Use of an observational cohort study to estimate the effectiveness of the New Zealand group B meningococcal vaccine in children aged under 5 years

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Background In July 2004 a strain-specific vaccine was introduced to combat an epidemic of group B meningococcal disease in New Zealand. We estimated the effectiveness of this vaccine in pre-school-aged children.

Methods We conducted a cohort analysis of all children in New Zealand who were aged 6 months to <5 years at the time the vaccine became available for that age group in their area. We defined cases as children who were diagnosed with laboratory-confirmed epidemic strain meningococcal disease. We calculated person-days-at-risk using data from the National Immunization Register and population estimates from Statistics New Zealand. We estimated vaccine effectiveness as \( \frac{1/C0}{\text{relative risk}} \).

Results Compared with unvaccinated children, fully vaccinated children were five to six times less likely to contract epidemic strain meningococcal disease in the 24 months after they became eligible to receive a full vaccination series, corresponding to an estimated vaccine effectiveness of 80.0% (95% confidence interval: 52.5–91.6) for children aged 6 months to <5 years and 84.8% (95% confidence interval: 59.4–94.3) for children aged 6 months to <3 years.

Conclusions With over 3 million doses administered to individuals aged under 20 years throughout New Zealand, combined evidence from the Phase I and II clinical trials, the descriptive epidemiology of meningococcal disease, and this study provide evidence supporting the effectiveness of this vaccine in the 2 years following vaccination.

Keywords Meningococcal vaccine, meningococcal disease, vaccine effectiveness, observational study

Introduction

Since 1991 New Zealand has experienced an epidemic of meningococcal disease, with the annual incidence increasing from 53 cases (1.6/100 000 population) in the pre-epidemic year of 1990 to a peak of 650 (17.4/100 000) in 2001, which then decreased to 541 cases (14.5/100 000) in 2003. The majority of cases were due to serogroup B with the subtype P1.7-2.4.
In July 2004 a strain-specific outer membrane vesicle vaccine prepared from a B:4:P1.7-2,4 strain (N298/254) was introduced. Prior to the introduction of this vaccine the highest rates of disease occurred in children aged under 5 years. The three-dose schedule, recommended to be given 6 weeks apart, was available to all children aged <20 years and was gradually implemented over a 2-year period staggered by geographic region and age group. Regions with the highest disease incidence were the first to receive the vaccine. Vaccination of infants aged under 6 months did not begin until February 2005 and from January 2006 a fourth dose was recommended for these infants and was to be administered at least 4 months after the third dose.

The vaccine demonstrated a satisfactory immunogenicity and safety profile in Phase I and II clinical trials. No Phase III clinical trials were undertaken, therefore no direct estimate of the vaccine’s efficacy was produced. However, the effectiveness of this vaccine has been estimated at 73% in those aged under 20 years, using a statistical model. A number of methods have been used to estimate the effectiveness of vaccines in the field. We undertook a cohort analysis to estimate the effectiveness of this vaccine in the 24 months following the completion of a properly spaced (i.e., 6 weeks apart) vaccination series in children who were aged 6 months to <5 years at the start of the immunization programme.

Methods

We included all children who were aged 6 months to <5 years at the time the vaccine became available for that age group in their district health board (DHB) in the eligible study cohort. We chose 6 months as the lower age limit because of the later start date for infants aged <6 months (which occurred up to 7 months after those aged 6 months and over started the immunization programme) and because of the different schedule recommended for these infants. We chose 5 years as the upper limit because meningococcal disease incidence had been historically highest in pre-school-aged children. We extracted individual records from the National Immunization Register (NIR) for each child who had been vaccinated with the meningococcal B vaccine. We calculated the time between doses and excluded any doses that were not properly spaced, i.e., second or third doses that were received <6 weeks (42 days) after a previous dose and fourth doses that were received <4 months (120 days) after the third dose. We also excluded any fourth doses given prior to January 2006 or given to children who had received a first dose when aged 6 months or over.

We defined ‘vaccinated’ children as having received three doses of the vaccine at least 6 weeks apart, ‘partially vaccinated’ as having received one or two doses at least 6 weeks apart and ‘unvaccinated’ children as having received no doses. Since no records were available for unvaccinated children, we calculated the number in each of the 21 DHBs by subtracting the vaccinated cohort from Statistics New Zealand population estimates for 2004. We assumed that the NIR was more accurate than the population estimates, so that if the population counts from the NIR were larger than the Statistics New Zealand estimates we used the NIR counts.

We calculated person-days-at-risk of contracting epidemic strain meningococcal disease for each child in the overall study cohort and assigned person-days-at-risk to the vaccinated, unvaccinated and partially vaccinated groups. Person-days-at-risk ceased to accumulate once a properly spaced fourth dose was received.

We followed every child in the study cohort for 24 months from the date their age group became eligible for a third dose of the vaccine in their DHB, i.e., 12 weeks after the date that vaccination of children aged 6 months to <5 years started in the DHB. Meningococcal disease is notifiable to Medical Officers of Health under the Health Act 1956, with case details recorded on a computerized database and managed nationally by the Institute of Environmental Science and Research (ESR). The case definition for notification is a clinically compatible illness with or without laboratory confirmation (i.e., by culture, PCR, Gram-negative diplococci or positive antigen test from a sterile site). Patient specimens and meningococci or meningococcal DNA from disease cases are referred to ESR’s Meningococcus Reference Laboratory for confirmation and strain characterization. Laboratory results are combined with notification data and used to identify cases of meningococcal disease that were due to the epidemic strain. The sensitivity of meningococcal disease surveillance in New Zealand has been estimated to be in excess of 87%.

We defined ‘cases’ as members of each of the study groups defined above who were notified with meningococcal disease and laboratory-confirmed as the epidemic strain during the DHB-specific 24-month study period. We matched case records with the NIR data set using the National Health Index, a unique identifier, to determine the number and timing of doses received prior to disease onset.

We calculated the relative risk (RR) as the ratio of the incidence of epidemic strain meningococcal disease in the vaccinated vs unvaccinated cohorts, and we calculated test-based 95% confidence intervals (95% CI). We calculated the vaccine effectiveness (VE) as $1 - RR$.

Because there were only limited data on the efficacy of meningococcal B vaccines in younger children, we conducted separate analyses for children aged 6 months to <3 years (which was the youngest group for which we had sufficient data to conduct meaningful analyses). For our primary analyses, we compared the incidence of epidemic strain
meningococcal disease in the vaccinated vs unvaccinated groups for both age groups. For a secondary analysis we also compared the partially vaccinated group with the unvaccinated group. In order to evaluate the sensitivity of our assumptions on the VE estimates, we conducted similar analyses in which we varied the minimum allowable interval between doses (4 vs 6 weeks). Finally, in order to assess the possibility of waning vaccine-induced immunity we separately estimated VE in the period 0–12 months and 13–24 months after children in the cohort became eligible to complete the vaccination series.

Results

The study cohort consisted of 258,421 children aged 6 months to <5 years at the time the vaccine became available for their age group in their DHB. Of these, 233,906 (90.5%) received at least one dose and 160,870 (62.3%) received at least three properly spaced doses during the 24-month follow-up period; only 15 (<0.01%) of these children received a fourth dose that was given as per the programme recommendations. There were 143,265 children in the cohort aged 6 months to <3 years, of which 130,011 (90.7%) received at least one dose and 89,776 (62.7%) received at least three properly spaced doses during the 24-month follow-up period and 15 (0.01%) received a fourth dose that was within the programme recommendations. In one region the number of children recorded in the NIR exceeded the Statistics New Zealand population estimate by 4.1% (corresponding to 1566 children) so we assumed that all children in this region were vaccinated with at least one dose and increased the population count by 1566.

The annual incidence of meningococcal disease decreased steadily in the years following the introduction of the vaccine to a total of 105 cases in 2007 (2.6 per 100,000).1 Fifty-four children from the entire cohort aged 6 months to <3 years were notified with meningococcal disease in the 24 months following eligibility to complete the vaccination series, corresponding to an estimated VE of 80.0% (95% CI: 52.5–91.6) (Table 1). For children aged 6 months to <3 years, fully vaccinated children were more than six times less likely to contract epidemic strain meningococcal disease during the 24-month follow-up period, corresponding to an estimated VE of 80.0% (95% CI: 52.5–91.6) (Table 1).

<table>
<thead>
<tr>
<th>Comparison groups</th>
<th>Age group</th>
<th>Number of vaccinated cases (person days at risk)</th>
<th>Number of unvaccinated cases (person days at risk)</th>
<th>Vaccine effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated vs unvaccinated</td>
<td>6 months to &lt;5 years</td>
<td>12 (101,936,906)</td>
<td>9 (15,286,382)</td>
<td>80.0% (52.5 to 91.6)</td>
</tr>
<tr>
<td></td>
<td>6 months to &lt;3 years</td>
<td>8 (56,679,206)</td>
<td>8 (8,638,364)</td>
<td>84.8% (59.4 to 94.3)</td>
</tr>
<tr>
<td>Partially vaccinated vs unvaccinated</td>
<td>6 months to &lt;5 years</td>
<td>7 (41,104,849)</td>
<td>9 (15,286,382)</td>
<td>71.1% (22.3 to 89.2)</td>
</tr>
<tr>
<td></td>
<td>6 months to &lt;3 years</td>
<td>6 (22,669,957)</td>
<td>8 (8,638,364)</td>
<td>71.4% (17.6 to 90.1)</td>
</tr>
</tbody>
</table>

1 The follow-up comprised a 24-month period from the date that children in the DHB became eligible for a third dose.
VE of 81.5% (95% CI: 57.8–91.9) for children aged 6 months to <5 years and 84.5% (95% CI: 61.5–93.8) for those aged 6 months to <3 years.

Separately estimating VE in the 0–12- and 13–24-month follow-up periods resulted in similar estimates of VE for the first 12 months, but much lower estimates in the second 12 months (Table 2). For the first 12 months following eligibility to complete a full vaccination series VE estimates were 81.5% or higher and their corresponding 95% CIs excluded zero. In contrast, the VE estimates for the second 12 months following eligibility to complete a full vaccination series were 50.2% or lower and the CIs were wide and included zero.

**Discussion**

Using a cohort of 258 421 children aged 6 months to <5 years who were eligible to receive the meningococcal B vaccine throughout New Zealand, our results suggest that the vaccine was around 80% effective in reducing the risk of epidemic strain meningococcal B disease in fully vaccinated children 24 months after completion of the recommended vaccination series. Furthermore, our results offer evidence that there is also benefit from partial vaccination (i.e. one or two properly spaced doses) in these age groups, although these estimates of VE are less precise. These results are consistent with that of a statistical model that was previously used to estimate VE in all age groups and explicitly controlled potential confounding factors such as the temporal progression of the epidemic, age, ethnicity, socio-economic status, seasonality and geographic region. A recent report on the descriptive epidemiology of meningococcal disease in New Zealand also shows a dramatic decline in the overall number and the seasonal peak of cases since the introduction of the vaccine in 2004.

Of course, no study, including ours, is without its inherent strengths and weaknesses. Importantly, we assumed that children remained in the same DHB for the entire follow-up period (since we only considered their DHB at the time that their age group became eligible for a third dose). Children who moved to another DHB likely had a different risk of exposure to epidemic strain *Neisseria meningitidis* and/or a different likelihood of being vaccinated; furthermore, their person-days-at-risk would have been misallocated and/or they may not have been counted as a case, both leading to misclassification error and possible bias. However, the effect of such misclassification is likely to be minimal since children are more likely to move to a neighbouring DHB (with similar vaccination start dates and therefore overlapping follow-up periods, as well as similar exposure risks and access to vaccination services) than one much farther away.

In addition, we calculated the unvaccinated population using Statistics New Zealand estimates and our VE estimates are therefore dependent on the accuracy of those population estimates. However even if the unvaccinated population aged 6 months to <5 years were increased by 10% the estimated VE would have been 82.3% (95% CI: 57.9–92.5). On the other hand, if it were decreased by 10% the estimated VE would have been 77.8% (95% CI: 47.2–90.6).

We did not conduct analyses to determine how the inclusion of cases that did not meet the case definition for laboratory-confirmed or epidemic strain meningococcal disease would have impacted our estimates of VE as this would likely increase misclassification error. However, there is no evidence to suggest that epidemic strain cases are more or less likely to be identified depending on vaccination status, therefore, this is unlikely to be a source of bias.

On the other hand, this cohort analysis enabled us to minimize several sources of potential confounding and/or imprecision. First, we included children from all of New Zealand, thereby enhancing the generalizability of our results. Second, we included all cases that occurred in a time period that spanned 2 calendar years so as to mitigate the impact of seasonal variability in disease risk/incidence. Finally, one of the strengths of this analytical approach derives from the fact that study participants contribute person-days-at-risk to both the vaccinated and unvaccinated groups, thereby serving, in part, as their own comparison subjects and minimizing the influence of uncontrolled confounding. Nonetheless, some confounding may still exist, despite these efforts, which could have caused us to over- or underestimate VE.

Several important questions about the effectiveness of this vaccine remain unanswered. Notably, neither

**Table 2** Meningococcal B vaccine effectiveness in children aged under 5 years, 0–12 months and 13–24 months follow-up period and dose interval of 6 weeks or more

<table>
<thead>
<tr>
<th>Follow-up period</th>
<th>Age group</th>
<th>Number of vaccinated cases (person days at risk)</th>
<th>Number of unvaccinated (person days at risk)</th>
<th>Vaccine effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12 months</td>
<td>6 months to &lt;5 years</td>
<td>4 (45 139 558)</td>
<td>7 (14 585 642)</td>
<td>81.5% (36.9 to 94.6)</td>
</tr>
<tr>
<td></td>
<td>6 months to &lt;3 years</td>
<td>2 (25 095 746)</td>
<td>6 (8 160 216)</td>
<td>89.2% (46.3 to 97.8)</td>
</tr>
<tr>
<td>13–24 months</td>
<td>6 months to &lt;5 years</td>
<td>8 (57 579 178)</td>
<td>2 (9 648 715)</td>
<td>33.0% (–215.7 to 85.8)</td>
</tr>
<tr>
<td></td>
<td>6 months to &lt;3 years</td>
<td>6 (32 055 405)</td>
<td>2 (5 315 858)</td>
<td>50.2% (–146.5 to 90.0)</td>
</tr>
</tbody>
</table>

aThe follow-up period started from the date that children in the DHB became eligible for a third dose.

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Several important questions about the effectiveness of this vaccine remain unanswered. Notably, neither
our study nor the aforementioned statistical model\textsuperscript{11} was able to reliably characterize VE in very young children aged <1 year in whom higher meningococcal disease rates continue to be observed,\textsuperscript{1,3,4} suggesting potentially lower VE in these infants. We restricted our analyses to children older than 6 months in order to simplify the analyses because a vaccine license covering infants aged under 6 months was not granted until February 2005, 7 months after the commencement of the immunization programme.\textsuperscript{7} Furthermore, in January 2006, it was recommended that infants who had received their first dose while aged <6 months should receive a fourth dose,\textsuperscript{7} meaning that these infants are not fully protected until they are at least 10 months of age.

We were also unable to offer definitive information on the likely duration of protection afforded by this meningococcal B vaccine. Although our estimates of VE in the 13- to 24-month period following eligibility to complete a full vaccination series were lower than the estimated VE during a 0- to 12-month follow-up period, these estimates were based on a relatively small number of accumulated person-days-at-risk and, therefore, had corresponding 95% CIs that were very wide and included zero.

With over 3 million doses administered to individuals aged under 20 years throughout New Zealand, the combined results of the Phase I and II clinical trials,\textsuperscript{2,8–10} the recent descriptive epidemiology of epidemic strain meningococcal disease, and this study provide consistent evidence supporting the effectiveness of New Zealand’s meningococcal B vaccine.

\section*{Funding}
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\section*{Acknowledgements}
We gratefully acknowledge the contribution of Charlotte Kieft (New Zealand Ministry of Health) for early work on the methodology and Richard Arnold (Victoria University of Wellington) for helpful comments on revisions to the manuscript.

\section*{Conflict of interest:} None declared.

\begin{table}[h]
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\begin{tabular}{|c|c|}
\hline
\textbf{KEY MESSAGES} & \textbf{With over 3 million doses administered to individuals aged under 20 years throughout New Zealand, this study provides evidence supporting the effectiveness of a strain-specific meningococcal B vaccine introduced to combat an epidemic.} \\
\textbf{\textbullet} & \textbf{Vaccine effectiveness was estimated to be 80\% for pre-school-aged children in the 24 months following vaccination.} \\
\textbf{\textbullet} & \textbf{Compared with unvaccinated children, fully vaccinated children were five times less likely to contract epidemic strain meningococcal disease.} \\
\hline
\end{tabular}
\end{table}

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\begin{enumerate}
\item Oster P, Lennon D, O’Hallahan J, Mulholland K, Reid S, Martin D. MeNZB\textsuperscript{TM}, a safe and highly immunogenic tailor-made vaccine against the New Zealand Neisseria meningitidis serogroup B disease epidemic strain. Vaccine 2005;23:2191–96.
\end{enumerate}


