

Progress towards eliminating Hib in Australia: An evaluation of *Haemophilus influenzae* type b prevention in Australia, 1 July 1993 to 30 June 2000

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Abstract

The status of *Haemophilus influenzae* (Hib) disease and its prevention by vaccination was reviewed for the period 1997 to 2000. This forms the background to a change in national vaccine policy, from the use of two Hib vaccines to the use of PRP-OMP only throughout Australia from May 2000. Notifications of Hib in the 7-year period between 1993 and 2000 declined by 87 per cent among children 0–4 years of age; adjustment for likely under-reporting increase this to a 95 per cent reduction. Among age groups not included in the immunisation program, there was also a substantial decline in notified cases. Overall, a minimum 430 cases and 13 deaths were prevented by Hib immunisation annually in Australia. Enhanced Hib surveillance recorded 532 cases over seven years, with 353 in unvaccinated persons, 74 fulfilling criteria for true vaccine failure and 75 partially immunised. Of unvaccinated cases, 60 and 182 were eligible for routine and catch-up immunisation respectively. Although the overall incidence for 0–4 years of age declined from 15 to 1.2 cases per 100,000 population, the proportion of cases under six months of age increased from 11 per cent to 23 per cent. Overall vaccine effectiveness, estimated using data from the last five years of the program, was 83 per cent (95% CI 71–91%), increasing to 90 per cent (95% CI 83–94%) when adjusted for under-reporting to the Australian Childhood Immunisation Register. Among Aboriginal and Torres Strait Islander people, the incidence of invasive Hib disease fell from 4.6 cases per 100,000 population to 0.7 cases per 100,000 population but the proportion of cases now occurring among Aboriginal or Torres Strait Islander people increased significantly, from 7 to 15 per cent. The Hib immunisation program in Australia has been highly successful. Nevertheless, experience in Australia and elsewhere indicates that continued careful monitoring of Hib disease, with high quality laboratory surveillance, remains important. *Commun Dis Intell* 2003;27:324–341.

Keywords: disease surveillance, disease control, *Haemophilus influenzae*, immunisation, vaccination

Introduction

Haemophilus influenzae type b (Hib) is a bacterium which causes serious morbidity and mortality, particularly in children. Conjugate Hib vaccines were first marketed in Australia in May 1992 for children over 18 months of age, and in January 1993 for children from two months of age. In April 1993, a publicly funded Hib immunisation program was introduced for infants across Australia; this was extended in July 1993 to all children under the age of five years. Up to May 2000, two different Hib vaccines were in general use. The first, conjugated to the outer membrane protein of *Neisseria meningitidis* (PRP-OMP), was used for all children in the Northern Territory and for Indigenous children elsewhere in Australia. The second was conjugated to a mutant

diphtheria toxin (HBOC) and was used in other children throughout Australia. In May 2000, the immunisation schedule was changed so that all children in Australia received PRP-OMP. The aim of this report is to describe the public health impact of the first seven years of the Hib immunisation program in Australia.

Invasive *Haemophilus influenzae* type b disease

Haemophilus influenzae occurs widely in humans, both as a colonising and disease-producing organism in the respiratory tract. Different types of *Haemophilus influenzae* can be distinguished on the basis of whether or not they possess a capsule and its characteristics. Non-encapsulated strains are associated with respiratory illness whilst encapsulated strains are associated with invasive

disease, that is serious disease where the organism can be isolated from a normally sterile site such as blood or cerebrospinal fluid (CSF). Of the many different capsulated strains, six (designated a-f) are known to cause disease in man. Prior to the introduction of immunisation one capsular serotype, *Haemophilus influenzae* type b, was the cause of nearly all cases of *Haemophilus influenzae* invasive disease.^{1,2,3}

Hib can cause a range of clinical illness. The commonest are meningitis, septicaemia and epiglottitis. Other manifestations include cellulitis, pneumonia and septic arthritis. Hib is predominantly a disease of childhood with over 80 per cent of cases worldwide occurring in children aged less than five years.⁴ In Australia, invasive Hib has been a notifiable disease in most Australian jurisdictions since 1990.

***Haemophilus influenzae* type b in Australia before immunisation**

Prior to the introduction of immunisation, Hib was the commonest cause of bacterial meningitis in Australian children.^{5,6} Special surveys of the incidence of Hib in Australia prior to the introduction of immunisation have produced a range of estimates (Table 1).^{2,3,4-9} The different estimates between studies in part reflect the use of different methods for defining and identifying cases, but also represent heterogeneity in the distribution of risk. Aboriginal communities in Australia have rates as much as 10 times higher than non-Aboriginal communities. The high incidence of Hib disease in Aboriginal people is compatible with the high burden of other infectious diseases in this community. A similar picture is seen amongst disadvantaged Indigenous communities in other countries.⁴ Non-Aboriginal children in central Australia also appear to be at increased risk of contracting invasive Hib disease.³

***Haemophilus influenzae* type b vaccines and the Australian schedule**

Vaccines using the polyribosylribitol phosphate (PRP) polysaccharide of the Hib capsule were first developed in the 1970s, but these vaccines produced a T-cell-independent immune response that was not effective in protecting children aged less than 18 months.¹⁰ Linking the PRP polysaccharide to a protein (conjugation), enhanced the immunogenicity of the vaccine by enabling T-cell stimulation. The first conjugated vaccine against Hib was licensed in Australia in May 1992 for children aged 18 months and over. Vaccines licensed for use in children aged more than six weeks became available in January 1993 (Table 2).

In May 1993 reimbursement of the cost of Hib vaccine was introduced for children born after February 1993.^{11,12} In July 1993 a fully funded infant Hib vaccination program was launched, and in

August 1993 a catch-up vaccination program for all children aged less than five years was launched (Table 3).

Between 1993 and June 2000, a different Hib schedule was recommended for Indigenous children and non-Indigenous children (Table 4). Studies of Hib epidemiology in the pre-immunisation era showed that Aboriginal children had a higher incidence of invasive Hib disease than non-Aboriginal children and an earlier mean age of onset. Serological evidence suggested that in young infants a single dose of the PRP-OMP vaccine elicited a better immune response than a single dose of the HbOC vaccine.¹³ Aboriginal children were therefore recommended to receive PRP-OMP at two and four months with a booster at 12 months whilst non-Aboriginal children were recommended HbOC at two, four and six months with a booster at 18 months. In June 2000 the Hib schedule was changed again with PRP-OMP at two and four months and a booster dose at 12 months being recommended for all children.

Methods

Study period

Hib immunisation became fully funded for all children as part of the Australian Standard Vaccination Schedule in July 1993 and remained unchanged until June 2000. The bulk of this report analyses data on Hib disease by financial year of disease onset. This allows analysis of seven complete years of the program: 1 July 1993 to 30 June 2000.

Data sources

Population denominators

For the years 1991 and 1996 resident populations were derived from the Australian Bureau of Statistics (ABS) Census of Population and Housing. For the intervening years, resident populations are estimated by ABS by adjusting the most recent five yearly Census of Population and Housing for births, deaths and net migrations. When calculating incidence rates by financial year, the estimated resident population for the year beginning the financial year was used. For example, for the financial year 1992–93 the denominator was the estimated resident population for 1992. (At the time of writing, estimated populations of those aged 0, 1, 2, 3 and 4 years were not available for 1999 and therefore the figures for 1998 have been used.)

National Notifiable Diseases Surveillance Scheme

Invasive Hib disease has been part of the National Notifiable Diseases Surveillance Scheme since its inception in 1990. The case definition used for notification of invasive Hib disease to the NNDSS is shown in Figure 1.

Table 1. Studies of the incidence of invasive *Haemophilus influenzae* type b disease in Australian children aged under 5 years

Source	Population	Period	Rate per 100,000
McGregor ²	ACT	1984–1990	63
Hanna ³	NT (Aboriginal)	1985–1988	529
	NT (non-Aboriginal)	1985–1988	92
McIntyre ⁶	Sydney	1985–1987	39
Gilbert ⁸	Victoria	1985–1987	59
Hanna ⁵	WA (Aboriginal)	1984–1988	150 (meningitis only)
	WA (non-Aboriginal)	1984–1988	27 (meningitis only)
Markey ⁹	NT (all)	1989–1993	141
	NT (Aboriginal)	1989–1993	278

Table 2. Conjugated *Haemophilus influenzae* type b vaccines licensed in Australia

Generic name	Trade name	Hib antigen	Conjugating protein
PRP-D	ProHIBit	Hib capsular polysaccharide	Diphtheria toxoid protein
HbOC	HibTITER	Hib capsular oligosaccharide	Mutant diphtheria toxoid protein (CRM 197)
PRP-OMP	PRP-OMPHIB	Hib capsular polysaccharide	Outer membrane protein of group B meningococcus
PRP-T	Act-HIB	Hib capsular polysaccharide	Tetanus toxoid protein

Table 3. Significant events in *Haemophilus influenzae* type b immunisation practice in Australia, 1992 to 2001

Year	Month	Event
1992	May	PRP-D (ProHIBit) approved for vaccination of infants aged at least 18 months.
1993	January	HbOC (HibTITER) and PRP-OMP (PRP-OMPHIB) marketed for use in children aged at least 2 months.
1993	April	PRP-T (Act-HIB) marketed for use in children aged at least 2 months.
1993	May	Reimbursement of vaccine cost for children born after February 1993.
1993	July	Fully funded national infant immunisation program.
1993	August	Fully funded one dose catch up campaign for children aged less than 5 years.
2000	February	Combined Hib (PRP-OMP)-hepB vaccine approved.

Table 4. Recommended *Haemophilus influenzae* type b immunisation for Indigenous and non-Indigenous Australian children, July 1993 to June 2000

	Recommended vaccine	Primary schedule	Booster dose
Indigenous children	PRP-OMP	2 & 4 months	12 months
Non-Indigenous children	HbOC	2, 4 & 6 months	18 months

Figure 1. Case definition* for notification of invasive *Haemophilus influenzae* type b disease to NNDSS

- a) a clinically compatible illness (meningitis, epiglottitis, cellulitis, septic arthritis, osteomyelitis, pneumonia, pericarditis or septicaemia), *and* either
- the isolation of *Haemophilus influenzae* type b (Hib) from blood, *or*
 - detection of Hib antigen in a clinical case, *or*
 - detection of Gram-negative coccobacilli where the organism fails to grow in a clinical case
- or
- b) a confident diagnosis of epiglottitis by direct vision, laryngoscopy or X-ray

* Note: The case definition for notification used in Victoria includes only isolates from cases of meningitis or epiglottitis.

Information collected through the NNDSS includes date of onset, age in years, gender and state or territory. A field for Indigenous status exists but is rarely completed. Notifications to NNDSS are through the provisions of local public health legislation; therefore each State or Territory health authority determines which diseases will be notifiable within its jurisdiction.

Although all states and territories were reporting invasive Hib to NNDSS by June 1993, there are a number of anomalies in the earlier Hib notification data. Western Australia did not start notifying cases until March 1993.¹⁴ Although Victoria, Tasmania, the Australian Capital Territory and South Australia did not officially start reporting invasive Hib until 1993, these four States did report substantial numbers of cases to NNDSS in 1991 and 1992. The Northern Territory officially started reporting Hib in 1991 but no cases were reported in 1991.

Due to the uncertainty about when states began reporting and the complexity introduced by trying to exclude certain states or territories from both the numerator and denominator for certain years or parts of years, this report has assumed that all states and territories started reporting in 1991. The effect of this is to underestimate the incidence of Hib in the years preceding the introduction of routine immunisation.

Data on notified cases of invasive Hib were obtained from the National Notifiable Diseases Surveillance Scheme as of 2 July 2001.

Haemophilus influenzae type b case surveillance scheme

The Hib case surveillance scheme is an enhanced surveillance system designed to collect supplementary information on cases of invasive Hib not available from the NNDSS. The HCSS was established in January 1994 with data collected retrospectively to 1 July 1993. State and Territory health authority officers complete an enhanced surveillance form for each case of invasive Hib disease. The case definition used to identify cases of invasive Hib disease from the HCSS data is shown in Figure 2.

Figure 2. Case definition used for *Haemophilus influenzae* type b case surveillance scheme data

- Isolation of Hib from a normally sterile site (blood/CSF/joint fluid)
- or
- identification of Hib antigen in serum, CSF, joint fluid or urine in the presence of an illness clinically compatible with invasive Hib disease (meningitis, septicaemia, epiglottitis, cellulitis, septic arthritis, osteomyelitis, pneumonia or pericarditis)
- or
- a confident clinical diagnosis of epiglottitis by direct vision, laryngoscopy or X-ray

Additional information collected through this enhanced surveillance scheme includes date of birth, clinical illness, immunisation status, ethnicity and outcome of the illness. Data on cases of invasive Hib were obtained from the HCSS as of 5 July 2001.

Estimating expected number of cases

In the first instance, the impact of immunisation on invasive Hib disease has been estimated by comparing the observed frequency of cases in the seven years 1993–94 to 1999–00 to the expected frequency in those years, based on the incidence reported in 1991–92 and 1992–93.

Age standardisation has been used to control for the effect of changes in the age structure of the population. The expected number of cases was calculated by multiplying the age-specific incidence rates derived from the aggregated data of 1991–92

and 1992–93 by the population at risk in each age stratum for the years 1993–94 to 1999–00. The age strata used were 0, 1, 2, 3, 4, 5–9, 10–14 and 15+ years. Because the age of some cases reported in 1991–92 and 1992–93 is not known (28/1,049) the pre-immunisation incidence rates used to estimate expected cases are underestimates.

Definitions of vaccine status

A number of definitions were applied to identify eligibility for vaccination and vaccination status of cases (Figure 3). Doses of vaccine given less than

15 days prior to disease onset were excluded from determination of immunisation status.

Vaccine coverage estimates

The Australian Childhood Immunisation Register contains information on the vaccination status of all Australian children born since 1 January 1996 and registered with Medicare. At the time of compiling this report data were available for immunisation encounters up to 30 June 2001.

A second or third dose assumption was used when estimating coverage. If the second PRP-OMP or third HbOC was recorded as having been given, it

Figure 3. Definitions of vaccination eligibility and vaccination status

1. Ineligible for vaccination

Born before 1 August 1988.

2. Catch-up cohort

Born between 1 August 1988 and 28 February 1993 inclusive.

3. Eligible for routine infant immunisation

Born from 1 March 1993 onwards.

4. Fully immunised

- One dose of any Hib vaccine given at age one year or older.
- Two doses of PRP-OMP before the age of one year.
- Three doses of HbOC before the age of one year.

5. Partially immunised

- One dose of any Hib vaccine before the age of one year.
- Two doses of HbOC before the age of one year.

6. Unimmunised

No Hib immunisations.

7. True vaccine failure

Invasive Hib disease (see HCSS case definition) with disease onset more than 14 days after:

- One dose of any Hib vaccine given at age one year or older;
- Second dose of PRP-OMP given before the age of one year;
- Third dose of any Hib vaccine given before the age of one year.

8. Apparent vaccine failure

Invasive Hib disease after:

- One dose of any Hib vaccine before the age of one year;
- Two doses of HbOC before the age of one year;
- One dose of any Hib vaccine given at age one year or older but before sufficient time has elapsed to be true vaccine failure;
- Two doses of PRP-OMP before the age of one year but before sufficient time has elapsed to be true vaccine failure;
- Three doses of HbOC before the age of one year but before sufficient time has elapsed to be true vaccine failure.

was assumed that the preceding doses had also been given. If a child was recorded as having both a second dose of PRP-OMP and a third dose of HbOC the child was categorised as being fully immunised with three doses of HbOC. This approach was used because the majority of children in Australia would have been eligible for the HbOC schedule rather than the PRP-OMP schedule.

Vaccine failure rate

To estimate the vaccine failure rate the number of true vaccine failures was divided by the number of children fully vaccinated. The failure rate was estimated separately for two doses of PRP-OMP before the age of one year and for three doses of HbOC before the age of one year. The number of children fully vaccinated by the age of one year was estimated from the ACIR for children born between 1 January 1996 (when the ACIR started) and 30 June 2000. True vaccine failures were identified for children born during the same period.

Estimating vaccine effectiveness

The screening method was used to assess vaccine effectiveness as this can be performed using data on the vaccination status of cases and the population vaccine coverage (Figure 4).

Figure 4. Formula for assessing vaccine effectiveness using screening method

$$VE = PPV - PCV / PPV (1 - PCV)$$

where

VE = vaccine effectiveness

PPV = proportion of population vaccinated (adjusted to exclude partially vaccinated)

PCV = proportion of cases vaccinated (excluding partially vaccinated)

As both age and year of disease onset may be associated with the risk of disease and independently associated with vaccination status, these factors may confound the relationship between vaccination status and disease status. To correct for these two potential confounding factors, vaccine effectiveness was estimated by fitting a logistic regression model as previously described,¹⁵ including age group and year of disease onset as covariates. Seven years, 1993–94 to 1999–00, and four age strata, 6 to 11 months, 12 to 23 months, 24 to 35 months and 36 to 47 months, were entered into the model.

Vaccine effectiveness (VE) was estimated for the primary Hib schedule of two doses of PRP-OMP or three doses of HbOC before the age of one year. VE estimates could not be calculated separately for the HbOC and PRP-OMP schedules because recording of Indigenous status on the ACIR was incomplete. This means that the number of children eligible but not fully vaccinated cannot be determined for each schedule separately.

All the children in the birth cohorts used to calculate vaccine effectiveness were eligible for the infant schedule. Where a child was recorded as having received three doses of a Hib vaccine but the type of vaccine was not recorded it was assumed that the vaccine was HbOC. As for the estimation of vaccine coverage, the second and third dose assumptions were used.

The proportion of cases vaccinated was adjusted to exclude partially vaccinated children. The proportion of cases vaccinated was calculated as the number of cases having received either two doses of PRP-OMP or three doses of HbOC divided by these cases plus unvaccinated cases.

For the purpose of estimating vaccine effectiveness, coverage with either two doses of PRP-OMP or three doses of HbOC was assessed in each of the four years 1996–97, 1997–98, 1998–99 and 1999–00. In each of these years, coverage estimates were stratified by age. The age strata used were 6 to 11.99 months, 12 to 23.99 months, 24 to 35.99 months and 36 to 47.99 months. Because the ACIR only started in 1996, coverage data were not available for any age bands prior to 1996 and for certain age bands after 1996. For years where coverage data were not available, the coverage value for that age band in the closest available year was used (Appendix A).

Coverage in each financial year was estimated by assessing the proportion of each relevant birth cohort who had received either two doses of PRP-OMP or three doses of HbOC by the mid-point of the financial year (1 January). The proportion of the population vaccinated (PPV) was adjusted to exclude partially vaccinated children. PPV was calculated as the number of children fully vaccinated (two doses of PRP-OMP or three doses of HbOC) divided by the number of children fully vaccinated and unvaccinated (no doses of Hib vaccine).

Coverage in catch-up cohort

Of the children who were eligible to receive one dose of Hib vaccine as part of the catch up campaign launched in August 1993, it is not known what proportion actually received the vaccine. An estimate of the proportion of this group vaccinated was calculated using the equation for estimating vaccine efficacy (Figure 4) and assuming vaccine effectiveness of full immunisation (Figure 3) of 90 per cent.

Results

National Notifiable Diseases Surveillance Scheme

Trends by age group over time

As of 2 July 2001, 1,621 cases of invasive Hib disease with disease onset between 1 July 1991 and 30 June 2000 were recorded on the NNDSS database. Overall, 55 per cent of cases were male. The number of notifications has declined substantially since the introduction of routine Hib immunisation (Figure 5). The rate of disease has declined in all age groups, but particularly in children aged less than five years (Figure 6).

Figure 5. Number of notifications of invasive *Haemophilus influenzae* type b disease, Australia, 1 July 1991 to 30 June 2000, by month and year of onset

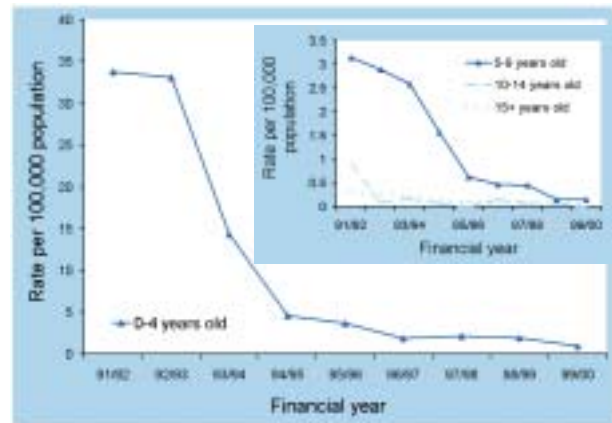


Source: National Notifiable Diseases Surveillance Scheme, 1 July 1991 to 30 June 2000.

Overall, if the age-specific incidence rates observed in 1991–92 and 1992–93 were to have occurred during the seven year period since the introduction of Hib immunisation (July 1993 to June 2000), 3,602 cases of invasive Hib disease would have been expected. However, only 572 cases were reported during this period, 84 per cent less than expected. This means that, over the last seven years, Hib immunisation has prevented more than 3,000 cases of invasive Hib disease. Of these, it would have been expected that around 90 (3%)⁴ would have died as a consequence of their infection. Or put another way, Hib immunisation has prevented at least 430 cases and 13 deaths each year in Australia.

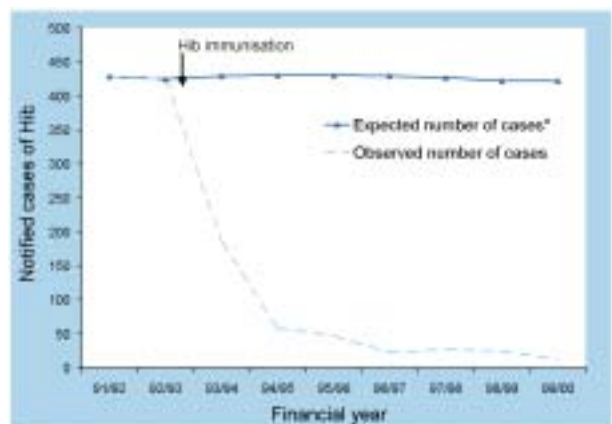
In children aged less than five years, 2,994 cases of invasive Hib disease would have been expected during the seven year post-immunisation period. There were actually 379 cases reported, 87 per cent less than expected (Figure 7).

Figure 6. Rate of invasive *Haemophilus influenzae* type b disease notifications per 100,000 population, Australia, 1991–92 to 1999–00, by financial year of onset and age at onset



Source: National Notifiable Diseases Surveillance Scheme, 1 July 1991 to 30 June 2000.

Figure 7. Observed and expected number of notified cases of invasive *Haemophilus influenzae* type b disease in children aged less than five years, Australia, 1991–92 to 1999–00



Source: National Notifiable Diseases Surveillance Scheme, 1 July 1991 to 30 June 2000.

* Expected number of cases calculated by multiplying the age-specific incidence rates derived from the aggregated data of 1991–92 and 1992–93 by the person years at risk in each age stratum for the years 1993–94 to 1999–00. Age strata used were 0, 1, 2, 3, 4 years.

Estimates of the incidence of invasive Hib disease in children under the age of five years derived from surveys undertaken in the pre-vaccination era are higher than the estimate obtained from the NNDSS data (Table 1). This is probably because there is under-ascertainment of cases through the NNDSS mechanism. Using estimates of invasive Hib disease

obtained from special studies in the pre-vaccination era gives a higher estimate of the effectiveness of the Hib vaccination program in children aged less than five years (Table 5).

Herd immunity effect

Herd immunity refers to the protection from a disease experienced by unvaccinated individuals in a community where there is reduced transmission of the infection as a result of a large proportion of the community being vaccinated. To detect a herd immunity effect as a result of routine Hib immunisation, changes in the incidence of invasive Hib disease in unvaccinated age groups were examined.

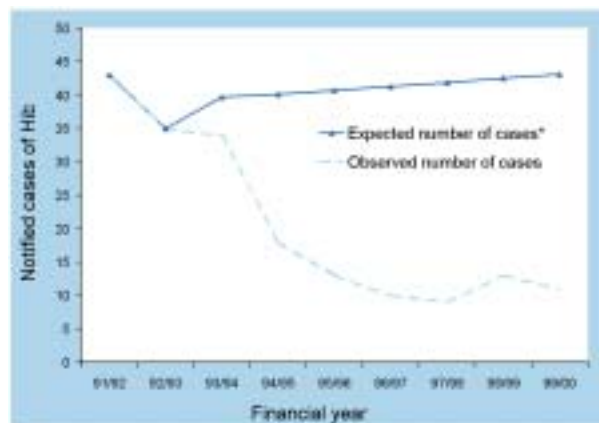
Throughout the period 1993–94 to 1999–00, any person aged 15 years or over would not have been eligible for immunisation. The expected number of cases in persons aged 15 years and older in the seven year period 1993–94 to 1999–00 was 290. The observed number of cases was 108, 63 per cent less than expected (Figure 8).

Between 1993–94 and the end of financial year 1997–98, individuals aged 10–14 years would also have been ineligible to receive Hib vaccination. The expected number of cases in the 10–14 years age group during the five years 1993–94 to 1997–98 was 30. The observed number was six, 80 per cent less than expected.

Trend by state over time

Figure 9 shows the crude incidence rate per 100,000 population for each state and territory in Australia by phases of the immunisation program. Comparing the 1992–93 incidence rate to the 1999–00 incidence rate reveals a reduction of between 86 per cent and 100 per cent in all states and territories (Table 6).

Figure 8. Observed and expected number of notified cases of invasive *Haemophilus influenzae* type b disease in people aged 15 years and older, Australia, 1991–92 to 1999–00



Source: National Notifiable Diseases Surveillance Scheme, 1 July 1991 to 30 June 2000.

* Expected number of cases calculated by multiplying the age-specific incidence rate derived from the aggregated data of 1991–92 and 1992–93 by the population at risk for the years 1993–94 to 1999–00.

Hib case surveillance scheme

The Hib case surveillance scheme collects information on each case of Hib disease that is not available from routine notifications. Examination of the HCSS data therefore provides a more detailed picture of the impact of immunisation on the epidemiology of invasive Hib disease, but lacks comparative data from the pre-vaccination period.

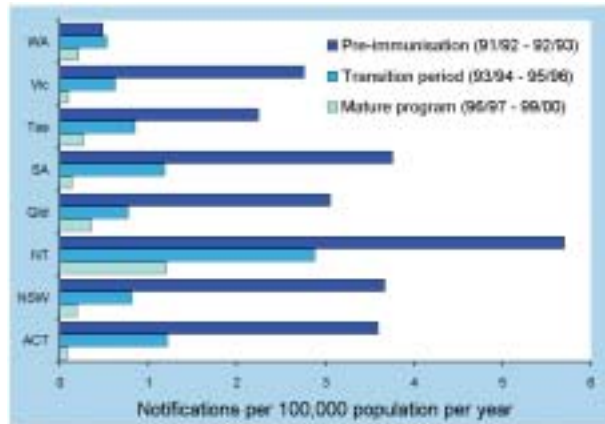
Table 5. Estimated reduction in the incidence of invasive *Haemophilus influenzae* type b in children less than 5 years of age, Australia, 1993–94 to 1999–00

Source	Rate per 100,000 population	Expected number of cases 1993–94 to 1999–00*	Program effectiveness† %
McGregor ²	63	5,689	93
Hanna ³	92 (non-Indigenous)	8,308	95
McIntyre ⁶	39	3,522	89
Gilbert ⁸	59	5,328	93
Markey ⁹	50 (non-Indigenous)	4,515	92

* Rate per 100,000 population multiplied by total person years at risk aged less than five years 1993–94 to 1999–00 divided by 100,000. Person years at risk aged less than five years 1993–94 to 1999–00 = 9,030,474.

† $[1 - (\text{observed cases in 0–4 year olds 1993–94 to 1999–00} / \text{expected})] \times 100$. Observed cases in 0–4 year olds 1993–94 to 1999–00 = 379.

Figure 9. Incidence of notified cases of invasive *Haemophilus influenzae* type b disease per 100,000 population, Australia, 1991–92 to 1999–00, by state or territory and financial year



Source: National Notifiable Diseases Surveillance Scheme, 1 July 1991 to 30 June 2000.

Table 6. Incidence of notified cases of invasive *Haemophilus influenzae* type b disease per 100,000 population, by state or territory and reduction in incidence between 1992–93 and 1999–00

State or territory	Year		Reduction* %
	1992–93	1999–00	
ACT	2.38	0.33	86
NSW	3.30	0.11	97
NT	11.30	0.52	95
Qld	2.87	0.31	89
SA	3.64	0.13	96
Tas	2.34	0.00	100
Vic	2.45	0.04	98
WA	0.96	0.05	95
Total	3.15	0.13	96

* $(1 - (99-00 \text{ rate} / 92-93 \text{ rate})) \times 100$.

As of 5 July 2001, 542 cases of invasive Hib disease with onset between 1 July 1993 and 31 June 2000 were recorded on the HCSS dataset. Five hundred and thirty-two cases satisfied the case definition for invasive Hib disease (Figure 2). The following analysis relates only to the 532 cases meeting the case definition. During the same period 572 cases were reported to the NNDSS. Enhanced surveillance data

are therefore available on 93 per cent of notified cases of invasive Hib disease.

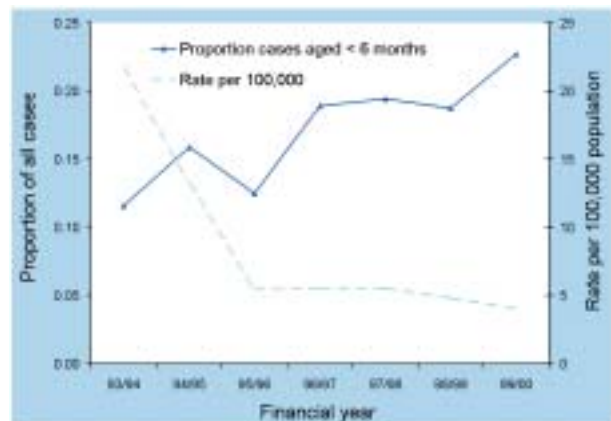
Age

Unlike the NNDSS, which only provides the age of cases in years before 1998, the HCSS provides the date of birth of persons with invasive Hib disease. The rate of disease in children aged less than six months of age is of particular interest, given the use of two different schedules in Australia. The primary HbOC schedule is not complete until six months of age whilst the primary PRP-OMP schedule is complete by four months of age.

During the study period, 77 cases of invasive Hib disease in children aged less than six months were reported to the HCSS. Although the rate of disease in children aged less than six months has declined since the introduction of immunisation, the decline has not been as great as in other age groups. Consequently, a greater proportion of cases now occur in children aged less than six months (Figure 10). This trend is statistically significant (chi-squared test for linear trend, $p < 0.05$). Over the time period being studied, the proportion of the population aged less than one year has remained stable at around 1.5 per cent, so this trend is not related to a change in the age structure of the population.

There has also been an increase in the proportion of cases occurring in older age groups. In 1993–94, 12 per cent (29/246) of cases were in people aged 15 years or over. In 1999–00, 30 per cent (7/23) of cases were aged 15 years or over.

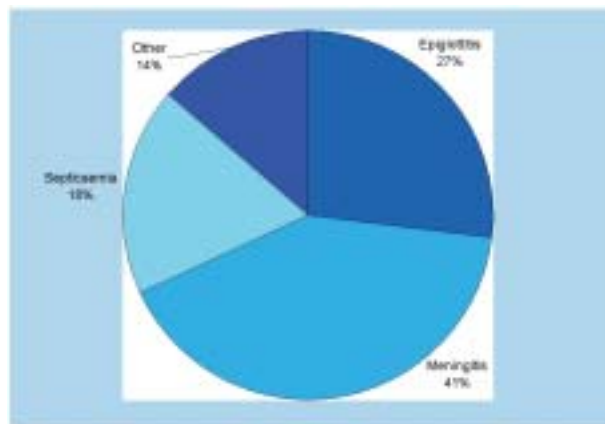
Figure 10. Proportion of all cases reported to HCSS occurring in children aged less than six months and reporting rate per 100,000 children aged less than six months, 1 July 1993 to 30 June 2000



Site of invasive disease

Over the period covered by the HCSS data, the commonest clinical presentation was meningitis followed by epiglottitis (Figure 11).

Figure 11. Cases of invasive *Haemophilus influenzae* type b disease reported to HCSS, Australia, 1 July 1993 to 30 June 2000, by clinical diagnosis, all ages



As shown in previous studies^{4,6,16,17} meningitis is the predominant clinical picture in children aged less than five years, whilst epiglottitis is the commonest presentation in older children (Table 7). In infants, meningitis is the presenting clinical picture in 67 per cent of cases. Since the introduction of immunisation there has been a decline in all clinical presentations of invasive Hib disease. In 1993–94 septicaemia accounted for 15 per cent of cases (36/242) whilst in

1999–00 it accounted for 32 per cent (7/22) of cases. However, four of the seven cases in 1999–00 were aged over 25 years, so this change is a reflection of the increased proportion of cases occurring in people aged over 15 years.

Of the 144 epiglottitis cases, 110 were laboratory confirmed by either the isolation of Hib from a normally sterile site or a positive Hib antigen test. Of the 110, the majority (103) had a positive blood culture. Therefore, of the 532 cases reported to HCSS, 6 per cent (34) were based on a clinical diagnosis of epiglottitis without laboratory confirmation. The proportion of reported cases based solely on a clinical diagnosis of epiglottitis without laboratory confirmation has not increased over time.

Case-fatality ratio

The case-fatality ratio appears to have been relatively stable over the seven year period with the exception of an unusually high case-fatality ratio in 1999–00 (Table 8).

Of the 26 fatal cases since 1993/94, 15 were male (58%) and two (8%) were Aboriginal or Torres Strait Islander people. Nine deaths occurred in children aged less than five years. The case-fatality ratio in children less than five years old was 2.4 per cent (9/371).

Vaccination status of cases

Information on vaccine status was not available for 30 of the 532 cases (6%) reported to HCSS with disease onset between 1 July 1993 and 30 June 2000.

Of the 502 cases for which information on vaccine status was available, 77 were fully immunised but only 74 (15%) were true vaccine failures, as three cases received the most recent dose of vaccine less than

Table 7. Clinical diagnosis of cases of invasive *Haemophilus influenzae* type b disease reported to HCSS, Australia, 1 July 1993 to June 2000, by age group

Illness	Age group in years					Total
	0 to 4	5 to 9	10 to 14	15 +	Unknown	
Cellulitis	22	1	1	0	0	24
Epiglottitis	76	35	1	29	3	144
Meningitis	192	19	1	6	0	218
Pneumonia	14	2	1	8	0	25
Septicaemia	56	6	3	31	1	97
Septic arthritis	6	2	0	1	0	9
Other	2	1	0	4	0	7
Unknown	3	1	0	4	0	8
Total	371	67	7	83	4	532

15 days prior to disease onset (Figure 12). The median age of the 74 true vaccine failures was 1.9 years and 61 per cent were male. Compared to all other cases combined, a higher proportion of true vaccine failures were of Aboriginal or Torres Strait Islander origin (12% vs 7%). The clinical presentation of true vaccine failures was not different from the clinical presentation of other cases. Of the 45 true vaccine failures who had received at least three doses of any Hib vaccine before the age of one year, 12 had received both the primary course of HbOC and a booster dose at age 18 months.

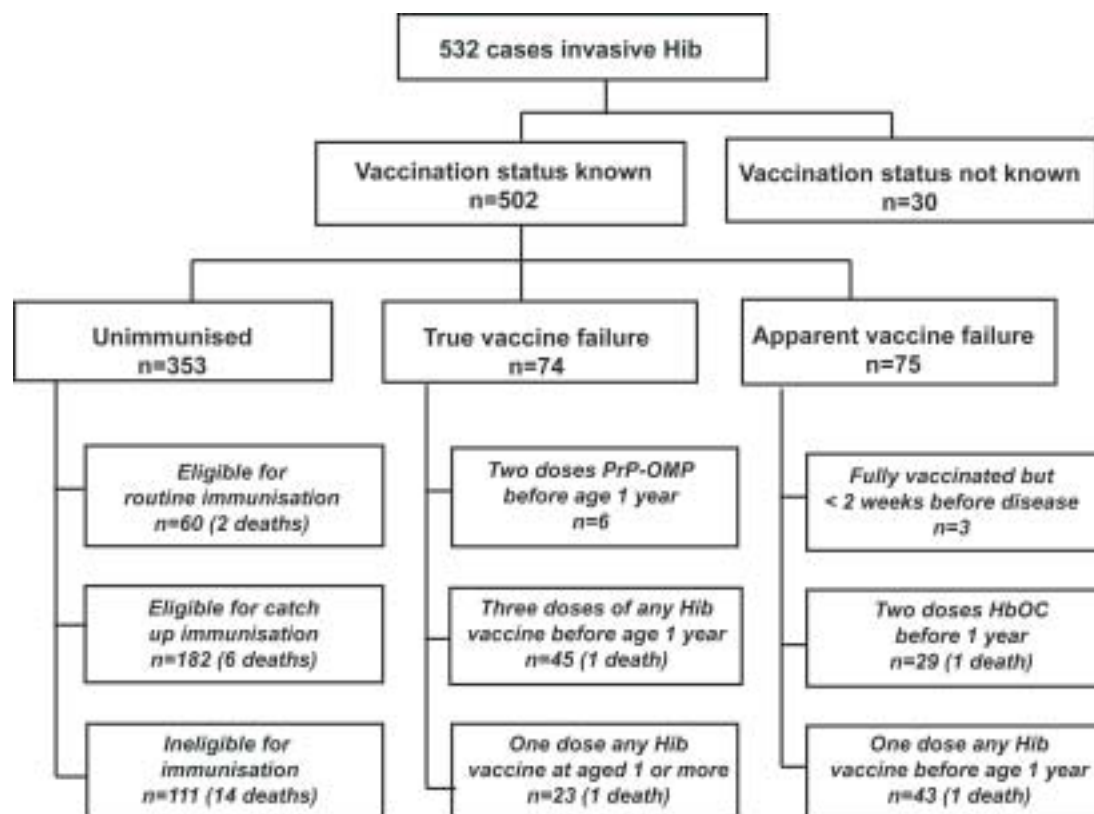
Three hundred and fifty-three cases (70%) were unimmunised: of these, 60 were eligible for routine immunisation and 182 for catch-up immunisation. The median age of the 60 cases eligible for the routine program was eight and a half months, half occurring in the first two years of the immunisation program. Of the 182 cases eligible for catch-up immunisation but receiving no vaccine, 90 per cent were in the first two years of the program. Their median age was 2½ years.

Of the partially immunised children, the median age of the 29 who had received two doses of HbOC before the age of one year was 7.2 months and, of the 43 who had received only one dose of vaccine before the age of one year, 4.7 months.

Table 8. Case-fatality ratio of cases reported to HCSS, Australia, 1 July 1993 to 30 June 2000

Outcome of illness	Financial year of onset							Total
	93/94	94/95	95/96	96/97	97/98	98/99	99/00	
Died	10	5	3	2	2	1	3	26
Survived	225	93	52	30	29	28	17	474
Unknown	7	9	1	5	5	3	2	32
Total	242	107	56	37	36	32	22	532
Case-fatality ratio (%)	4.1	4.7	5.4	5.4	5.6	3.1	13.6	4.9

Figure 12. Vaccination status of 532 cases of invasive *Haemophilus influenzae* type b reported to HCSS, 1 July 1993 to 30 June 2000



Potentially preventable cases

Disease occurring in unimmunised or partially immunised individuals is considered to have been potentially preventable by HbOC immunisation if the individual was aged over 6½ months of age at disease onset. By this age individuals could have received three scheduled doses of HbOC and had two weeks for an immune response to develop. Disease occurring in unimmunised or partially immunised individuals is considered to have been potentially preventable by PRP-OMP immunisation if the individual was aged over 4½ months of age at disease onset. By this age, individuals could have received two scheduled doses of PRP-OMP and had two weeks for an immune response to develop. Children who were not eligible for routine immunisation because they were born before March 1993 have been excluded from this analysis. Using these criteria, of the 532 cases of invasive Hib disease occurring between 1 July 1993 and 30 June 2000, a total of 53 (10%) might have been prevented by more timely HbOC immunisation, and 86 (16%) might have been prevented by more timely PRP-OMP immunisation (Table 9). There is also the possibility that the potential to complete the vaccination schedule with a booster dose at 12 months of age would further reduce cases in the second year of life, depending on relative vaccine effectiveness after various numbers of doses.

Table 9. Age distribution of cases potentially preventable by HbOC vs PRP-OMP vaccine

Immunisation status of case eligible for routine vaccination	Number of cases	Age	
		>4½ months	>6½ months
Unimmunised	60	41	25
Two doses HbOC before age 1 year	29	27	16
One dose of any Hib vaccine before age of 1 year*	38	18	12
Total	127	86	53

* Five cases have been excluded who were not eligible for routine vaccination.

Vaccine failure rate

In the cohort of children born between 1 January 1996 and 30 June 2000, 6 per cent are recorded on the ACIR as having received two doses of PRP-OMP before their first birthday and 82 per cent are recorded as having received three doses of HbOC by their first birthday. However, the ACIR is known to underestimate coverage, particularly in the early years of the Register, so the denominator will be underestimated.

Sixty-eight cases of Hib disease in children born after 1 January 1996 are recorded on the HCSS. Of these, 16 were true vaccine failures. Fourteen had received three doses of HbOC by their first birthday and two had received two doses of PRP-OMP before their first birthday. Based on these denominator estimates, crude vaccine failure rates of 1 in 68,100 for three doses of HbOC before the first birthday, and 1 in 34,732 for two doses of PRP-OMP before the first birthday, can be calculated. This does not take into account the higher disease incidence in many, predominantly indigenous, recipients of PRP-OMP.

Vaccine effectiveness

In the initial logistic regression model, there was no difference in estimated vaccine effectiveness across the four age bands, but there was a significant difference across years. The vaccine effectiveness estimates for the years 1993–94 and 1994–95 were significantly higher than for other years. Since the proportion of the population vaccinated in these two years was extrapolated from data available in later years, the vaccine coverage values for these years are likely to be less accurate than estimates for later years. The model was therefore run again, excluding data from the years 1993–94 and 1994–95.

After this exclusion there was no effect by year or age, so the data were pooled to give an overall estimate of vaccine effectiveness across the years 1995–96 to 1999–00 and ages 6 to 47 months. In this model vaccine effectiveness was 83 per cent, 95 per cent confidence limits 72 per cent to 91 per cent.

The screening method is relatively sensitive to errors in the estimated proportion of the population vaccinated.¹⁸ Vaccine coverage as measured by the ACIR is known to underestimate coverage by between 2 and 5 per cent.¹⁹ To assess the effect of underestimating vaccine coverage on vaccine efficacy the model was re-run with higher values for vaccine coverage. If the estimates of the proportion of the population vaccinated are increased by 3 per cent, vaccine effectiveness becomes 90 per cent, with 95 per cent confidence limits of 83 per cent to 94 per cent.

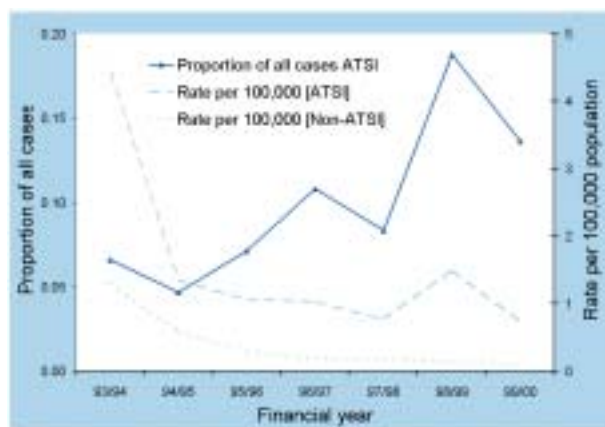
Coverage in the catch-up cohort

Forty-one per cent (221) of cases of invasive Hib disease occurring between 1 July 1993 and 30 June 2000 were children eligible for the catch-up campaign. Of these 221 cases, 182 were unimmunised, 24 fully immunised, six partially immunised and nine of unknown immunisation status. After excluding partially immunised children and cases where immunisation status was unknown, the proportion of cases fully vaccinated was 11.6 per cent (24/206). Assuming a vaccine effectiveness of 90 per cent gave an estimate of the proportion of children eligible for the catch-up campaign who were vaccinated of 57 per cent.

Aboriginal and Torres Strait Islanders

Aboriginal and Torres Strait Islanders status was recorded in 89 per cent (473/532) of reports to HCSS during the period 1 July 1993 to 30 June 2000. The estimated proportion of the Australian population who are of Aboriginal origin is around 2 per cent, yet 8 per cent of cases (41) were recorded as being of Aboriginal origin. There were equal numbers of male and female cases. Since the introduction of immunisation, the absolute number of cases in Aboriginal people has declined; however, there has been an increase over time in the proportion of cases occurring in this population group (Figure 13). As the proportion of the Australian population who are of Aboriginal origin has remained stable over the period 1993–94 to 1999–00, this trend is not related to changes in the proportion of the Australian population that are of Aboriginal origin. The trend is statistically significant (chi-squared test for linear trend, $p=0.02$).

Figure 13. Proportion of cases of invasive *Haemophilus influenzae* type b disease reported to HCSS who are reported as being of Aboriginal origin, Australia, 1 July 1993 to 30 June 2000



Source of ATSI population data: *The health and welfare of Australia's Aboriginal and Torres Strait Islander people*. Australian Bureau of Statistics, Commonwealth of Australia, 2001.

The median age of the 429 non-Aboriginal cases where age was known was 2.4 years (mean 10.2 years) whereas the median age of the 41 Aboriginal cases was 0.9 years (mean 3.7 years). Of the 26 deaths from invasive Hib between 1 July 1993 and 30 June 2000, two (8%) were recorded as being Aboriginal, and 16 of the 41 Aboriginal cases (39%) were reported from the Northern Territory.

Of the 41 reported Aboriginal cases, 20 had received no vaccinations—10 were eligible for routine immunisation, eight were eligible for a catch-up dose and two were not eligible for immunisation. Nine of the 41 Aboriginal cases (22%) were true vaccine failures, compared to 56 of 432 (13%) cases reported as non-Aboriginal. All nine had received at least two doses of PRP-OMP and five had received three doses of PRP-OMP. No deaths occurred amongst Aboriginal true vaccine failures.

Epiglottitis accounted for 30 per cent (129/432) of invasive Hib cases in non-Aboriginal people but only 5 per cent (2/41) of cases in Aboriginal persons. The case-fatality ratio in cases of Aboriginal origin was 4.9 per cent (2/41) which is similar to the case-fatality ratio of 4.6 per cent (20/432) seen in non-Aboriginal cases.

Discussion

Impact of immunisation on the epidemiology of *Haemophilus influenzae* type b

The introduction of routine Hib vaccination in Australia has resulted in a dramatic and substantial reduction in the incidence of invasive Hib disease. This is the first review of the impact of Hib vaccines nationally since the results of the first three years of the program (July 1993 to June 1996) were reported in 1997.²⁰ In the four years 1996–97 to 1999–00, the average annual rate of invasive Hib disease in children less than five years of age was 1.7 cases per 100,000 population. This compares to a rate of 1.4 cases per 100,000 population in the United States of America (USA) in 1998 and 1999 and 1.6 in 2000,²¹ and 1.8 cases per 100,000 population in the United Kingdom (UK) in 2000.²²

Although the reduction has been most marked in the target population of children aged less than five years, reduced incidence has been seen in all age groups, even those not eligible for immunisation. This herd immunity effect has been seen in other countries^{22–26} and demonstrates the impact of widespread immunisation on transmission of Hib in the community. This substantial herd immunity effect occurs because conjugate Hib vaccines prevent not only Hib disease but also carriage of Hib in the nasopharynx.^{26–28}

Two methods were used in this study to estimate the impact of Hib immunisation. The first method compared the observed number of notifications with

expected numbers based on notified cases prior to July 1993. Estimates derived in this way are likely to be underestimates for two reasons. Firstly, during the early years of the NNDSS not all states and territories were reporting. Consequently, notification data prior to July 1993 are relatively more incomplete than later notification data. Projected numbers of notifications based on notifications prior to July 1993 are therefore underestimates. Secondly, information on age was missing from a proportion of cases reported to NNDSS in 1991, 1992 and 1993, therefore these cases had to be excluded from the calculation of the age-standardised rates.

The second method used to estimate the impact of Hib immunisation compared the observed number of notifications with expected numbers estimated from special surveys in the pre-Hib immunisation era. Estimates derived using this method are likely to be overestimates. This is because case ascertainment is likely to have been more complete in the pre-vaccination studies than for the routinely collected NNDSS data.

Given that the results of the two estimation methods are likely to represent upper and lower boundaries of the true program effectiveness, it is reasonable to conclude that Hib immunisation has reduced the incidence of Hib in children less than five years by between 87 per cent and 95 per cent.

As in other studies,²² there is no evidence that immunisation has altered the clinical spectrum of invasive Hib disease. Meningitis remains the commonest presentation in infants and children aged less than five years, with epiglottitis being the predominant presentation in older children. In Australia, epiglottitis is more common than septicaemia even when epiglottitis cases without laboratory confirmation are excluded. In many other countries, septicaemia is commoner than epiglottitis.²⁹ This feature of the Australian epidemiology of Hib was observed prior to the introduction of immunisation^{2,6,8} and has also been observed in several Scandinavian countries.³⁰ It remains unexplained.

The case-fatality ratios observed since 1993–94 are consistent with previously published reports from Australia^{3,6,8} and other developed countries.^{21,29,31,32} The reason for the high case-fatality ratio in 1999–00 is not clear, but the low total number of cases does mean that small changes in the number of deaths can result in large changes in the case-fatality ratio.

Since the introduction of immunisation a greater proportion of cases has occurred in children aged less than six months. This reflects the fact that immunisation does not fully protect until the primary course is complete and has been observed elsewhere.²⁹ The move from HbOC to PRP-OMP may improve this situation in Australia, as the PRP-OMP primary course is completed at four months as opposed to six months, assuming that the effectiveness of two doses of PRP-OMP is at least equivalent to three doses of HbOC.

Overall, the number of reported Hib cases in males slightly exceeds the number reported in females. This pattern was found in pre-immunisation data in Australia^{2,6,8} and elsewhere.³² A pre-vaccination study in the Northern Territory reported a higher rate of Hib disease in Aboriginal females than in Aboriginal males, particularly for *Haemophilus influenzae* meningitis.^{3,5} In Aboriginal cases reported to the HCSS since 1993, the gender ratio was equal with more male meningitis cases than female.

Although the incidence of invasive Hib disease has declined substantially in the Aboriginal population, the decline has not been as great as that seen in other populations. Aboriginal people remain at higher risk than other members of the population and now constitute a greater proportion of all cases than in the pre-immunisation period. Between 1996–97 and 1999–00, the average annual incidence rate in Aboriginal children aged less than five years was 6.7 cases per 100,000 population. This remains lower than a rate of 14 cases per 100,000 population reported by the United States of America in American Indian and Alaskan Native children aged less than five years in 1998–2000.²¹ Despite the introduction of immunisation, Aboriginal children are still infected at a younger age than non-Aboriginal children. Indigenous populations in other countries suffer higher rates of Hib carriage and disease than non-Indigenous populations despite good vaccine coverage.^{24,33,34} Persistent carriage has been implicated in a resurgence of Hib disease in Alaska following a change from PRP-OMP to HbOC for primary immunisation.³⁴

The proportion of cases of invasive Hib that present with epiglottitis remains much lower in Aboriginal children than in non-Aboriginal children. Although previous studies in Australia have failed to identify epiglottitis in any Aboriginal children,^{3,35,36} two cases were identified through enhanced national surveillance.

Strain typing

The enhanced Hib surveillance scheme does not attempt to verify the strain of *Haemophilus influenzae* reported. It is likely that laboratory capacity to type isolates of *Haemophilus influenzae* is becoming increasingly limited. In the USA, serotype was reported for around 80 per cent of all invasive *Haemophilus influenzae* cases reported between 1998 and 2000 and only 30 per cent of these were type b.²¹ Aggregated data from nine European countries between 1996 and 1998 showed that 90 per cent of *Haemophilus influenzae* isolates from children aged under 15 years were typed and 58 per cent of these were type b.²⁹

Hanna found that 15 per cent of invasive *Haemophilus influenzae* infections in Aboriginal children were caused by non-type b strains.³ The continuing higher incidence and the increased vaccine failure rate seen in the Aboriginal population could be partly explained by higher carriage and incidence of non-type b disease in this population group, if some *H. influenzae* isolates were incorrectly identified as type b.³⁷

Vaccine effectiveness

Measures of the effectiveness of an immunisation program using observed and expected disease rates cannot separate the direct protection to individuals afforded by immunisation and the indirect protection provided by herd immunity. Vaccine effectiveness estimates using the screening method measure only the direct protective effect of immunisation. Using this method vaccine effectiveness in Australia was high with no observed variation in effectiveness by age.

In the initial logistic regression model the vaccine effectiveness in the years 1993–94 and 1994–95 was significantly higher than other years. These years were excluded from the model as this finding was probably a consequence of inaccurate coverage estimates in these years. In 1993–94 and 1994–95, vaccine coverage was likely to be lower than in later years. However, because data were not available from the ACIR, coverage data for these years was extrapolated from later years. Consequently the 1993–94 and 1994–95 coverage estimates used in the model are probably overestimates, which would inflate vaccine effectiveness estimates. This is because vaccinated cases are actually coming from a smaller population of vaccinated people than is assumed, making the true incidence in the vaccinated population higher than estimated, and falsely raising vaccine effectiveness.

The value of booster doses of Hib conjugate vaccines has been debated for some time.^{38–40} Over the seven year immunisation period, the incidence of invasive Hib in children aged 18 to 30 months was about 40 per cent lower than in children aged 6 to 18 months. However, this may not be attributable to the effect of the 18 months HbOC booster dose as pre-immunisation data show an age-dependent risk of disease, with two-year-olds having a 30 per cent lower incidence than one-year-olds.

Vaccine failures

The vaccine failure rate appears to be higher for PRP-OMP than HbOC and higher in Aboriginal children than in non-Aboriginal children. However, since Aboriginal children are at increased risk of Hib compared to non-Aboriginal children, the apparently high failure rate of PRP-OMP in the Aboriginal population may be a reflection of increased exposure to infection in this population rather than of poor vaccine performance. It might also represent a higher rate of non-type b infection, which will not be prevented by Hib vaccination.

Of 114 cases occurring in children eligible for routine vaccination and aged six months or older, 27 (24%) were unimmunised, 30 (26%) were under-immunised, and 51 (45%) were fully immunised. Vaccination status was unknown for six cases. In the USA in 1998–2000 only 35 per cent of Hib cases in children aged six months or older had completed the primary series. Therefore, in Australia vaccine failures appear to constitute a higher proportion of Hib cases than in the USA. A recent collaborative study found that in Australia a similar proportion of Hib cases occurred in vaccinated children as in the UK, Ireland and Germany, but that this was higher than in a number of other European countries.²⁹ Why this might be so is not clear and warrants enhanced efforts to identify possible reasons for vaccine failures. There is evidence that a significant proportion of vaccine failures are related to underlying immunological or clinical problems,^{22,40} data not currently routinely collected in the HCSS.

Surveillance methods

A clinical diagnosis of epiglottitis, without microbiological confirmation, was the criteria for notification of only 6 per cent of Hib cases to the enhanced surveillance system. Seventy per cent of epiglottitis cases were confirmed by blood culture. It is possible that the specificity for Hib disease of a clinical diagnosis of epiglottitis may have changed following the introduction of Hib immunisation. However, as these cases constitute only a small proportion of total epiglottitis, it seems unnecessary to alter the current case definition to exclude clinically identified epiglottitis.

The reasons for the apparently high rate of vaccine failures in Australia and the continued increased risk amongst Aboriginal children are issues which may be at least partially addressed by improving laboratory typing of isolates of *Haemophilus influenzae* and acquiring detailed medical histories in vaccine failures.

Achieving elimination or eradication of *Haemophilus influenzae* type b disease in Australia

Hib is now an infrequent cause of illness in Australia, however control of Hib can be improved. About half the cases occurring in children aged over six months could be prevented by improved timeliness of immunisation. The recent change to the PRP-OMP schedule from the HbOC schedule has the potential to further reduce the number of cases of Hib disease, by decreasing the age at which the primary schedule is completed.

It is conceivable that indigenous Hib disease could be eradicated from Australia, but gaps in our understanding remain. The investigation of vaccine failures, particularly in Aboriginal children, and further characterisation of *Haemophilus influenzae* carriage and disease in this population could help to further improve control of Hib. The re-emergence of Hib in a Native Alaskan population following a change in the vaccine used, recent increases in Hib disease in the UK and the isolation of unusually pathogenic non-b *Haemophilus influenzae* serotypes are all reminders that control of Hib should not be taken for granted.^{22,35,41}

It is important that enhanced surveillance of *Haemophilus influenzae* disease at the laboratory and public health level is continued in Australia.

Appendix A

Birth cohorts used to estimate vaccine coverage for vaccine effectiveness estimates

Encounters up to: Age band	Financial year			
	1 July 1996– 30 June 1997	1 July 1997– 30 June 1998	1 July 1998– 30 June 1999	1 July 1999– 30 June 2000
	1 January 1997 Birth cohort	1 January 1998 Birth cohort	1 January 1999 Birth cohort	1 January 2000 Birth cohort
6 to 11.99 months	2 January 1996 to 1 July 1996	2 January 1997 to 1 July 1997	2 January 1998 to 1 July 1998	2 January 1999 to 1 July 1999
12 to 23.99 months	Unavailable	2 January 1996 to 1 January 1997	2 January 1997 to 1 January 1998	2 January 1998 to 1 January 1999
24 to 35.99 months	Unavailable	Unavailable	2 January 1996 to 1 January 1997	2 January 1997 to 1 January 1998
36 to 47.99 months	Unavailable	Unavailable	Unavailable	2 January 1996 to 1 January 1997

Appendix B

Calculation of the proportion of cases in catch-up cohort vaccinated

Denominator = all cases of invasive Hib occurring between 1 July 1993 and 30 June 2000 in children eligible for the catch-up campaign (date of birth 1 August 1988 to 28 February 1993).

Numerator = cases of invasive Hib occurring between 1 July 1993 and 30 June 2000 in fully vaccinated children eligible for the catch up campaign (date of birth 1 August 1988 to 28 February 1993). Excluding partially immunised children (n=6) and vaccination status unknown (n=9).

Calculation

$$PCV = 24/24+182 = 0.116$$

$$VE = PPV - PCV / PPV (1 - PCV)$$

$$0.9 = PPV - 0.116 / PPV (1 - 0.116)$$

$$0.9 = PPV - 0.116 / 0.884 PPV$$

Multiply through by 0.884 PPV

$$0.884 PPV \times 0.9 = PPV - 0.116$$

$$0.796 PPV = PPV - 0.116$$

Subtract PPV from each side

$$-0.204 PPV = -0.116$$

$$0.204 PPV = 0.116$$

$$PPV = 0.116 / 0.204$$

$$PPV = 0.57$$

References

1. Koo W, Oley C, Munro R, Tomlinson P. Systemic *Haemophilus influenzae* infection in childhood. *Med J Aust* 1982;2:77–80.
2. McGregor AR, Bell JM, Abdool IM, Collignon PJ. Invasive *Haemophilus influenzae* infection in the Australian Capital Territory region. *Med J Aust* 1992;156:569–572.
3. Hanna JN. The epidemiology of invasive *Haemophilus influenzae* infections in children under five years of age in the Northern Territory: a three-year study. *Med J Aust* 1990;152:234–236, 238, 240.
4. Peltola H. Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. [Review] *Clin Microbiol Rev* 2000;13:302–317.
5. Hanna JN, Wild BE. Bacterial meningitis in children under five years of age in Western Australia. *Med J Aust* 1991;155:160–164.
6. McIntyre PB, Leeder SR, Irwig LM. Invasive *Haemophilus influenzae* type b disease in Sydney children 1985 to 1987: a population-based study. *Med J Aust* 1991;154:832–837.
7. Harris A, Hendrie D, Bower C, Payne J, de Klerk, Stanley F. The burden of *Haemophilus influenzae* type b disease in Australia and an economic appraisal of the vaccine PRP-OMP. *Med J Aust* 1994;160:483–488.
8. Gilbert GL, Clements DA, Broughton SJ. *Haemophilus influenzae* type b infections in Victoria, Australia, 1985 to 1987. *Pediatr Infect Dis J* 1990;9:252–257.
9. Markey P, Krause V, Boslego JW, Coplan PM, Dargan JM, Kaplan KM. The effectiveness of *Haemophilus influenzae* type b conjugate vaccines in a high risk population measured using immunization register data. *Epidemiol Infect* 2001;126:31–36.
10. Peltola H, Kayhty H, Sivonen A, Makela H. *Haemophilus influenzae* type b capsular polysaccharide vaccine in children: a double-blind field study of 100,000 vaccinees 3 months to 5 years of age in Finland. *Pediatrics* 1977;60:730–737.
11. McIntyre P. Invasive *Haemophilus influenzae* type b disease. *Aust Fam Physician* 1993;22:1782–1789.
12. McIntyre PB, Chey T, Smith WT. The impact of vaccination against invasive *Haemophilus influenzae* type b disease in the Sydney region. *Med J Aust* 1995;162:245–248.
13. Shapiro ED, Ward JI. The epidemiology and prevention of disease caused by *Haemophilus influenzae* type b. [Review] *Epidemiol Rev* 1991;13:113–142.
14. Annual report of the National Notifiable Disease Surveillance System, 1993. *Commun Dis Intell* 1994;18:518–548.
15. Farrington CP. Estimation of vaccine effectiveness using the screening method. *Int J Epidemiol* 1993;22:742–746.

16. Clements DA, Guise IA, MacInnes SJ, Gilbert GL. *Haemophilus influenzae* type b infections in Victoria, Australia, 1985 to 1989. *J Infect Dis* 1992;165 Suppl 1:S33–S34.
17. Gilbert GL. Epidemiology of *Haemophilus influenzae* type b disease in Australia and New Zealand. *Vaccine* 1991;9 Suppl:S10–3; discussion S25.
18. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field. Further observations. *Epidemiol Rev* 1988;10:212–241.
19. Hull B, Lawrence G, MacIntyre CR, McIntyre P. Immunisation coverage: Australia 2001. Canberra: Commonwealth Department of Health and Ageing; 2002.
20. Herceg A. The decline of *Haemophilus influenzae* type b disease in Australia *Commun Dis Intell* 1997;21:173–176.
21. Progress toward elimination of *Haemophilus influenzae* type b invasive disease among infants and children—United States, 1998–2000. *MMWR Morb Mortal Wkly Rep* 2002;51:234–237.
22. Heath PT, McVernon J. The UK Hib vaccine experience. *Arch Dis Child* 2002;86:396–399.
23. Moulton LH, Chung S, Croll J, Reid R, Weatherholtz RC, Santosham M. Estimation of the indirect effect of *Haemophilus influenzae* type b conjugate vaccine in an American Indian population. *Int J Epidemiol* 2000;29:753–756.
24. Millar EV, O'Brien KL, Levine OS, Kvamme S, Reid R, Santosham M. Toward elimination of *Haemophilus influenzae* type b carriage and disease among high-risk American Indian children. *Am J Public Health* 2000;90:1550–1554.
25. Rushdy A, Ramsay M, Heath PT, Azzopardi HJ, Slack MP. Infant Hib vaccination and herd immunity. *J Pediatr* 1999;134:253–254.
26. Barbour ML, Mayon-White RT, Coles C, Crook DW, Moxon ER. The impact of conjugate vaccine on carriage of *Haemophilus influenzae* type b. *J Infect Dis* 1995;171:93–98.
27. Adegbola RA, Mulholland EK, Secka O, Jaffar S, Greenwood BM. Vaccination with a *Haemophilus influenzae* type b conjugate vaccine reduces oropharyngeal carriage of *H. influenzae* type b among Gambian children. *J Infect Dis* 1998;177:1758–1761.
28. Forleo-Neto E, de Oliveira CF, Maluf EM, Bataglin C, Araujo JM, Kunz LF Jr, et al. Decreased point prevalence of *Haemophilus influenzae* type b (Hib) oropharyngeal colonization by mass immunization of Brazilian children less than 5 years old with Hib polyribosylribitol phosphate polysaccharide-tetanus toxoid conjugate vaccine in combination with diphtheria-tetanus toxoids-pertussis vaccine. *J Infect Dis* 1999;180:1153–1158.
29. Handford S, Andrews N, Rushdy A, Ramsay M, Slack M, Heath P. An evaluation of *Haemophilus influenzae* type b (Hib) vaccination and description of risk factors for Hib vaccine failure in Europe 1996–1999. Final Report. London: PHLS Communicable Disease Surveillance Centre; 2002.
30. Claesson BA. Epidemiology of invasive *Haemophilus influenzae* type b disease in Scandinavia. *Vaccine* 1993;11 Suppl 1:S30–S33.
31. Booy R, Hodgson SA, Slack MP, Anderson EC, Mayon-White RT, Moxon ER. Invasive *Haemophilus influenzae* type b disease in the Oxford region (1985–91). *Arch Dis Child* 1993;69:225–228.
32. Anderson EC, Begg NT, Crawshaw SC, Hargreaves RM, Howard AJ, Slack MP. Epidemiology of invasive *Haemophilus influenzae* infections in England and Wales in the pre-vaccination era (1990–2). *Epidemiol Infect* 1995;115:89–100.
33. Singleton R, Bulkow LR, Levine OS, Butler JC, Hennessy TW, Parkinson A. Experience with the prevention of invasive *Haemophilus influenzae* type b disease by vaccination in Alaska: the impact of persistent oropharyngeal carriage. *J Pediatr* 2000;137:313–320.
34. Galil K, Singleton R, Levine OS, Fitzgerald MA, Bulkow L, Getty M, et al. Reemergence of invasive *Haemophilus influenzae* type b disease in a well-vaccinated population in remote Alaska. *J Infect Dis* 1999;179:101–106.
35. Bower C, Condon R, Payne J, Burton P, Watson C, Wild B. Measuring the impact of conjugate vaccines on invasive *Haemophilus influenzae* type b infection in Western Australia. *Aust N Z J Public Health* 1998;22:67–72.
36. Hanna JN, Wild BE, Sly PD. The epidemiology of acute epiglottitis in children in Western Australia. *J Paediatr Child Health* 1992;28:459–464.
37. Smith-Vaughan HC, McBroom J, Mathews JD. Modelling of endemic carriage of *Haemophilus influenzae* in Aboriginal infants in Northern Australia. *FEMS Immunol Med Microbiol* 2001;31:137–143.
38. Booy R, Heath PT, Slack MP, Begg N, Moxon ER. Vaccine failures after primary immunisation with *Haemophilus influenzae* type-b conjugate vaccine without booster. [Erratum in *Lancet* 1997;349:1630.] *Lancet* 1997;349:1197–1202.
39. Coen PG, Heath PT, Garnett GP. The Hib immunization programme in the Oxford region: an analysis of the impact of vaccine administration on the incidence of disease. *Epidemiol Infect* 1999;123:389–402.
40. Heath PT, Booy R, Griffiths H, Kimball A, Hindiyeh M, Carroll K, et al. Clinical and immunological risk factors associated with *Haemophilus influenzae* type b conjugate vaccine failure in childhood. *Clin Infect Dis* 2000;31:973–980.
41. Adderson EE, Byington CL, Spencer L, et al. Invasive serotype a *Haemophilus influenzae* infections with a virulence genotype resembling *Haemophilus influenzae* type b: emerging pathogen in the vaccine era? *Pediatrics* 2001;180:E18.