The effectiveness of *Haemophilus influenzae* type b conjugate vaccines in a high risk population measured using immunization register data

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SUMMARY

The Northern Territory of Australia has had historically very high incidence rates of invasive *Haemophilus influenzae* type b disease in children less than 5 years of age, with the burden of disease greatest among Aboriginal infants less than 12 months. This study documents the impact of conjugate Hib vaccines introduced in 1993. Immunization rates were monitored using an existing immunization register, and case finding was done retrospectively using hospital and laboratory records. Following the vaccine introduction, the incidence fell abruptly to a seventh of its pre-vaccination level, in both Aboriginal and non-Aboriginal children. The effectiveness of PRP-OMPC (PedvaxHIB™) was 97·5% and the overall effectiveness of the vaccination programme was 86·3%. The study shows Hib immunization as an effective intervention while discussing continuing needs for Hib control in high risk populations. It also illustrates the benefit of immunization registers in the evaluation of immunization programmes and assessment of vaccine effectiveness.

INTRODUCTION

In the 1980s, several reports documented a very high incidence of childhood infection caused by invasive *Haemophilus influenzae* type b (Hib) in the Northern Territory (NT) of Australia [1, 2]. In Central Australia the incidence in Aboriginal children was 991 per 100 000, one of the highest measured rates worldwide [1]. The reports also revealed that 40% of Aboriginal cases occurred prior to 6 months of age with 12% occurring between 2 and 4 months.

When three conjugate Hib vaccines first became available in Australia in 1992–3, PRP-OMPC vaccine was chosen for the NT because of its demonstrated immune response following the first dose of the primary series [3]. PRP-OMPC was introduced into the NT Childhood Vaccination Schedule in April 1993 and provided free of charge to all infants born after 1 December 1992. Several Hib cases in older infants and toddlers led to a catch up programme, which included all children less than 5 years of age (born after July 1988). Under this programme, non-Aboriginal children born before December 1992 were recommended Hb-OC vaccine, and all Aboriginal children were recommended PRP-OMPC.

Computer-based immunization registers were established in some districts in the NT in the late 1980s, and by 1993, it was estimated that in the northern rural districts 90% of the children aged less than 6 years were on the unified NT immunization register†. [4]. This jurisdictional register notably pre-dates the Australian Childhood Immunization Register (ACIR) which was established in 1996. Using this register together with hospital laboratory and infection con-

trol records, we undertook a study of the effectiveness of our regional Hib conjugate vaccine programme by review of Hib disease incidence and vaccination rates in the NT between 1989 and 1996.

METHODS

A case of invasive Hib disease was defined as a child less than 5 years of age with a clinically compatible illness from whom Hib was isolated from a sterile site. The pre-vaccination era was defined as that from January 1989 until the end of June 1993, and the vaccination era from July 1993 until the end of December 1996. A child was considered adequately immunized 2 weeks after receiving a second dose of Hib vaccine before the age of 12 months or 2 weeks after receiving one dose of vaccine after the age of 12 months. An infant who had only one dose of vaccine while less than 12 months of age was considered partially immunized. Vaccine effectiveness was defined as the proportional reduction in disease incidence in the vaccination era compared to the pre-vaccination era in the defined population; that is, effectiveness = (incidence in pre-vaccination era − incidence in vaccination era) × 100/(incidence in pre-vaccination era).

The NT has a population of about 175000 (27% Aboriginal) in an area of 1·35 million km². From 1989–94, there was no NT-wide formalized data collection or notification of Hib disease. Therefore, case finding was determined retrospectively, with data coming from hospital laboratories and infection control records in the five main towns in the NT. In December 1994, Hib disease became a legislated notifiable disease in the NT via laboratory notification.

An extract was taken from the NT immunization database and summarized using SAS statistical software. The number of children on the register who were partly or adequately immunized against Hib disease at the end of each month was calculated together with the total number of vaccines given during that month. The mean vaccination coverage throughout the vaccination era was calculated as the area under the curve of adequately immunized children as a proportion of the area under the curve of the total children on the register. The number of children less than 5 years of age on the immunization register was nearly always higher than the NT estimate population using Australian Bureau of Statistics (ABS) data, adjusted for Aboriginal under-numeration [5]. For this reason we applied the mean vaccine coverage figure to the ABS population estimates (considered more accurate) to determine the denominators for vaccine effectiveness, rather than calculating the child-years directly from the register.

Three effectiveness calculations were made. Firstly, the overall effectiveness of the programme was calculated using the total number of cases and child-years based on the under-5 population in 1991 (pre-vaccination era) and 1995 (vaccination era). Secondly, the effectiveness in the population who received any Hib vaccine was measured. This was done by comparing the incidence in the pre-vaccination era in those children who would have received at least one Hib vaccine had the programme existed (that is, the population 2·5 months to 5 years) with the incidence of the disease in the vaccination era in those children who received at least one Hib vaccine. The denominator for this latter incidence was derived by multiplying the total number of child-years in the vaccination era by the mean coverage rate calculated from the register data (see above). Finally, the effectiveness of adequate immunization with PRP-OMPC was calculated using a similar strategy.

RESULTS

A total of 119 cases were identified from the 8 years 1989–96 with 93 cases occurring in Aboriginal and 26 in non-Aboriginal children. The mean age of Aboriginal cases was 10·2 months (median 7·2 months, range 2·4–43·2 months) compared to 17·3 months (median 14·5 months, range 6·2–36·6 months) for non-Aboriginal cases. A large proportion (73·1%) of Aboriginal cases occurred below 1 year of age, compared with 42·3% of non-Aboriginal cases. The number of cases by disease and indigenous status is presented in Table 1.

There were 107 cases during the pre-vaccination era with the age distribution illustrated in Table 2. The overall incidence of invasive Hib disease in the pre-vaccination era was 141 per 100000 child-years with the incidence in the Aboriginal population being over five times that in the non-Aboriginal population (Relative Risk 5·5; 95% CI 3·7–8·4; P < 0.001).

Analysis of the immunization data examined the number of vaccines given per month and revealed the pattern illustrated in Figure 1. This illustrates the beginning of the vaccine programme in April 1993, the introduction of the catch-up programme in June 1993 and the peak number of vaccines, 3200, given in July 1993.

Table 1. *Cases of invasive* H. influenzae *type b infection under 5 years, by disease category and indigenous status, NT 1989–96*

	Aboriginal		Non-Aboriginal		Total	
	Number	%	Number	%	Number	%
Meningitis	31	26·1	14	11·8	45	37·8
Bacteraemia only*	21	17·6	1	0·8	22	18·5
Bacteraemia/Illness not identified†	23	19·3	5	4·2	28	23·5
Pneumonia	12	10·1	1	0·8	13	10·9
Epiglottitis‡	0	0·0	2	1·7	2	1·7
Septic arthritis	1	0·8	0	0·0	1	0·8
Other	5	4·2	3	2·5	8	6·7
Total	93	78·2	26	21·8	119	100·0

* Blood culture positive and clinical disease documented.
† Blood culture positive but clinical disease unspecified/unknown.
‡ The two cases of epiglottitis were those in which a positive blood culture was taken from a clinical case of epiglottitis.
Note: Percentages are the proportion of all cases.

Table 2. *Cases and incidence* of invasive* H. influenzae *type b infection under 5 years, by age and indigenous status, in the pre-vaccination and vaccination eras, NT 1989–96*

|	Aboriginal		Non-Aboriginal		Total	
	Number	Incidence	Number	Incidence	Number	Incidence
Pre-vaccination era						
Less than 4 months	9	447	0	0	9	177
4–11 months	53	1315	10	164	63	621
12–23 months	18	298	7	77	25	164
24–47 months	4	33	6	33	10	33
48–59 months	0	0	0	0	0	0
Total	84	278	23	50	107	141
Vaccination era						
Total	9	37	3	8	12	19
Relative Risk		0·13		0·16		0·14
95% CI		0·07–0·26		0·05–0·52		0·08–0·25

* Cases per 100000 child years.
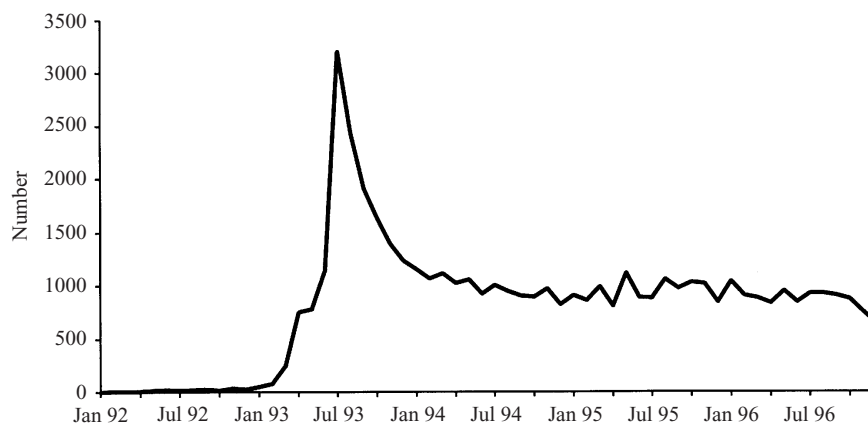
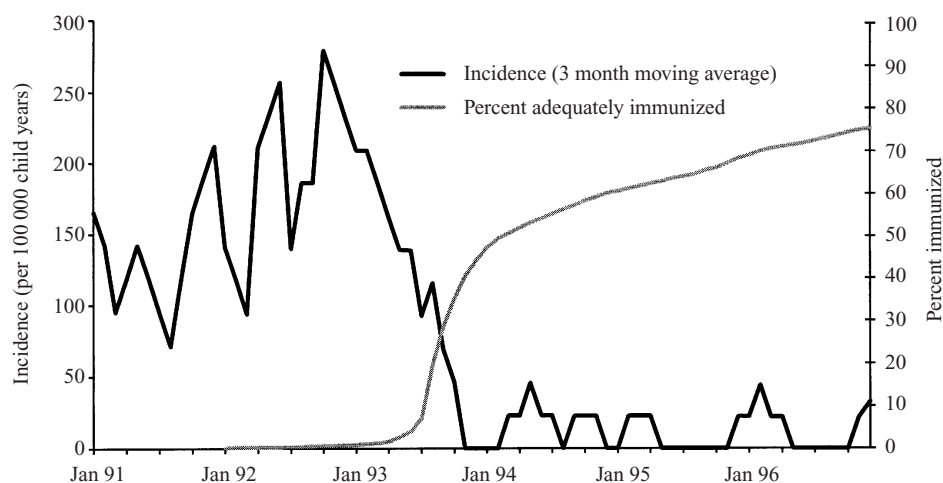**Fig. 1.** Number of Hib vaccine doses given per month: Northern Territory, 1992–6.

Fig. 2. Incidence of invasive Hib disease compared with overall Hib immunization coverage, under 5s, NT 1991–6.

Table 3. *Vaccine effectiveness results*

	Pre-vaccination era		Vaccination era			
Effectiveness	Cases	Child-years	Cases	Child-years	Effectiveness	95% CI
Overall effectiveness	107	75951	12	62293	86·3	75·2–92·5
Immunised with any Hib vaccine*	106	72786	5	41175	91·7	79·6–96·6
Adequately immunised with PRP-OMPC†	95	70254	1	29546	97·5	82·0–99·7

* At least one dose of any conjugate vaccine. The calculations are based on the population 2·5 months–5 years.
† Two doses before 12 months of age or one dose after 12 months of age. The calculations are based on the population 4·5 months–5 years.
Notes:
1. Child-year calculations in the pre-vaccination era are derived from the estimated under 5 population for 1991.
2. Child-year calculations in the vaccination era are derived from the estimated under 5 population for 1995, and the immunization coverage rates from the immunization register.

The curved line in Figure 2 illustrates the proportion of children less than 5 years of age who were adequately immunized against Hib disease, calculated at the end of each month. The proportion adequately immunized was greater than 50% one year after the introduction of the vaccine and increased throughout the study period to be 75·2% at the end of 1996. According to the recommendations of the NT catch-up schedule, 85% of immunized children on the register were vaccinated with PRP-OMPC and the remainder with Hb-OC.

Invasive Hib disease incidence declined in the NT less than 5-year-old population from 141/100000 during the pre-vaccination era to 19/100000 in the vaccination era. The relative risk of invasive Hib disease after the introduction of the vaccine (the incidence ratio) was 0·14 overall, with 95% confidence intervals (CI) given in Table 2. The incidence in the highest risk group (Aboriginal infants aged 4–11 months) fell from 1315 to 185 per 100000 child-years with a similar relative risk of 0·14 (95% CI 0·06–0·33). The downward trend in the incidence of invasive Hib disease and the uptake of the vaccine in the community is illustrated in Figure 2.

The overall vaccine effectiveness in all children less than 5 years regardless of whether a vaccine was received was 86·3%. The vaccine effectiveness for that population which received at least one dose of any conjugate vaccine was 91·7% and 98·5% in the group adequately immunised with PRP-OMPC (Table 3).

DISCUSSION

The impact of conjugate vaccines on invasive Hib disease has been well documented [6–8], with most studies relying on survey data or vaccine usage to predict vaccine uptake in the population studied. This study used data from an established jurisdictional immunization register to document the increasing proportion of the immunized population as it co-incided with the fall in disease incidence. Data from the register also were used to calculate vaccine effectiveness estimates.

Mapping community uptake of the vaccine with the falling disease rates demonstrated that the vaccination programme had an impact on disease rates even before the proportion of children adequately immunized reached 50%. The effect of the catch-up programme on the slope of the curve illustrates the success of this programme. In future programmes the slope of the immunization curve could be used as an interim measure of the success of the programme or as a comparison with other programmes.

The incidence rates of invasive Hib disease in the pre-vaccination era reported here are lower than those reported in a previous NT study [1]. This difference may be because the earlier study included non-type b *Haemophilus influenzae* disease and because contemporaneous case finding was more thorough. Under-ascertainment of invasive Hib disease in both studies may be attributed to the conservative case definition used but also to cases in isolated communities not reaching a hospital where cultures are taken before antibiotic treatment is given. In remote communities pneumonia and other febrile illnesses are often treated with daily parenteral antibiotics without cultures. Cases of invasive Hib disease thus may have been undetected or unconfirmed. If the true pre-vaccination incidence rate were higher than predicted in this report, the true vaccine effectiveness estimates would also have been higher.

During the study period, the number of children less than 5 years enrolled on the immunization register nearly always exceeded that number of NT residents less than 5 years estimated from ABS data, suggesting that an unknown proportion of children were enrolled twice or had enrolled and then left the NT. It is unlikely, however, that individual immunizations would have been recorded more than once; hence this over-estimation of the number of children on the register would have led to a diminution in vaccine coverage rates and a lower vaccine effectiveness estimation. Opportunistic cleaning of the immunization data occurred at the NT district levels and centrally but no formal evaluation of the register was carried out during the study period.

It is important that the success of Hib vaccination programmes does not lead agencies into complacency regarding disease control activities. Since the completion of this study (1997 to September 2000) 5 cases (2 unimmunized, 3 immunized, all Aboriginal) have been reported in the NT, emphasising the need for ongoing surveillance, vaccine monitoring, investigation of vaccine failures, and maintenance of vaccine promotion programmes. In addition, laboratories need to maintain strict protocol and standards for the typing of *Haemophilus influenzae* isolates, or refer specimens to a central laboratory. Invasive disease due to non-type b *Haemophilus influenzae* continues, and exacting surveillance of these diseases is warranted to observe changes in incidence which may be relevant to future vaccine development [9]. The investigation of vaccine failures also is crucial, as these may be markers for regions of high Hib carriage, poor community coverage, or poor vaccine handling and administration.

The introduction of PRP-OMPC has resulted in the reduction or elimination of measured Hib carriage in several populations [10, 11]. However, in a study of native Alaskans with previous high rates of invasive Hib disease (similar to NT Aboriginal rates), where rates fell dramatically following the introduction of PRP-OMPC, a change to a different vaccine saw Hib disease increase [12], suggesting that carriage rates might remain at significant levels even in well vaccinated populations. The possibility also has been raised that older, never vaccinated children or isolated pockets of poor coverage could serve as reservoirs for reintroduction of the organism [13]. Another Alaska study encouragingly showed an overall reduction in invasive Hib disease in unimmunized persons 10 years and older after the introduction of an infant Hib vaccine programme, suggesting a herd immunity effect. However, an increase in cases of non-type b HI was reported [14]. In one study of the NT Aboriginal population, higher than expected Hib carriage rates have been found following the introduction of Hib vaccine [15]. These findings reinforce the need to acknowledge the unique epidemiology of Hib in the NT and to continue providing early protection with PRP-OMPC, to achieve high immunization coverage rates, and to promote comprehensive disease surveillance.

The rapid demise of a debilitating and potentially fatal disease following the introduction of Hib conjugate vaccines has been demonstrated, as have the advantages of a central immunization register as a tool for evaluating immunization programmes and measuring vaccine effectiveness. Despite the sparse population, with vast distances separating small and isolated communities, well-established health service delivery pathways facilitated the introduction of new vaccines such that disease incidence fell within months of programme commencement; today Hib disease is rare in the NT.

REFERENCES

1. Hanna J. 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**: 234–40.
2. Hanna J. The epidemiology and prevention of *Haemophilus influenzae* infections on Australian Aboriginal children. J Paediatr Child Health 1992; **28**: 354–61.
3. Santosham M, Wolff M, Reid R, et al. The efficacy in Navajo infants of a conjugate vaccine consisting of *Haemophilus influenzae* type b polysaccharide and *Neisseria meningitidis* outer-membrane protein complex. N Engl J Med 1991; **324**: 1767–72.
4. Guthridge S, Patel M. High immunisation uptake for two year olds in the remote Northern Territory. Commun Dis Intell 1993; **17**: 566–7.
5. Australian Bureau of Statistics. *Census characteristics of the Northern Territory: Catalogue No. 2710.7.* Canberra: AGPS, 1993; 16–9.
6. Harrison LH, Tajkowski C, Croll J, et al. Postlicensure effectiveness of the *Haemophilus influenzae* type b polysaccharide-*Neisseria meningitidis* outer-membrane protein complex conjugate vaccine among Navajo children. J Pediatr 1994; **125**: 571–6.
7. Shinefield HR, Black S. Postlicensure surveillance for *Haemophilus influenzae* type b oligosaccharide CRM-197 conjugate vaccine in a large defined United States population: a four-year eight-month follow-up. Pediatr Infect Dis J 1995; **14**: 978–91.
8. 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**: 245–8.
9. Gratten M, Morey F, Hanna J, et al. Type frequency and distribution of *Haemophilus influenzae* in central Australian Aboriginal children with invasive disease. Med J Aust 1994; **160**: 728–9.
10. Barbour ML. Conjugate vaccines and the carriage of *Haemophilus influenzae* type b. Emerg Infect Dis 1996; **2**: 176–82.
11. Takala AK, Eskola J, Leinonen M, et al. Reduction of oropharyngeal carriage of *Haemophilus influenzae* type b (Hib) in children immunised with an Hib conjugate vaccine. J Infect Dis 1991; **164**: 982–6.
12. Galil K, Singleton R, Levine OS, et al. Re-emergence of invasive *Haemophilus influenzae* type b disease in a well-vaccinated population in remote Alaska. J Infect Dis 1999; **179**: 101–6.
13. Dargan JM, Coplan PM, Kaplan KM, Nikas A. Reemergence of invasive *Haemophilus influenzae* type b disease in Alaska: Is it because of vaccination with polyribosylribitol phosphate outer membrane protein complex (PRP-OMPC) or failure to vaccinate with PRP-OMPC? J Infect Dis 2000; **181**: 806–8.
14. Perdue DG, Bulkow LR, Gellin BG, et al. Invasive *Haemophilus influenzae* disease in Alaskan residents aged 10 years and older before and after infant vaccination programs. JAMA 2000; **283**: 3089–94.
15. Smith-Vaughan H, Sriprakash KS, Leach AJ, Mathews JD, Kemp DJ. Low genetic diversity of *Haemophilus influenzae* type b compared to non-encapsulated *H. influenzae* in a population in which *H. influenzae* is highly endemic. Infect Immun 1998; **66**: 3403–9.