age-based routine vaccination or vaccines as recommended for other risk factors.[9, 10] Most cases of bacterial meningitis in children with cochlear implants (except implantation surgery related) in the US resulted from acute otitis media due to pneumococcal infections or non-typeable *H. influenzae* (NTHi).[10] The recommendation is that children should be fully immunised according to the routine immunisation schedule, prior to and after implantation, as age appropriate.

Epidemiology

Globally, significant declines in Hib disease occurred within a few years of Hib vaccines being added to the national immunisation schedules. Hib-associated mortality reduced by 90% over 5 years.[11]

The number of countries that include Hib-PRP into their national immunisation schedule has increased from 61 in 2000 to 193 in 2024 (i.e., all the WHO member-states except in China, where it is available privately). Global coverage for three doses of Hib vaccine in 2024 was 78%, ranging from 34% in the Western Pacific region to 93% in the European region.[12]

The burden remained high in regions with low immunisation coverage or no Hib vaccine on the schedule.[6, 7] Surveillance by the Global Invasive Bacterial Vaccine Preventable Disease Surveillance network (GISN) identified that *H. influenzae* was one of the three main causes of meningitis during 2014 to 2019 in children under 5 years with a case-fatality rate of around 6%. Of the serotyped *H. influenzae* isolates, around a half were type b.[13]

Despite very high immunisation coverage, some European countries have reported an increase in Hib cases in recent years.[14, 15] Over an 11-year surveillance period (2012 – 2023) in the UK, 2% (118/5,852) of invasive Hi isolates were Hib.[11] Hib cases fluctuated between 5 – 21 cases per epidemiological year. Adjusted incidence decreased from 23 cases during 2012/13 to eight cases in 2020/21 and decreased further (six cases) after COVID-19 pandemic restrictions were lifted. However, incidence returned to pre-pandemic levels in 2022/23 (12 cases). The majority of cases (84%) were in adults, and the median age for Hib was 51 years (IQR 37 – 64). Most of the adult cases had underlying medical conditions and presented with bacteraemic pneumonia. Of the 19 cases in children, the median age was 2 years (IQR 0 months – 2 years). Nearly all of the children were previously healthy and had various clinical presentations.[11] One characteristic of the cases in Europe and the UK was an increased detection of Hib clonal complex ST-6 strain or its derivatives, which may be an emerging vaccine-escape strain with the potential to become more invasive or a better coloniser.[11]

Historical epidemiology in New Zealand

As seen elsewhere, cases of invasive Hib in New Zealand declined rapidly when a combined diphtheria, tetanus whole-cell pertussis and conjugated Hib vaccine (DTwPH) was introduced in January 1994 for aged children under 5 years. It was given as Hib-associated hospital admissions reduced by more than 80% within two years of the introduction of Hib vaccine: from an annual age-standardised hospitalisation rate of 13.5 per 100,000 in 1993 to 2.19 per 100,000 in 1995.[16] Likewise, meningitis and epiglottitis rates declined by 82% and 87%, respectively. This occurred despite low vaccination coverage rates at the time. Hib vaccine was highly effective at reducing nasopharyngeal carriage of Hib.[16]

However, the percentage of cases in infants aged under 6 months increased proportionately. In 2000, the vaccine was changed to a PRP-OMP formulation in a Hib-HepB combination (Comvax). In 2008, DTaP-IPV-HepB/Hib was introduced, which was less protective against Hib after the first and second doses than Hib-HepB, but reduced the number of vaccinations given to infants and enabled the introduction of pneumococcal vaccinations.

Current New Zealand epidemiology

Currently, the number of Hib cases notified is low but young children continue to be most affected. Between 1 January 2019 and 30 December 2024, 8 of the 13 cases notified to EpiSurv were aged under 5 years (see Figure 1 for age distribution per year). The majority of cases were unvaccinated (9/13) (see Figure 2 for immunisation status). All the cases were hospitalised. By prioritised ethnicity, four were Māori, four Pacific and five European/Other. No cases were notified in 2022.(personal communication, PHF Sciences, 12 Aug 2025). As of October 2025, one case was reported in August 2025.[17]

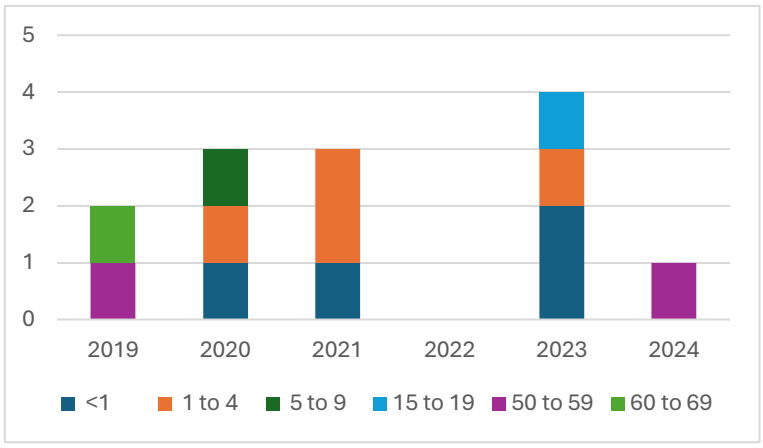

Figure 1: Hib notifications by age groups, 2019 – 2024 (Source EpiSurv, PHF Science)

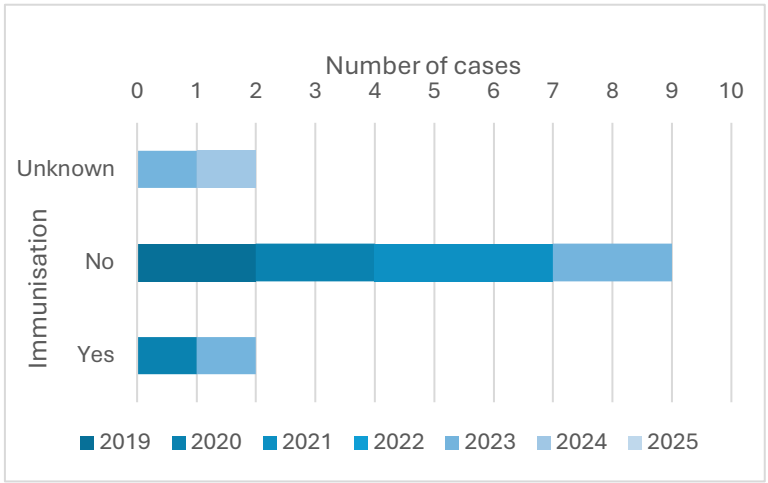

Figure 2: Hib notifications by immunisation status, 2019 – 2024 (Source EpiSurv, PHF Science)

Other invasive *H. influenzae* strains

Unfortunately, Hib is not the only invasive strain of *H. influenzae*. Increasing numbers of cases of non-type b strains are being reported, globally. For example, cases of invasive *H. influenzae* type a (Hia) and type f (Hif) are increasing, and non-typeable *H. influenzae* (NTHi) is the most prevalent cause of invasive disease in several countries.[14, 15, 18-20]

In Ontario, Canada during 2014 – 2018, invasive *H. influenzae* disease increased in older adults aged ≥65 years, primarily caused by NTHi (74.2% of cases), Hia (8.9%) and Hif (10.2%).[18] More than a quarter of the NTHi isolates were not susceptible to ampicillin.

A study in Spain found that most of the 260 invasive *H. influenzae* isolates investigated between 2011 and 2018 were from adults. The majority were non-encapsulated NTHi (79.2%), mainly affecting the elderly (64%, 103/161 aged ≥ 65 years). Encapsulated isolates were more common in preschool children (55.6%, 30/54 aged <5 years). Serotype b was the most characterised encapsulated serotype (13.5%), followed by serotype f (3.1%), serotype a (2.7%) and serotype e (1.5%).[20]

Over an 11-year surveillance period (2012 – 2023) in the UK, there were 6,681 cases of invasive *H. Influenzae* disease notified. Most cases serotyped were NTHi (83%, 4881/5852), followed by Hif (10%), Hie (3%), Hib (2%), Hia (1%) and Hid (0.3%). There were no type c cases. Following the COVID-19 pandemic, NTHi cases declined by 68% from 425 cases in 2019/20 to 136 cases in 2020/21 but, as seen for Hib, increased again in 2022/23 (to 576 cases). Cases of invasive Hia had been increasing since 2016/17 (with a small decline during pandemic year 2020/21) from 5 cases to 21 cases in 2022/23.[11]

Summary

Non-typeable *H. influenzae* and other non-type b strains account for the majority of invasive Hi infections, particularly in adults. Hib remains a cause of disease in children and adults, but cases are rare. Since Hib remains in circulation, there is a risk that declines in immunisation coverage will both directly affect children and, through loss of herd immunity, increase the risk of Hib in high-risk adults.

International immunisation schedules

Hib-PRP is generally administered in a combined vaccine to infants and then given as a booster either as a combined vaccine or as a monovalent (single component) vaccine in the second year of life. Some special groups are recommended additional Hib vaccinations. Vaccine recommendations in individual countries are influenced by epidemiology and serotype prevalence.

Table 1: International immunisation schedule for Hib vaccinations (as of October 2025)

Country	Routine schedule	Special groups	Available vaccines
New Zealand	6 weeks, 3 months, 5 months 15 months	All children and adults who are: • post-haematopoietic stem cell transplant (HSCT) • post-chemotherapy, • asplenia or pre/post splenectomy • post-solid organ transplant • pre/post cochlear implants • renal dialysis • other severe immunosuppression	DTaP-IPV-HepB/Hib (PRP-T) monovalent Hib
Australia	6 weeks or 2, 4, 6 months 18 months	• Asplenia or pre/post splenectomy • post HSCT	DTaP-IPV-HepB/Hib (PRP-T) DTaP5-IPV-HepB-Hib-(PRP-OMP) monovalent Hib
Canada	2, 4, 6, 12-23 months (usually 18 months)	1 extra dose >5 years, if at risk: • asplenia or hyposplenia (including sickle cell disease) • cochlear implant • primary immunodeficiency • HIV • Post-HSCT • malignant haematological disorders • pre/or post solid organ transplant	DTaP-IPV-HepB/Hib (PRP-T) DTaP-IPV-Hib (PRP-T) monovalent Hib
UK	8, 12, 16 weeks, 18 months catch up not recommended for those aged >10 years, unless are close contacts in an outbreak.	No recommendation for immunocompromised, asplenia or HIV, unless re-immunisation is required after treatment.	DTaP-IPV-HepB/Hib (PRP-T or PRP-OMP) Hib-MenC (until Apr 2026) – being replaced with DTaP-IPV-HepB/Hib
US	from 6 weeks – 2 months, 6 months 12-15 months	Adults* and children: • post HSCT* • chemotherapy or radiation treatment • anatomical or functional asplenia* • elective splenectomy* • HIV infection • Immunoglobulin deficiency • Early-component complement deficiency	Monovalent Hib • PRP-T • PRP-OMP (2-dose primary course) DTaP5-IPV-Hib (PRP-T) DTaP5-IPV-HepB-Hib (PRP-OMP) Vaxelis (3-dose primary only)

Sources:

- https://www.tewhatuora.govt.nz/for-health-professionals/clinical-guidance/immunisation-handbook/7-haemophilus-inuenzae-type-b-hib-disease
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- https://assets.publishing.service.gov.uk/media/683f012a7cbfa6ac6e0d32ce/Green_Book_on_immmunisation_Chapter_16__Hib_14_5_25.pdf
- https://www.rivm.nl/en/documenten/vaccination-schedule-nip-march-2024
- https://www.cdc.gov/vaccines/vpd/hib/hcp/index.html

Review of recent literature

A search of recent literature over the last decade yielded very few references since Hib is generally well controlled in infants, and immunisation against Hib is established in most countries. Presented is some recent evidence around the safety, immunogenicity and effectiveness of Hib-PRP conjugate vaccines. See Summary of evidence tables for details of the publications reviewed.

Safety

The safety of Hib-PRP conjugate vaccines is very well established and these vaccines have been given to millions of children over more than 30 years.[1] Local reactogenicity is increased with combination vaccines compared with individual vaccines. (See Table 3 for a summary of safety studies).

After more than 9.6 million doses of DTaP-IPV-HepB/Hib (Infanrix-Hexa) from 2009 – 2018 in Australia, the frequency of the top 10 most commonly reported adverse events were consistent with clinical trials, product information and other safety surveillance.[2] Similarly, VAERS reports after over two million doses in 2019 – 2023 found no new or unexpected safety issues in the US.[21]

GSK post-market passive surveillance, conducted over 17 years, in more than 100 countries and following 159 million commercial doses, found similar findings to Australia. The most common spontaneously reported adverse events were related to vaccination errors, such as mistakes in vaccine scheduling. Adverse events of special interest include extensive limb swelling, which is seen at a rate of <0.1%, and a known class effect of all DTaP vaccines. Reported cases increased in Italy when mandatory AE reporting was introduced. Hypotonic hyporesponsive episodes and convulsions with or without fever are associated rarely (<1 per 100,000 doses) with DTaP-IPV-HepB/Hib and when coadministered with PCV13 (as noted on the Infanrix-Hexa data sheet).[22] An observed-to-expected analysis of sudden unexplained death in infants (SUDI) occurring within 0–19 days after DTaP-IPV-HepB/Hib vaccination demonstrated that the number of observed deaths was lower than the expected incidence during both the first and second years of life.

No serious safety concerns were identified around giving DTaP-IPV-HepB/Hib with other infant scheduled vaccine. The incidence of fever was similar to that observed with the coadministered vaccine alone. Those with a history of febrile seizures can be offered paracetamol to reduce the risk of fever with MenB and PCV13.[23] When coadministered with MMRV, fever was observed at both days 0 – 2 (as expected for DTaP-IPV-HepB/Hib) and days 4 –12 (as expected for MMRV). Rates of fever were higher in the coadministered group than expected for DTaP-IPV-HepB/Hib alone but similar to MMRV alone.[23]

Summary

The safety of DTaP-IPV-HepB/Hib is very well characterised following almost 20 years of use, globally. No recent studies have investigated the safety of Hib-PRP-T or Hib-PRP-OMP alone, but these have a very well characterised safety profile after three decades of use and no safety concerns have arisen.

Immunogenicity

Long-term protection against Hib has been classified by an antibody titre of >1 µg/ml following a primary course and short-term seroresponse of 0.15 µg/ml.[1] The following will review the immunogenicity of PRP-T and PRP-OMP vaccines. See Table 4 for details of studies.

DTaP-IPV-HepB/Hib

Anti-PRP antibody concentrations were lower when Hib-PRP was given as a combination vaccine than as a separate monovalent vaccine.[24] These differences were less pronounced following booster doses. Combining Hib-PRP into DTaP-IPV-HepB/Hib (Infanrix-Hexa®) vaccine did not interfere with the immune responses to the other vaccine antigens after three-dose primary vaccination, or after DTaP and Hib or DTaP-IPV-HepB/Hib booster doses.[24]

Coadministration

GSK reviewed the immunogenicity of DTaP-IPV-HepB/Hib (Infanrix-Hexa) when coadministered with other schedule vaccine, from 34 studies conducted over 18 years (of which 21 studies were supported or sponsored by GSK).[23] The review identified no clinically significant interference with antigen responses. The studies included coadministration with MenACWY (CRM or TT conjugated), meningococcal B (Bexsero®), PCV10 or 13, oral rotavirus and MMRV. The majority showed at least 98% seroconversion rates to Hib. When paracetamol was administered, there was no impact on the Hib seroprotection, even when the magnitude of antibody levels was reduced.[23]

Antenatal vaccination with Tdap

Seroprotection rates against Hib-PRP were similar after a DTaP-IPV-HepB/Hib primary course (starting at around age 2 months) between infants whose mothers received antenatal Tdap (from 27 weeks' gestation) and those who receive antenatal placebo.[25] At one month post primary vaccination, 96% (95% CI 93 – 98%) of the Tdap group and 95% (91 – 97%) of the placebo group had anti-Hib-PRP IgG levels of at least 0.15 µg/ml. In the Tdap group, IgG levels of at least 1 µg/ml (for long-term protection) were reached by 64% (59-70%) of infants compared with 65% (59-71%) of placebo infants. [25]There was no evidence of interference of maternally derived antibody on the infant's humoral immune response to Hib-PRP.

Summary

Combined DTaP-IPV-HepB/Hib has been used for almost 20 years. Although immunogenicity is reduced compared with single antigen (monovalent) Hib vaccine, there appears to be no clinically significant impact on seroprotection. Likewise, no clinically significant reduction in antibody levels is seen when given in combination with other schedule vaccines, with paracetamol or in infants who were exposed to Tdap antenatally.

OMP-conjugated Hib vaccine

Neisseria meningitidis outer membrane protein (OMP) conjugated Hib-PRP vaccine is more immunogenic than tetanus toxoid conjugated Hib-PRP vaccines, and hence, requires only two doses rather than three for a primary course. This vaccine is advantageous in populations in whom invasive Hib disease is most prevalent at a younger age (ie before age 6 months), such as the Native American populations.[1]

Based on a phase 4 RCT, the Academic Committee for Immunization Practices (ACIP) at the US CDC recommended that a primary course of either two doses of monovalent Hib-PRP-OMV (Pedvax-Hib,

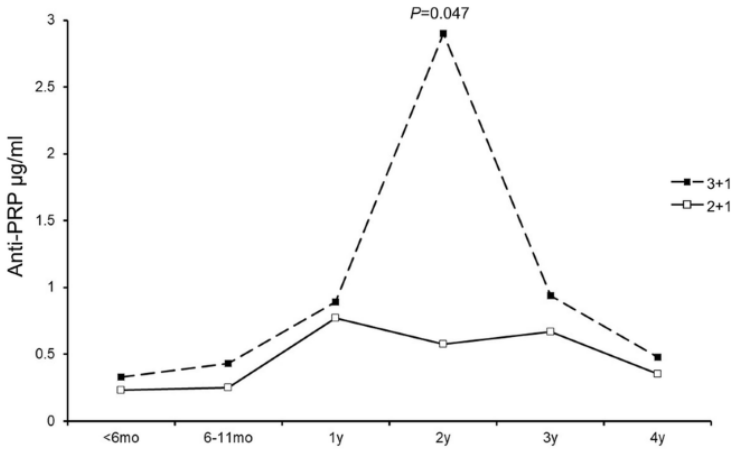
at age 2 and 4 months) or three doses of hexavalent DTaP-IPV-HepB-Hib-PRP-OMV (Vaxelis, at ages 2, 4, 6 months) be given to American Indian/Alaskan Native children followed by a booster dose at ages 12 – 15 months of any available monovalent Hib-PRP vaccines (OMP or TT conjugated) [Vaxelis it is not indicated for a booster dose in the US].[26] No difference in antibody protection (Hib-PRP IgG ≥15 µg/ml) was seen at 30 days after dose 1 between hexavalent and monovalent Hib-PRP-OMP, but for long term protection, significantly more infants had Hib IgG >1 µg/ml at 150 days after the primary course with three-dose hexavalent vaccine compared with two doses of monovalent Hib-PRP (84% vs 72%, p = 0.03).[26]

Summary

A two-dose primary course of Hib-PRP-OMP containing vaccine is recommended for immediate protection of infants who are highest risk from invasive Hib at a young age, such as indigenous North American peoples, because seroprotective antibody levels are reached sooner than for PRP-T conjugated vaccines. However, three-doses of a PRP-T-containing vaccine induce higher antibodies levels associated with longer lasting protection. Booster doses with vaccines containing either PRP-OMP or -T are recommended from the second year of life to extend protection.

Change in schedule

A seroprevalence study conducted in France compared antibody levels in children aged under 5 years vaccinated with a 2+1 schedule with those given a 3+1 schedule in infancy.[14] During 2017 – 2019, France reported an increase in Hib cases with several vaccine failures. From 501 invasive bacterial isolates, 56 were Hib including 37 (66%) from children aged under 5 years — these represented 13% of all the Hi cases aged under 5. The median age was 0.8 years (range 0.2 – 4.7 years). All the vaccinated cases had received the 2+1 immunisation schedule (at ages, 2, 4 and 11 months) that commenced in 2013. Unlike the children vaccinated with a 3+1 schedule (ages 2, 3, 4 and 16–18 months), antibody levels did not peak at age 2 (see Figure 3).[14] Serum samples, originally collected from 232 children age <5 years at admission with suspected invasive bacterial infections, were analysed by ELISA for anti-PRP IgG. Six of these samples were fully immunised Hib cases, all had received a 2+1 schedule. The median age of these cases was 2.5 years (range 1.2 – 4.1 years). At the time of infection, all of the children had anti-PRP IgG levels below 1 µg/ml, with GMC of 0.4 µg/ml (95% CI 0.16 – 0.98). The median delay between dose 3 and the onset of disease was 1.6 years (range 0.3 – 3.2 years).



3+1 group	29	14	29	25	17	16
2+1 group	22	21	27	12	9	11

Figure 3: Distribution of anti-PRP IgG levels among children aged <5 years. Median values per age group according to vaccine schedule (2+1 or 3+1). Number of children in each group is given in table. (Hong et al 2021, open access)

Special groups

Current immunogenicity data for Hib-PRP vaccines is limited in individuals with primary or secondary immunocompromise and other high-risk populations.

Individuals with complement deficiencies are highly recommended Hib vaccination. A study of 18 people with complement 2 deficiency (C2D) demonstrated complement function and bactericidal capacity was improved after Hib-PRP vaccination.[27] Serum bactericidal assay (SBA, using autologous serum) activity after vaccination was inversely correlated with serum concentrations of Hib-specific antibodies. Although these patients have dysfunctional classical and lectin complement pathways, some are able to bypass this dysfunction through the mannose-binding lectin (MBL)-dependent activation of the alternate pathway. However, individuals with concomitant MBL and C2 deficiencies are at highest risk, particularly if unvaccinated.[27]

Summary

Combined Hib vaccines (DTaP-IPV-HepB/Hib) show slightly reduced immunogenicity compared with monovalent Hib but achieve clinically protective antibody levels, including when coadministered with other vaccines, paracetamol, or following antenatal Tdap vaccination. PRP-OMP conjugates offer early protection to high-risk infants, while PRP-T provides better long-term immunity. A 3+1 schedule induces stronger seroprotection than 2+1, particularly at age 2 years. Hib vaccination is beneficial in complement-deficient individuals by enhancing bactericidal function.

Efficacy, effectiveness and impact

Since Hib conjugate vaccines have been used routinely for three decades, new evidence around efficacy and effectiveness is limited. The positive impact of Hib vaccinations was seen acutely from the start of the immunisation programmes. The use of combination vaccines and alternative scheduling have been more recently investigated. The impact on carriage of *H. influenzae* (Hi) strains is also of interest, with other encapsulated types replacing type b. See Table 5 for details.

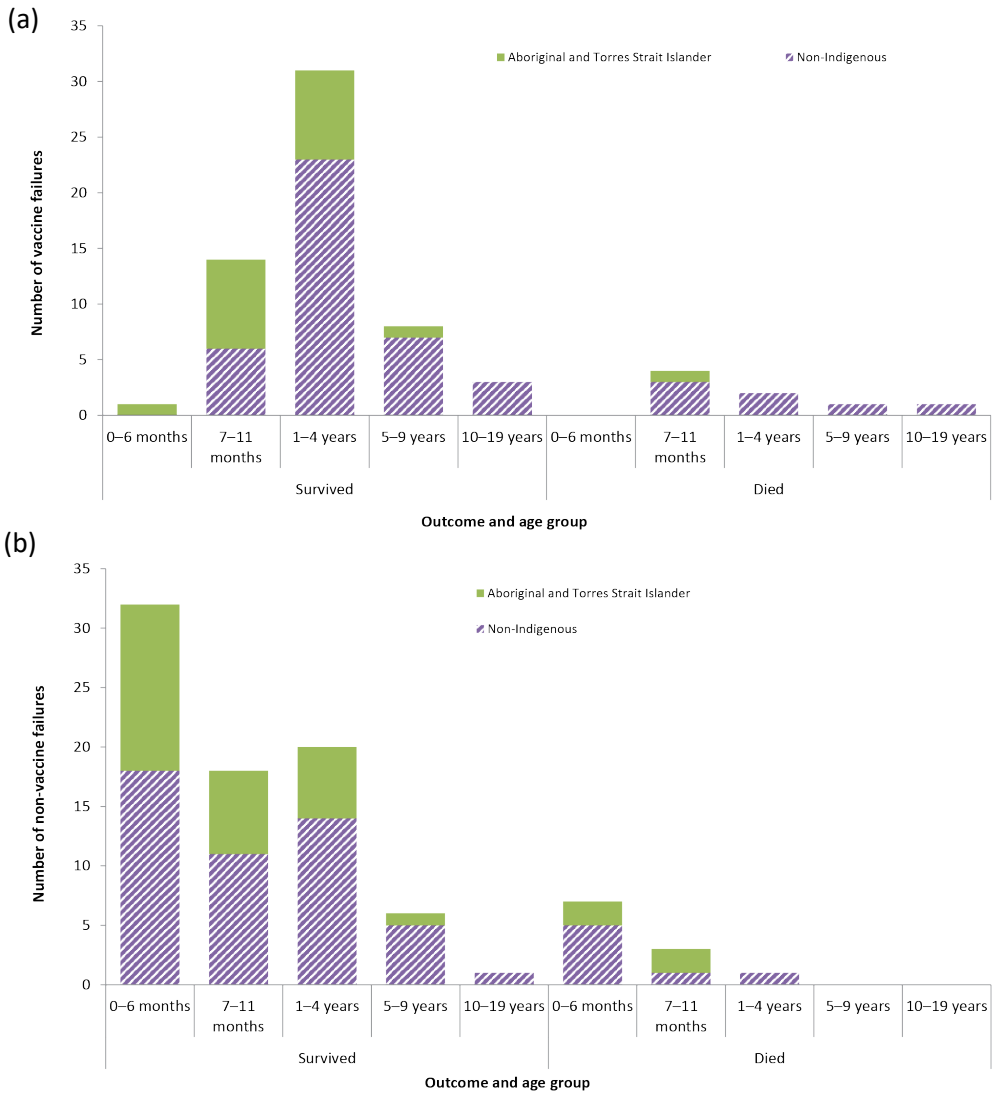
Vaccine failures

Some European countries have noted an increase in invasive *H. influenzae* cases over recent years. For example, a prospective surveillance study in Portugal examined 140 invasive Hi isolates collected from children aged 0 – 17 years over a 12-year-period (2010 – 2021) across 40 hospitals.[15] A comparison between last 6 years with the first 6 years showed a significant increase in total invasive Hi infections, Hib infections and vaccine-failures: incidence risk ratios (IRR) for all invasive Hi = 1.86 (95% CI 1.29 – 2.64, $p < 0.001$); Hib = 2.96 (1.44 – 6.54, $p = 0.001$); vaccine failure = 2.94 (1.19 – 8.29, $p = 0.011$). Of the invasive cases, just under 50% were caused by encapsulated Hi and the remainder were caused by NTHi. Around 30% (41 cases) of the invasive Hi infections were Hib, and 26/41 (63%) were considered Hib vaccine failures, 19/41 (73%) were aged under 5 years and 12 /41 (46%) were younger than 18 months (i.e. before the 18-months booster dose).[15] The majority were previously healthy (20/22 with information). All 25 of the isotyped Hib cases were of ST6 clonal complex. The vaccine schedule was unchanged (given at ages 2, 4, 6 and 18 months) but there had been changes in the valency of the combination vaccine given over the time period, alongside the addition of PCV13 and MenB vaccines to the schedule. The study concluded that high vaccination coverage (>95%) does not eliminate the risk for invasive Hib and a few vaccine failure cases occur each year. No clear predisposing factors were identified associated with the increase in Hib cases and vaccine failures. Changes in herd immunity and consequent colonisation were suggested to potentially influence risk.[15]

Hib incidence was reviewed in Australia following the death of two children with invasive Hib in 2017.[28] A total of 345 invasive Hib cases were notified between 2000 and 2017. Of these, 153 were born after 1 January 2000. Although, Hib incidence was already low prior to 2000 and the incidence further declined by 55% between 2000 and 2017, there was a marked disparity between Indigenous (Aboriginal Torres Strait Islander, ATSI) and non-indigenous children (IRR 8.34; 95% CI 5.83 – 11.79). Cases in the ATSI population were significantly younger than non-ATSI children – median age 15 months vs 14 years, with 46% vs 18% aged under 1 year. Overall, the incidence of Hib in unvaccinated children was 8-times higher than those who received at least one dose of Hib-PRP vaccine.[28]

In Australia during 2000 to 2017, vaccine failure occurred in 45% of cases (64/145) aged 8 weeks and over, seven were immunocompromised.[28] The numbers of vaccine failures and non-vaccine failure cases are given in Figure 4. Of the vaccine failure cases, 88% were fully immunised for age: around half were fully immunised with PRP-T and three-quarters with PRP-OMP. Time to disease onset since the last vaccine dose was longer for PRP-OMP than PRP-T. However, there was no evidence of increasing vaccine failure over the time of the surveillance period. This review emphasised the importance of timely vaccination, especially in Indigenous children who are disproportionately affected by Hib. Ongoing surveillance is needed to monitor for three-dose vaccine failures following a change in the booster dose schedule in 2018, from age 12 months to 18 months.[28]

Figure 4: Number of Hib (a) vaccine failures and (b) others born from 1 January 2000 onwards, by clinical outcome, Aboriginal and Torres Strait Islander status and age group, Australia, 2000–2017 (Maguire et al 2020, open access)



Summary

Although there are rare cases of Hib in fully immunised children, vaccination is highly protective against invasive Hib in young children. No discernible factors have been identified that are associated with breakthrough infections. Close monitoring is required to ensure that the immunisation schedule continues to provide adequate protection. Disparities in Hib incidence have been observed in Indigenous children in Australia and elsewhere. This could be associated factors that promote transmission, such as higher rates of nasopharyngeal carriage, crowded living situations and smoke exposure, and delayed immunisation.

Change of vaccine or schedule

The effectiveness of Infanrix-Hexa was reviewed in Australia using data and peer-reviewed papers published between 2009 and 2018, following more than 9.6 million doses of DTaP-IPV-HepB/Hib.[2] It found that timely primary series (starting at age 6 weeks or 2 months) and increased immunisation coverage rates had improved disease control for Hib, particularly in indigenous Aboriginal and Torres Strait Island children. No resurgence in disease had occurred with a switch from PRP-OMP to PRP-T Hib vaccines. Rather than changes in vaccine effectiveness, any disparities in annual incidence rates were related to differences in vaccine uptake; uptake had increased from 84.9% to 92.5% for Aboriginal vs 91.7% to 94.0% for all children.[2]

Cases of Hib were increasing in the Netherlands in 2016. A case-control study was conducted to evaluate whether vaccine effectiveness against invasive Hib disease in children aged under 5 years changed with a switch from pentavalent DTaP-IPV-Hib to hexavalent DTaP-IPV-HepB/Hib in 2011.[29] Findings showed that vaccine effectiveness against Hib did not decrease over time with the introduction of hexavalent vaccine: pentavalent/other VE 92% (95% CI 86 – 91%) vs hexavalent VE 94% (89 – 97%); odds ratio 0.72 (0.36 – 1.45), p = 0.36. Despite very high immunisation coverage (exceeding 95% for those born since 2011) and constant vaccine effectiveness, the authors queried whether waning immunity in the older cohort could increase carriage of Hib and thereby increase the risk of infection of younger children. Protection against Hib waned significantly with time after a booster dose: from 91 – 99% in children aged 1–2 years to 61% – 82% in those aged 3–4 years (p = 0.0008). The effect of this potentially increased carriage may have been more pronounced with small declines in immunisation coverage, as seen in the later birth cohorts born in 2013 (at 93.9%) and 2014 (94.2%).[29]

During 2020 and 2021, the increase in Hib incidence continued in the Netherlands, despite reductions in most respiratory infections due to COVID-19 control practices.[30] Conversely, there was a substantial decrease in NTHi cases during 2020 and 2021. In 2019, the infant schedule vaccine changed from DTaP3-IPV-HepB/Hib to DTaP5-IPV-HepB/Hib (see Figure 5). From 2020, infants born to mothers who were vaccinated with Tdap antenatally were offered a 2+1 primary course of DTaP5-IPV-HepB/Hib (and 3+1 was offered those not vaccinated antenatally). Steens et al reviewed whether these changes effected vaccine effectiveness. Based on a small number of cases, overall, there was no indication of a change in vaccine effectiveness against Hib disease in children under 5 with the changes in primary schedule or vaccine composition in the Netherlands. Vaccine effectiveness, based on population coverage at age 2 years, was estimated to be 97% (78 – 97%) in 2021 and 92% (88 – 95%) in 2015 – 2019.[30]

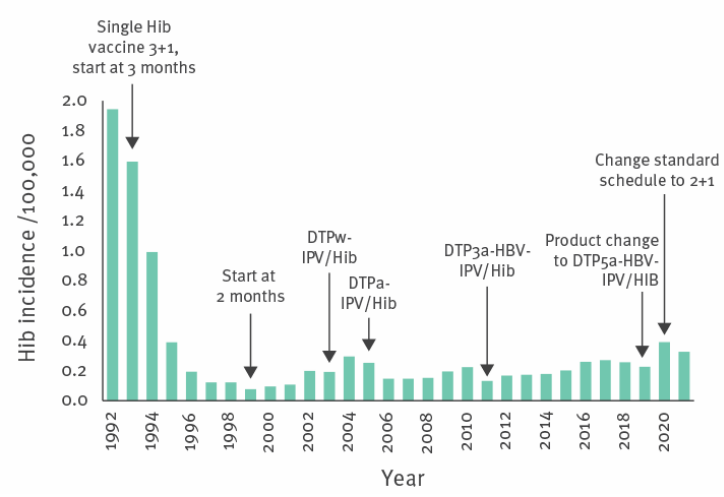


Figure 5: Hib incidence related to the vaccination schedule, Netherlands (Steens 2021, open access)

Summary

Despite high Hib vaccination coverage and stable vaccine effectiveness, recent European data show a rise in invasive Hib cases and vaccine failures, especially in young children. Waning immunity, potential changes in bacterial carriage, and slight declines in coverage may contribute, although no clear risk factors were identified. Studies from Australia and the Netherlands confirm that vaccine schedule changes, with immunisation coverage of over 90%, have not reduced effectiveness of Hib immunisation, but ongoing surveillance remains essential as vaccine failures do occur.

Summary of evidence

Table 2: Burden of Hib and non-type b *Haemophilus influenzae*

Outcomes	Ref	Participants	Results		Findings
Invasive Hi disease, England	11	Surveillance for invasive H. influenzae infections. 2012 - 2023	6681 case, 5852 genotyped. • NTHi = 4881 cases (83%) • type f = 591 (10%) • type e = 189 (3%) • type a = 54 (1%) Case-fatality rate – low irrespective of age, underlying conditions, clinical presentation (no deaths reported since 2016).	118 cases (2%) Hib median age for Hib 51 years, most adults 84% (99/118) with underlying conditions and bacteraemic pneumonia 19 cases in children (16%): • age <1 = 13 cases (11%) • age 1-5 y = 6 cases (5%) • healthy, with a range of Hib presentations	NTHi accounts for the majority of invasive H. influenzae disease in England. A recent increase in Hia has been reported. Invasive Hib is extremely rare across all age groups in England. Most cases occur in adults with underlying conditions, diagnosed with bacteraemic pneumonia.
Invasive Hi disease, France	14	Seroprevalence study, 2017-2019 Serology, see Table 4	Increase in Hib 2017-2019, with several vaccine failures 501 isolates. • 365 (72.6%) of Hi were NTHi and Hif 10% most commonly aged >5 years • Hib 56 cases (7%); 37 (66%) under 5y and were 13% of all Hi cases in <5s • Hia 20 (4%), 13 (65%) Hia cases aged <5 Median age Hib cases 0.8y (range 0.2 – 4.7y) 53/56 Hib isolates were clonal complex ST-6		An increase in total Hi cases was seen between 2017-2019 in France.
Hib in Australia	[28]	surveillance, 2000-2017			

Abbreviations: Hi – Haemophilus influenza; Hia, Hib, Hif – types a, b, f *H. influenzae*; NTHi – non-typeable *H. influenzae*

Table 3: Vaccine safety

Outcomes	Ref	Participants	Results	Findings
Review of effectiveness of Infanrix-hexa	2	Reviewed data and peer-reviewed papers, Australia, 2009-2018; schedule 2, 4, 6m More than 9.6 million doses of DTaP-IPV-HepB/Hib	• 627 / 9066 AE reported to DAEN related solely to DTaP-IPV-HepB/Hib. • Most frequently reported – injection site reaction (105 reports, 1.1/100K), fever (62) and vomiting (30). • Annual frequency of 10 most common AE is consistent with clinical trials and product information.	Confident about the reliability of its safety profile. Consistent findings with clinical trials, product information and other safety surveillance.
VAERS	21	Reports following DTaP-IPV-HepB/Hib June 2019 to June 2023 Total 2 million doses given in US.	501 reports, 332 (66.3%) coadministration with ≥1 other vaccine. Vaccination errors most common (310, 61.9%). 21 (4.2%) serious, 3 deaths. MedDRA PTs – fever (51, 10.2%), injection-site erythema (27, 5.4%), vomiting (24, 4.8%), injection-site swelling (23, 4.6%)	These findings are consistent with pre-licensure studies. There were no new or unexpected safety issues, except for a high proportion of vaccine errors.
DTaP-IPV-HepB/Hib 17 years	22	GSK passive surveillance. From launch in 2000, over 17 years (Oct 2017). Authorised in over 100 countries, more than 40,000 infants in clinical trials and 159 million commercial doses	10 most commonly reported AEs – range 0.75 – 7.74 per 100,000 doses: • Fever, crying, injection site erythema and swelling. • Injection site pain, irritability, vomiting, somnolence and hypotonia also frequently reported. • Vaccine error 'inappropriate schedule of vaccine administrations' 5th most common event. AESI: • Extensive limb swelling (ELS) – class effect of all DTaP vaccines – increase in reporting mainly due to mandatory AE reporting in Italy and safety reporting during pertussis outbreaks elsewhere. (rates ranged from 19.8 Poland to 1.1 France per 100K; substantially below those in clinical trials at 0.01-0.1% postmarket vs 0.1-1% clinical trials) • Convulsion with/without fever and hypotonic hyporesponsive episodes (plus somnolence and hypotonia) 5 most common neurological AE (rate 0.43-0.85 per 100,000 doses). Coadmin with PCV13 increased HHE and convulsions (~1% and 3% difference) – from 2010 no difference seen in Italy from where most spontaneous cases reports had come from (75% of reports). • SUDI – observed-to-expected analysis – 238 reports – underlying conditions identified in 104 cases. Analysis showed for any risk period between 0-19 days post vaccination, number of SD cases after DTaP-IPV-HepB/Hib was significantly lower than expected cases in first and second year of life.	AEs are consistent with established safety profile. Spontaneous AEFI reporting is prone to bias, especially when all AEs are required to be reported or how new a vaccine is. Also lacks appropriate comparator groups. A general increase in AEFI reports seemed related to increased ELS reporting, but not in all countries, so a true increase in reactogenicity is unlikely with this combination vaccine. Post-marketing surveillance rates of ELS were 10-100-fold lower than in clinical trials. A small increase in risk of convulsions with or without fever and HHE are noted on the product label associated with coadministration of DTaP-IPV-HepB/Hib and PCV13.

Outcomes	Ref	Participants	Results	Findings
Coadministration	23	GSK review, 34 studies, 21,000 participants over 18 years. Coadministration with 12 different vaccines.	Coadministered with meningococcal C or ACWY (CRM or TT conjugated) vaccines: • >4000 infants, no SAE considered causally related to coadministration. • Drowsiness, fever, injection-site pain more frequent with coadmin MenACWY-TT • No statistically significant difference coadmin vs sequential. Coadmin MenB (plus PCV7) • Reactions associated with MenB. Prophylactic paracetamol recommended. Coadmin with PCV • Not assessed separately. (More PCV10 than PCV13 studies) • Post-marketing analysis indicated risk of convulsions (+/- fever) and HHE – those with history of febrile convulsions be closely monitored 2-3 days post vaccination. • Paracetamol – can reduce risk of febrile convulsions. Particularly for those with a history of seizures. Coadmin rotavirus • Well tolerated, conjunctivitis and rash more common (4% vs 0.5% and 2% vs 0%) in coadmin group. • One cases of Kawasaki disease considered vaccine related. Coadmin with MMRV • Fever at day 0-2 from DTaP-IPV-HepB/Hib and day 4-12 MMRV – both time points for those who received them concurrently. • Higher rates of fever in coadmin group than DTaP-IPV-HepB/Hib alone, similar for MMRV alone. • No SAE.	• There are no safety concerns around giving DTaP-IPV-HepB/Hib concomitantly with other infant schedule vaccines • In some cases concomitant vaccinations can increase the risk for fever. Paracetamol can be used to reduce risk of febrile convulsions, particularly for those with a history of seizures.

Abbreviations: AE – adverse events; AEFI – adverse events following immunisation; AESI – adverse events of special interest; DAEN – database of adverse event notifications; ELS – extensive limb swelling; HHE – hypertonic-hyporesponsive episode; MedDRA PT – Medical Dictionary for Regulatory Activities preferred terms; MenACWY-TT; meningococcal group ACWY vaccine conjugated with tetanus toxoid; SAE – serious adverse events; SD – sudden death; SUDI – sudden unexplained infant death; VAERS – vaccine adverse event reporting system

Table 4: Immunogenicity

Outcomes	Ref	Participants	Results	Findings
Infants				
Coadmin DTaP-IPV-HepB/Hib	23	GSK review, 34 studies, 21,000 participants over 18 years. Coadministration with 12 different vaccines.	Coadministered with ACWY (CRM or TT conjugated) vaccines: (at ages 2, 3, 4, 12 m) • One month after 3rd doses: 100% of infants had seroprotective antibody titres against Hib (plus PCV10). • Another study showed non-inferiority in children aged 12-23 months when given concurrently or sequentially 98-100% had seroprotective Hib antibodies Coadmin MenB (plus PCV7) • 98-100 had seroprotective Hib antibodies after coad and seq administration in 3 studies. • Receipt of paracetamol did not impact Hib response (≥96% seroprotected) Coadmin with PCV • All studies demonstrated a reduction in the magnitude of the antibody response when paracetamol was administered when PCV13 or PCV10 coadministered with DTaP-IPV-HepB/Hib – but did not affect proportion of those who achieved seroprotection/positivity. Not seen after booster. • Effect of paracetamol was not seen with MenB and PCV7 coadmin. Coadmin with MMRV • Did not impair immune response to DTaP-IPV-HepB/Hib antigens.	Coadministration did not negatively impact immunogenicity and seroprotective response rates for the vaccine antigens. No clinically significant interference was shown in clinical trials.
Booster DTaP-IPV-HepB/Hib	24	Randomised open-label trial in US – compared 3 primary doses DTaP-IPV-HepB/Hib with DTaP-IPV-HepB and separate Hib. Also following booster doses with DTaP and Hib or DTaP-IPV-HepB/Hib	Consistent with previous studies – anti-PRP antibody GMC were lower with combination vaccine that separate Hib. Less pronounced after Hib booster. Similar proportions achieved short-term protection (≥0.15µg/ml) following primary course and booster, and those achieved longer term protection (≥1µg/ml) after booster in DTaP-IPV-HepB/Hib and DTaP-IPV-HepB plus Hib separate vaccinations.	Combining Hib into DTaP-IPV-HepB/Hib did not interfere with the immune response to the other vaccine antigens., after primary vaccination or DTaP and Hib boosters.
Impact maternal vaccination	25	Phase 4 (GSK-sponsored) multi-country study. 601 infants, 296 received Tdap in pregnancy (from 27 weeks gestation), 305 placebo controls vaccinated with DTaP-IPV-HepB/Hib from age 2 months (schedules varied)	Infants seroprotection similar between groups at 1 month post primary vaccination: • Anti-DT, anti-TT – 100% for all ; anti-HBs 99.2% vs 98.5% • Hib-PRP (>0.15ug/ml) – 95.9 (92.7 – 97.9) Tdap vs 94.5% (91.0 – 96.9) placebo; (>1.0 µg/ml = 64.7 (58.6 – 70.4) Tdap vs 65.3 (59.3 – 71.0) control • Vaccine response rates against pertussis antigens were lower in Tdap group than controls	No evidence that maternally derived antibodies interfered with the infant response to Hib-PRP in terms of seroprotection rates or antibody levels after primary course with DTaP-IPV-HepB/Hib.

Continued over page

Outcomes	Ref	Participants	Results	Findings
OMP-conjugated Hib vaccine				
American Indian and Alaska Native infants	26	ACIP recommendations Phase 4 prospective open label RCT comparing DTaP-IPV-HepB-Hib (ages 2, 4, 6m, Vaxelis 3.0µg PRP-OMP) and Hib-PRP-OMP (aged 2, 4m 7.5µg PRP) vaccine in 330 Navajo Nation and Alaskan Native infants (age 42-90 days for first vaccination). Re-emergence of Hib in AI/AN	• Anti-Hib IgG, non-inferiority lower 95% CI >0.67. • Post dose 1 – GMCR met non-inferiority 30 days • Short term protection (Hib IgG ≥0.15 µg/ml) – hexa 75.7% vs monovalent 71.2% , p=0.39 • Post primary immunity (150 days, long term Hib IgG ≥1 µg/ml) 3 dose Hexa – 83.6% vs 2 dose monovalent 71.8%; p=0.03	Recommendations: primary series of either 2-dose monovalent PRP-OMV or 3 dose Hexa. booster – Vaxelis is not indicated as booster in the US (it is in Europe). Any formulation of Hib monovalent can be given at ages 12-15 months.
PRP-OMP hexa valent vaccine	31	Vaxelis – not approved for use in NZ. Summary of 5 phase 3 studies	Mixed regime of PRP-OMP containing vaccine as 3-dose primary course and PRP-T containing vaccine as 15-month booster induced very high Hib response (GMC ~50µg/mL)	
Comparison of hexavalent booster doses	5	Vaxelis – 3 µg Hib PRP conjugated to 50µg OMP Hexyon – 12µg Hib PRP conjugated to 22-36µg TT per dose booster doses at 167 infants age 11-13 months in those previously received 2 dose primary course of either vaccine	Comparable antibody-specific responses between groups: • D30 % ≥ anti-Hib IgG ≥1 µg/ml = 89.0 (79.5 – 95.1) Vaxelis vs 90.8 (81.9-96.2) Hexyon. • Response rates were higher after infant series with Vaxelis – more robust pre-booster responses than TT-conjugate combination vaccines.	Supported use of Vaxelis as a booster dose in a mixed hexavalent vaccine regimen. Findings were consistent with other interchangeability studies for combination vaccines.

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Outcomes	Ref	Participants	Results	Findings
2+1 schedule, France	14	Seroprevalence study Immunisation in France from 1992 3+1 (2, 3,4 and 16-18m) 2013 2+1 (2,4, 11m) coverage at 24m in 2017 = 95.4%	Increase in Hib 2017-2019, with several vaccine failures 501 isolates Of 56 Hib, 37 (66%) under 5y and were 13% of all Hi cases in <5s Median age 0.8 (range 0.2 – 4.7y) Vaccine failures – 24 children vaccinated 9 completely, 15 partially (1 or 2 doses), 13 unvaccinated. All vaccinated with 2+1 schedule. 2 cases in 2017, 11 each 2018 and 2019 Sera from 6 completely vaccinated cases • median age 2.5y (range 1.2-4.1) • all anti-PRP IgG <1µg/ml • GMC 0.40 µg/ml (95% CI 0.16-0.98) • Median delay between dose 3 and disease onset 1.6y (rang 0.3-3.2y) • 1 month post infection – GMC 6.59 µg/ml (2.85-15.22, p=0.01) Comparison – 130 sera pre 2013 (3+1) and 102 born since 2013 (2+1), divided by age Median anti-PRP IgG aged 2 years 2.9 µg/ml in 3+1 and 0.58 (2+1) p = 0.047 Proportion with short-term protection (>0.15 µg/ml) was lower for 2+1 group long term (>1µg/ml) 56% vs 25% (no stat diff)	Unlike children vaccinated with 3+1, antibody levels did not peak at age 2 years in children vaccinated with 2+1 Decline in titre are proposed as the reason for vaccine failures in 2+1 vaccinated children and titres of 0.15µg/ml may not be adequate for short term protection.
Older adults and special groups				
C2 deficiency	27	18 people with complement 2 deficiency (C2D) and 26 controls vaccinated with Act-HIB (age 10-adult). Mean age 38y C2D and 30y controls. Classical and lectin complement pathways dysfunctional. Bypass via mannose-binding lectin (MBL) dependent activation of alternate pathway.	• Complement function with serum bactericidal assay (SBA) - SBA response was increased in C2D after vaccination - Proportion with adequate SBA did not differ before or after vaccination. - Increased after vaccination in both C2D and controls. - In C2D persons, SBA after vaccination was inversely correlated to serum concentrations of Hib-specific antibodies. • MBL-dependent C2 bypass mechanism influences SBA activity of C2D serum. Putting those with concomitant MBL and C2 deficiency at high risk of infection. Particularly in unvaccinated.	Results demonstrated the value of vaccination in patients with C2D, with increased bactericidal capacity using post-vaccination sera with autologous complement.

Abbreviations: anti-HBs – anti-hepatitis B surface antigen antibody; C2D – complement-2 deficiency; DT – diphtheria toxoid; DTaP-IPV-HepB/Hib – diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B and *H. influenzae* type B combined vaccine; GMC – geometric mean concentration; Hib-PRP – *Haemophilus influenzae* type b polyribosylribitol phosphate; MBL – mannose-binding lectin; MenB – meningococcal B vaccine; MMRV – combined measles, mumps, rubella and varicella vaccine; PCV – pneumococcal conjugate vaccine (10 or 13 valent); SBA – serum bactericidal assay; Tdap – tetanus-diphtheria-acellular pertussis combined vaccine; TT – tetanus toxoid; y - years

Table 5: Effectiveness

Outcomes	Ref	Participants	Results	Findings
Infants				
Review of effectiveness of Infanrix-hexa	2	Reviewed data and peer-reviewed papers, Australia, 2009-2018; schedule 2, 4, 6m More than 9.6 million doses of DTaP-IPV-HepB/Hib GSK funded review.	• Over the time period, immunisation coverage in Indigenous children increased from 84.9% to 92.5% (all children 91.7 to 94.0%) • No reports of polio, diphtheria, tetanus. Hepatitis B in under 12m, 10-20-fold lower than national average. • Although there are disparities in annual rates (5.6 vs 0.4 per 100,000 ATSI vs non-ATSI) aged <5, this represents <2 cases per year and remains well controlled within indigenous population. • No resurgence in disease was seen with switch from OMV conjugated to TT conjugated vaccine in Australian Indigenous people. Disparities were related to vaccine uptake.	Timely primary series, starting from age 6 weeks or two months, and increased coverage rates has improved disease control for Hib, particularly in indigenous children with DTaP-IPV-HepB/Hib vaccine.

Vaccine failure, Portugal	15	Prospective national surveillance study between 2010 – 2021 in 40 hospitals in Portugal. 140 isolates collected through surveillance from children aged 0-17 years vaccine given at age 2, 4, 6 and 18 months between 2010-16 pentavalent age 2, 4, 6 and tetravalent at 18 months. Since 2017, pentavalent at 4 and 18, hexavalent at 2 and 6 months.
		
		Vaccine failure - ≥2wk after 1 Hib from age 12months or ≥1 after ≥2doses <1y.
			Serotyping – encapsulated 69/140 (49.3%) remaining NTHi (71/140, 50.7%).
			Serotype b = 41 cases (29.3% total invasive *H. influenzae* isolates),
			Other types = a (14.3%), e (1.4%) and f (4.3%)
			• 26 Hib cases (63%) considered vaccine failure
			  ○ 19 (73%) <5 y
			  ○ 12 (46%) age <18 months before booster
			
			comparing last 6 years with first 6 years – significant increase in total invasive Hi infections (IRR 1.84 (1.29-2.64, p<0.001)
			• Hib IRR 2.96 (1.44-6.54, p=0.001)
			• VF IRR 2.94 (1.19-8.29, p=0.011
			• VF –21.6% (19/88) vs 13.5% (7/52) total Hi-ID cases (p=0.232)
			• 2 deaths in VF group, 0 in non-VF group.
			
			20 / 26 children were previously healthy, 4 no information
			all 25 cases typed belonged to ST 6
			?interference from Men B and PCV13 vaccines – lower Ab titres increase colonisation and lower herd immunity. Serology 2015-2016 showed protective antibodies (>1µg/ml) in 88.5% 2-4 year olds and >75% in over 10s.Only 0.6% had titres <0.2 µ/ml
				High vaccination coverage >95% does not eliminate risks for ID and a few cases of VF can occur each year. No predisposing factors were clearly identified as to why there has been a significant increase in Hib and vaccine-failure cases. Both Hi colonisation and serosurveys should be implemented alongside surveillance for invasive Hi.

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Outcomes	Ref	Participants	Results		Findings
Vaccine failure Australia	28	Notifiable disease surveillance (NNDSS), 2000-2017, 345 cases focus on 153 cases born after 1 Jan 2000. Two deaths in 2017 of vaccinated children prompted this review. Vaccination status obtained from Australian Immunisation Register. In 2018, booster dose was moved from age 12 months to 18 months	Incidence: • All-age invasive Hib halved from 0.13 / 100,000 population 2000 to 0.06 in 2017 (IRR 0.45; 0.21-0.90; p = 0.0016) • 153 / 345 cases born after 2000, 51 (33%) ATSI • ATSI vs non-indigenous IRR 8.34 (5.83-11.79) with no evidence of a decrease vaccine type: • Era 1 (2000-2005 PRP-OMP) vs Era 2 (2010-2017, PRP-T) incidence 20.5 vs 17.5; p<0.01 ages: • Median age of notification: 8 years, 45% <5 and 11% aged ≥70 y • Similar rates between ages 0-6 m and 7-12 months (1.61 and 1.68) ATSI wsa younger than non-indigenous – median 14 months vs 14 years (46% vs 18% <1 year) deaths • Case fatality rate 12.4% (19 deaths / 153); median age 7 months (range 37 day to 10 years) 6 cases had underlying conditions	Vaccine effectiveness: • no vaccine vs ≥1 dose incidence 8x higher (16.6/100,000 vs 1.9/100K) • VF = 45% of cases (65/145) aged ≥8 weeks. 7 (11%) immunocompromised and 6 (9%) died. • VF 88% (n=57) were fully immunised for age; ~ ½ fully immunised with PRP-T and ¾ fully immunised with PRP-OMP • Time to VF after last dose PRP-OMP 23m (37d-11y) vs PRP-T 6 months (34d-6y); total 13m (34d – 11y) • No evidence of increasing VF with time.	Hib cases were already low prior to 2000. Although Hib declined by 55% from 2000 to 2017, there was a marked disparity between indigenous and non-indigenous children. Emphasised importance of timely vaccination, esp in Indigenous children who are disproportionately affected by Hib. Ongoing surveillance needed to monitor 3-dose vaccine failures with moving of booster.

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Outcomes	Ref	Participants	Results	Findings
Invasive Hib, vaccine change	29	Case-control study, Netherlands to estimate effectiveness of DTaP-IPV-HepB/Hib from 2011.(given at ages 2, 3, 4, 11m). Cases from 2003-2016 <5y vs controls matched by date of birth. Increase in Hib reported in 2016 that coincided switch to hexa from penta (DTaP-IPV-Hib) vaccine from 2011. Did addition of HepB component change effectiveness against Hib?	included 159 cases and 1590 controls, median age 1.5 y (IQR 0.8-2.9) 91 cases (57%) vs 1408 (89%) controls vaccinated. Immunisation coverage from 94.2% in 1999 to 96.1% in 2016 Overall VE – 92.8% (95% CI 88.7-95.4%), no differences between year of onset (p=0.97) • No difference in VE between vaccine (penta/other vs hexa) = 91.8% (86.1-95.1) vs 94.0% (89.0-96.8); OR 0.72; 0.36-1.45; p=0.36 • Highest VE aged 1-2 years – 91.1-99.0%; highest VE for this cohort from 2011 with Hexa vaccine (but not significantly diff from early cohorts) • Lowest VE 3 – 4 years = 60.7-82.3%; p= 0.0008 • Booster dose was found to be important – VE 77% after 3 primary doses vs 95% after 4 doses in those aged >1 year.	Hib vaccine effectiveness did not decrease over time or with introduction of Hexa combination vaccine. VE waned with age. Increase in Hib likely to be due to factors other than the change in the immunisation programme. Question arose as to whether increased carriage in older children with waning immunity increases risk to younger infants, even with constant VE – particularly if the immunisation coverage declined.
2+1 schedule	30	Netherlands, from 2020 infants vaccinated antenatally given 2+1 schedule at 3, 5, 11m vs 3+1 schedule at 2, 3, 5, 11m (no antenatal vaccination or born prematurely). Vaccine product changed from pentavalent (DTaP-IPV-/Hib) in 2011, to hexavalent DTaP3-IPV-HepB/Hib and then to hexavalent DTaP5-IPV-HepB/Hib vaccine in 2019 = differ carrier, adjuvant and length of Hib component.	Increase in Hib during 2020 and 2021 when most respiratory infections decreased. • 40% of Hib cases were under 5 years – increase in incidence from <2.6 per 100,000 1996-2019 to 3.3 and 2.6 in 2020 and 2021. • 17-19 vaccinated cases had received 4 doses vaccine. • vaccine failures 2020 = 10, and 2021 = 8 to Aug vs 8/year in previous 5 years. Based on population coverage at age 2 years: • VE estimated 97% (78-97) in 2021 vs 92% (88-95) in 2015-2019 = overall VE unchanged • Lower uptake in 2021 Vaccine failure defined as Hib when under 12 month and received ≥2 doses or aged >12m, received primary and booster or at least one dose >1st birthday	Based on a small number of cases, overall, no indication of a change in vaccine effectiveness with a change in schedule and vaccine composition.

Abbreviations: As for Table 4; IRR – incidence risk ratio; VE – vaccine effectiveness; VF – vaccine failure

Literature search

Medline

- *Haemophilus Infections/ and Haemophilus Vaccines/ and Humans/ and Haemophilus influenzae/ and Vaccination/ = 101
    - limit to (english language and humans and yr="2018 -Current") [12/8/2025] = 6, selected 5
- *Haemophilus influenzae/ and Vaccination/ 237
    - limit to (english language and humans and yr="2015 -Current") = 18, selected 10
- Selected 26, removed 3 duplicates (24 Sept. 2025)

SCOPUS

- title/abstract/Keyword: “Hemophilus influenzae type b” vaccine, 2015-2025, English = 2269
- title/abstract/Keyword "haemophilus influenzae b vaccine” publication year 2018 < 2026 limit to "English" = 65 Selected 10
- Keyword "haemophilus influenzae b" Publication year 2018-<2026 “English" = 71 Selected 12 removed duplicates

Further references were obtained from the above literature, casual searches as keywords emerged and grey literature. Total library 69 references.

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