**Haemophilus influenzae type b disease in Auckland children during the Hib vaccination era, 1995–2009**

Bonnie Leung, Susan Taylor, Dragana Drinkovic, Sally Roberts, Phil Carter, Emma Best

**Abstract**

**Aim** To characterise *Haemophilus influenzae* type b (Hib) invasive disease in the era of Hib vaccination, in children of the greater Auckland region of New Zealand.

**Method** Identification of sterile site culture positive Hib via the Auckland hospital laboratories databases and national laboratory surveillance database in the time period; 1995 to 2009.

**Results** There were a total of 26 cases in the Auckland Region. Over the 15-year period, the annual incidence of invasive Hib disease was 0.61 per 100,000 (95% CI: 0.4–0.9) for children aged under 15 years and 1.65 per 100,000 (95% CI: 1.1–2.5) for children aged under 5 years. Ninety-two percent were under 5 years and 54% were under 1 year. Sixty percent of the children were of Māori and Pacific ethnicity. The predominant diagnosis was meningitis, accounting for 15 cases (60%). There were no fatalities. Forty-eight percent of affected children were completely unimmunised with the Hib vaccine which has been fully funded on the National Immunisation Schedule since 1994.

**Conclusion** Since the introduction of the Hib vaccine, the disease rates have greatly reduced in the Auckland region. Although ethnic disparities have improved amongst the cases that occur, immunisation rates in cases are low and infants remain most at risk. Current emphasis on intensifying immunisation programmes to achieve higher vaccination rates and timeliness of delivery will help in efforts to achieve elimination of the disease in New Zealand.

*Haemophilus influenzae* (Hi) is a Gram-negative coccobacillus that exists as one of six distinct capsulated strains or as a non-encapsulated strain. The encapsulated serotype b (Hib) is a recognised cause of life-threatening invasive infection in children under 5 years. Prior to vaccination in New Zealand, Hib caused 95% of Hi invasive disease in infants and children.\(^1\)

In Auckland, disease rates were reported as 43 per 100,000 in children under 5 years, with rates in Pacific and Māori children even higher (57 per 100,000).\(^2\,^3\) Over a quarter of these cases occurred in the first 6 months of life. Hib was the major pathogen of bacterial meningitis in infants and young children in Auckland prior to vaccination.\(^3\)

New Zealand has had effective immunisation against Hib since 1994 as part of the National Immunisation Schedule. Since then there has been a 90% reduction in incidence of Hib disease in children aged under 5 years.\(^1\) Immunisation reduces the frequency of asymptomatic colonisation of Hib, but in the unimmunised child, severe...
Hib invasive disease may still occur. We reviewed the cases of Hib disease in the paediatric population in Auckland after the implementation of the Hib vaccine over the 15-year period of 1995 to 2009.

Method

All cases of invasive Hib disease occurring in children under 15 years from the Auckland Region, between first of January 1995 through to end of December 2009 were ascertained and reviewed. Hib cases were included if there was a laboratory confirmed isolate of Hib from a sterile site. Study investigators at the Auckland District Health Board, Counties Manukau District Health Board and Waitemata District Health Board laboratories searched their databases and cross referenced with the Environmental Science and Research (ESR) national database to ensure all cases were identified. Paper and computer scanned medical records were reviewed. Typing information was provided by ESR. From the end of 1997 all invasive Hi isolates referred to ESR were further tested by polymerase chain reaction for the presence of capsular gene and type b capsule. Hib became a notifiable disease in 1996 and notification data along with isolate typing was provided from the ESR national reference laboratory.

Cases included in the analysis were from the Auckland Region. One case was excluded as the child was not resident in the Auckland Region at the time of illness onset.

Changes to the National Immunisation Schedule regarding the Hib vaccine were reviewed over the period from 1994 through to 2009. In 1994, the Hib vaccine was first introduced as a component of the quadrivalent vaccine (DTwPH). This was changed to the polyribosylribitol phosphate outer membrane protein (PRP-OMP) Hib vaccine in 2000 as it offered more antibody protection after early doses, enabling better protection of young infants.

In 2008, a hexavalent polyribosylribitol phosphate tetanus toxoid (PRP-T) Hib vaccine was introduced which involves a primary course of three doses and a booster at 15 months.  

Immunisation status was categorised in the following way; Complete, Partial, Missed and Unimmunised. Children who received all doses of the Hib vaccine including the booster were categorised into “Complete”. Those that were up to date for their age group but too young to receive all doses and booster were categorised into “Partial”.

Children that had received a Hib vaccine but missed other age-appropriate doses were categorised into “Missed”. Finally children that had not received any immunisations were categorised into “Unimmunised”.

Rates were calculated using Statistics New Zealand estimated resident population denominators. Each case’s address at diagnosis was used to assign 2006 census area unit codes enabling an area-based NZ Deprivation Index 2006 decile to be assigned. Data were compiled and analyzed using SPSS version 16.0.

Ethical approval was obtained from the Northern Regional Ethics committee in January 2010.

Results

A total of 26 paediatric cases of Haemophilus influenzae type b (Hib) disease were identified in the Auckland Region between 1995 and 2009. Complete clinical records were available for 25 of 26 cases.

The annual incidence over the 15-year time period, was 0.61 per 100,000 for children aged under 15 years and 1.65 per 100,000 for children aged under 5 years. The incidence of invasive Hib in the Auckland Region did not vary significantly over time during this period. However it is significantly less than the pre-vaccine rate reported for the Auckland Region for 1981–1987 (Figure 1).

During 1995–2009, the highest rates were observed in children aged less than 6 months (5.2 per 100,000), and rates in children less than 1 year remained significantly
higher than rates in children aged 3 to 14 years (Table 1). The majority of cases were aged less than 1 year and all but 2 cases were aged less than 5 years.

**Figure 1. Incidence of invasive *Haemophilus influenzae* type b disease in children aged 0–14 years, Auckland Region 1981–87 (pre-vaccination period) and 1995–2009**

There were no significant differences in incidence by gender, ethnicity and New Zealand Deprivation Index (NZDep) at their home residence (Table 1).
Table 1. Sociodemographic data of Auckland children with *Haemophilus influenzae* type b disease, 1995–2009

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases (N)</th>
<th>Rate per 100,000</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 months</td>
<td>8</td>
<td>5.17</td>
<td>2.46-10.47</td>
</tr>
<tr>
<td>6-12 months</td>
<td>6</td>
<td>3.88</td>
<td>1.59-9.76</td>
</tr>
<tr>
<td>1-2 years</td>
<td>5</td>
<td>0.86</td>
<td>0.31-2.09</td>
</tr>
<tr>
<td>3-14 years</td>
<td>7</td>
<td>0.21</td>
<td>0.09-0.44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Cases (N)</th>
<th>Rate per 100,000</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>12</td>
<td>0.55</td>
<td>0.30-0.97</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>0.67</td>
<td>0.39-1.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Cases (N)</th>
<th>Rate per 100,000</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Māori</td>
<td>9</td>
<td>1.13</td>
<td>0.57-2.21</td>
</tr>
<tr>
<td>Pacific</td>
<td>6</td>
<td>0.74</td>
<td>0.30-1.66</td>
</tr>
<tr>
<td>European &amp; Other</td>
<td>10</td>
<td>0.38</td>
<td>0.20-0.71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NZDep Decile</th>
<th>Cases (N)</th>
<th>Rate per 100,000</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>14</td>
<td>0.53</td>
<td>0.31-0.91</td>
</tr>
<tr>
<td>8-10 (most deprived)</td>
<td>11</td>
<td>0.67</td>
<td>0.36-1.22</td>
</tr>
</tbody>
</table>

Amongst cases of invasive Hib disease only 3 (12%) children were completely immunised (Table 2). There were 15 cases of meningitis (60%). Eight of these children were unimmunised, three had missed immunisations, two were partially immunised and two completely immunised.

The median age of children with Hib meningitis was 1.9 years. Other presentations included pneumonia which accounted for five cases (20%), epiglottitis in two cases (8%), bacteraemic sepsis, septic arthritis and facial cellulitis involving one case each (4%).

Seven (28%) children had significant underlying conditions, including one with congenital heart disease, two with syndromic developmental delay (Down’s syndrome, Wolf-Hirschhorn Syndrome), one with motor development delay, one with dysplastic kidney and two with recurrent pneumonia.

Of these seven children, six were unimmunised; two due to parental choice. Five of the children were seeing tertiary services prior to Hib disease and only one was fully immunised.
Table 2. Immunisation status and sequelae of invasive *Haemophilus influenzae* type b disease in children aged 0–14 years, Auckland Region 1995-2009

<table>
<thead>
<tr>
<th>Immunisation status</th>
<th>Number of Hib vaccines received</th>
<th>N (%)</th>
<th>Sequelae after Hib disease N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unimmunised</td>
<td>No Hib vaccines received</td>
<td>12 (48%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Missed</td>
<td>At least one Hib vaccine received but missed other age-appropriate doses</td>
<td>6 (24%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Partial</td>
<td>Up to date for their age at presentation but too young to receive all doses</td>
<td>4 (16%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Complete</td>
<td>All doses of the Hib vaccine including the booster received</td>
<td>3 (12%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

Complete treatment data was available for 23 cases. Fourteen cases used cefotaxime alone or followed by amoxycillin, cefuroxime or amoxycillin/clavulanate. The median duration of treatment was 10 days (range of 5 to 57 days). Amoxycillin resistance was present in two of the Hib isolates. One isolate also had intermediate resistance to rifampicin but all were susceptible to ceftriaxone, cefuroxime, co-trimoxazole and amoxycillin/clavulanate.

Of the 26 isolates, two were nontypable by conventional typing and were identified by polymerase chain reaction to have both the capsule and type b gene present. Both of these cases had clinically consistent findings of invasive Hib disease which included septic arthritis in a 6-month-old unimmunised infant and facial cellulitis in a 3-month-old infant who had received one Hib vaccine.

There were no fatalities, although five children had sequelae after the Hib disease. Four children with meningitis had significant neurological consequences including paresis, delayed motor development and hearing impairment requiring cochlear implants. The child who presented with septic arthritis had a knee effusion for a month. Two of these children had missed immunisations and two were unimmunised.

**Discussion**

In this retrospective study of invasive Hib disease during the era of Hib vaccination in children between 1995 and 2009, 26 cases were identified in the greater Auckland Region. The overall incidence over the 15-year time period was 0.61 per 100,000 for children aged less than 15 years and 1.65 per 100,000 for children aged less than 5 years.

This is markedly reduced from rates of 14 per 100,000 for under 15 years and 41 per 100,000 for under 5 years in the pre-vaccination period of 1981 to 1987 in Auckland and indicates that elimination of Hib disease in New Zealand is achievable.

Meningitis was the predominant diagnosis with other classic and life-threatening presentations of Hib also observed.

The decrease in the incidence of invasive Hib disease in the Auckland Region is consistent with prior New Zealand literature observing a 90% reduction of disease in children under 5 years since the vaccine was introduced in 1994. *Haemophilus influenzae* type b immunisation is postulated to prevent at least 80 cases of meningitis and 30 cases of epiglotitis every year in children under 5 years in New Zealand.
Our observed Auckland rate is consistent with national surveillance data from 1997 to 2005, which indicates mean annual rate of Hib disease of 0.77 per 100,000 (standard deviation 0.42) children under 15 years.  

Hib disease rates in Auckland compare favourably with those reported in Australia and other developed countries. Since the introduction of Hib immunisation in Australia in 1993, incidence rates for the period from 1997 to 2000 were reported as 1.7 cases per 100,000 in children under 5 years.

Similar reductions in Hib disease have been seen in other countries with routine Hib immunisations such as the United States (1.4 per 100,000 children under 5 years) and United Kingdom (1.8 per 100,000). However significantly higher rates of invasive Hib disease are still observed amongst Australian Aboriginal children despite high vaccine coverage (6.7 per 100,000 in children under 5 years).

More recently, Australian national Hib disease rates have declined further to 0.5 per 100,000 in children aged under 5 years, whilst still remaining higher in the Northern Territory (1.2 per 100,000).

Although 60% of our cohort were Māori and Pacific, the small number of total cases is likely to have meant ethnic differences in Hib incidence were not statistically significant. This is in contrast to the pre-vaccine period in New Zealand where Māori and Pacific children had higher rates of invasive disease and were younger at presentation. However, one of the potential benefits of immunisation is to eliminate Hib invasive disease and reduce ethnic health inequalities which may otherwise be difficult to address with other health interventions. The same improvement across ethnic groups was also observed in the New Zealand meningococcal B campaign.

Our review demonstrates young children continue to be the age group most at risk with 56% of cases aged less than 1 year, consistent with the pre-vaccine data in the Auckland Region where 60% of Hib cases were infants.

Of the 14 cases aged less than 1 year, only one was completely immunised. Five children were unimmunised (36%) and the other 8 had either partial or missed immunisations. Current governmental health targets are important in working toward not only achieving 95% of children being fully immunised by the age 2 years, but also timely immunisation, particularly of infants.

Delayed infant immunisation is a risk for acquisition of Hib in indigenous communities leading to persistent carriage. The higher rate of Hib disease enduring in Auckland in light of Australia’s improved national rate demonstrate carriage and transmission still occur in our young and unimmunised children. Efforts to eliminate invasive Hib disease should mean that each case be regarded as a sentinel event and indicative of ongoing Hib transmission within a reservoir, whether it be a family or a community with poor health access.

Of the seven children with pre-existing medical conditions, six were unimmunised; two by parental choice. Of the five children seen by tertiary services prior to the episode Hib disease, only one was fully immunised. This highlights an avenue of missed opportunity where encouraging adequate immunisation during consultations for other medical conditions would benefit children at increased risk.
Prior to the introduction of immunisation, Hib invasive disease had a case fatality proportion of 5 to 10%. Furthermore, survivors of Hib meningitis had a 15 to 30% risk of long-term neuro-developmental impairment. Although no fatalities were observed in this study, sequelae occurred in 20%. Following with meningitis, consequences were severe and long standing.

Amongst invasive Hib isolates, 85% were susceptible to amoxycillin. Although national susceptibility of all invasive Hi isolates demonstrates increasing amoxycillin resistance over the past decade, our small numbers in this review did not show trends of increasing amoxycillin resistance. Current empiric therapy for paediatric meningitis usually includes third generation cephalosporins to which all Hib isolates remain susceptible.

This study also demonstrated the impact of vaccination at both at the population and individual level. Although immunisation has reduced the overall incidence of Hib within the Auckland Region, for the individuals that had invasive Hib, poor immunisation uptake was apparent. Only 12% were fully immunised and almost half were unimmunised. In most cases, the reason for the child being unimmunised was not specified in medical records.

Limitations include the fact that hospital admission and mortality data were not searched for International Classification of Diseases (ICD) codes consistent with invasive Hib. A prior New Zealand Hib disease review identified a very small number of additional cases using ICD9 codes. Hospital admission and mortality data are currently coded using ICD10 codes which are unable to distinguish Hib from other capsular Hi or nontypable cases without chart or laboratory data review. Thus the number of additional cases of true Hib missed by our review of both national and local laboratory databases is likely to be very small.

One of the strengths of this review was laboratory database search including sterile and non sterile site paediatric Haemophilus influenzae isolates. This enabled detection and inclusion of cases such as those nontypable by conventional methods but detected by polymerase chain reaction and shown to be consistent clinically.

**Conclusion**

In Auckland, Hib is now a rare disease following effective Hib immunisation and New Zealand is moving toward elimination of the disease. However opportunities to improve immunisation still exist. Immunisation rates are poor amongst those with Hib invasive disease and young children remain most at risk.

Opportunities for immunisation of children should be encouraged, particularly amongst those with prior specialist medical contact. Furthermore, emphasis should be placed on implementing existing immunisation programmes to further raise uptake rates and timeliness of immunisation.
Competing interests: Nil.

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