Original Contribution

A Prospective Study of the Effectiveness of the New Zealand Meningococcal B Vaccine

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The effectiveness of a new group B strain-specific meningococcal vaccine referred to as "MeNZB," developed by Chiron Vaccines (Siena, Italy) in collaboration with the Norwegian Institute of Public Health, was assessed in a prospective observational study following a nationwide vaccination program in New Zealand. The vaccination program began in July 2004, and the study uses data from January 2001 to June 2006. A generalized estimating equation model was used to estimate vaccine effectiveness that included potential confounding variables, such as disease progression over time, age, ethnicity, socioeconomic status, seasonality, and geographic region. The model provides strong statistical evidence for a vaccine effect ($p < 0.0001$), with estimated disease rates 3.7 times higher in the unvaccinated group than in the vaccinated group (95% confidence interval: 2.1, 6.8) and a vaccine effectiveness of 73% (95% confidence interval: 52, 85). An estimated 54 epidemic strain meningococcal cases were prevented in the 2 years since the vaccination program began (95% confidence interval assuming a fixed population size: 22, 115). In a sensitivity analysis, these estimates proved to be robust to modeling assumptions, including population estimates, estimates of the numbers vaccinated, effects of partial vaccination, and temporal autocorrelation.

epidemiologic methods; evaluation studies; generalized estimating equation; immunization programs; meningococcal infections; Poisson regression; product surveillance, postmarketing; vaccines

Abbreviations: GEE, generalized estimating equation; NIR, National Immunization Register.

Beginning in 1991, New Zealand experienced an epidemic of meningococcal disease. By the end of 2003, over 5,293 cases and 216 deaths had been reported (1). The peak of the epidemic occurred in 2001 (with 650 reported cases), and case numbers decreased in each successive year; however, there were still substantial numbers in 2003 (541 reported cases) and 2004 (342 reported cases) (2). A majority of these cases (an estimated 72 percent in 2003) were caused by a specific group B strain defined as B4:P1.7b,4 (3, 4) (the "epidemic strain"). A "tailor-made" vaccine against this strain, referred to as "MeNZB," was developed by Chiron Vaccines (Siena, Italy), in collaboration with the Norwegian

Institute of Public Health (5), using expertise developed in response to the epidemic in Norway in the 1970s and 1980s (6, 7).

The MeNZB vaccine demonstrated satisfactory safety and immunogenicity profiles in phase I and II trials (1, 8, 9). Based on these results, as well as experience with other group B meningococcal outer membrane vesicle vaccines used extensively elsewhere (10–15), a large randomized controlled efficacy trial of MeNZB was not undertaken in order to meet the imperative of rapid epidemic control. A nationwide Meningococcal B Immunisation Programme (the "Programme") of all children aged from 6 weeks

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to 19 years was implemented (Ministry of Health, Chiron Corporation, University of Auckland, unpublished manuscript). Delivery of the three-dose MeNZB series began in July 2004 for children aged from 6 months to 19 years in parts of Auckland and then gradually was extended to the rest of the nation and to younger age groups. In January 2006, a fourth MeNZB dose was recommended for infants who had started their vaccination series before the age of 6 months. The rollout of the vaccine was staggered by region and age group, reflecting historical disease patterns and the requirement of intensive safety monitoring, vaccine availability, and the concurrent implementation of a computerized National Immunization Register (NIR). The Programme was completed at the end of June 2006 and achieved 80 percent coverage of eligible children according to NIR.

The evaluation of the postlicensure effectiveness of the vaccine relies on observational methods (16) but takes advantage of the staggered rollout to separate vaccination effects from the progression of the epidemic over time. A generalized estimating equation (GEE) rates model was used to estimate the incidence of disease in the vaccinated and unvaccinated groups, while accounting for the covariates of region-specific disease rates, age, ethnicity, socioeconomic status, disease progression over time, and seasonality. A sensitivity analysis was done to determine the robustness of the results to various assumptions of the model and data estimates.

MATERIALS AND METHODS

Approval for this study was granted by the Ministry of Health on the advice of the Meningococcal Management Team, a team made up of representatives of the Ministry of Health, Chiron Vaccines, Auckland University, and other advisors.

Description of study data

The study population consisted of all New Zealand residents of all ages in the period January 2001–June 2006. The study population was stratified by vaccination status, demographic variables, and time. Demographic-by-time strata were defined by the following factors, which are known to affect meningococcal disease rates (refer to Martin et al. (2)).

- Year: 2001–2006.
- Season: defined as quarters: January–March, April–June, July–September, October–December. The quarter July–September roughly covers the New Zealand winter and has consistently shown the highest rates of meningococcal disease.
- Geographic region: Two categorizations were considered: 1) the 21 district health boards and 2) regions, amalgamations of district health boards into four larger areas that divide the North Island into three sections (Northern, Midland, and Central), and the fourth area is the South Island (Southern).
- Socioeconomic status: As measured by quintiles of the New Zealand index of socioeconomic deprivation from the 2001 census (designated the "NZDep01 deprivation index") (17), high levels of deprivation indicate low socioeconomic status.
- Age: grouped to capture the major risk categories: less than 1 year, 1–4 years, 5–19 years, and 20 or more years.
- Ethnicity: categorized as Maori, Pacific peoples, or other.
- Vaccination status: not vaccinated or vaccinated.

Estimates of the total size of each demographic stratum in each time period were obtained from Statistics New Zealand using the 2001 census as a base and projecting the population estimates to 2002–2006 assuming medium growth rates. Small areas with unclassified deprivation were excluded from the analysis (these regions totaled less than 0.1 percent of the total population estimate).

Estimates of the sizes of the vaccinated populations (subjects who received at least three doses of the vaccine) and partially vaccinated populations (subjects who received one or two doses) in each demographic-by-time stratum were obtained from NIR reports. Since the NIR reports gave the total number of children vaccinated by the end of each quarter (rather than the dates of vaccination for each), we assumed that these children were covered for half of the quarter (on average). Individuals who received doses either later or earlier than the recommended 6-week intervals were treated in the same way as those who received their doses on time. The unvaccinated populations were estimated as the total population minus the vaccinated and partially vaccinated populations.

The numbers of cases in each demographic-by-time stratum were obtained from routinely collected surveillance data. Surveillance of meningococcal disease in New Zealand is based on a combination of notification and laboratory data. Clinicians are required to report suspected meningococcal disease cases to Medical Officers of Health under the Health Act 1956. Data on reported cases are recorded onto the computerized database EpiSurv. Both patient specimens and meningococci or meningococcal DNA obtained from cases are referred to the Institute of Environmental Science and Research for confirmation of disease and for characterization of the strain. Laboratory information is combined with the EpiSurv data for analysis. The vaccination status of cases was established from the NIR and then verified by use of surveillance data.

A meningococcal disease case was defined as an individual who was diagnosed by a clinician as having a clinically compatible illness laboratory confirmed (either by polymerase chain reaction or by isolation) with the epidemic strain. Meningococcal disease cases with unknown deprivation or ethnicity were excluded from analysis.

Technical information and assumptions

The GEE rates model compared disease rates only in the vaccinated and unvaccinated populations, and the partially vaccinated population was excluded from the analysis. In the sensitivity analysis, however, the effect of partial vaccination was estimated.

We assumed that the NIR of vaccinations was more accurate than the Statistics New Zealand population estimates,

so that if the number of children vaccinated or partially vaccinated in a particular stratum was larger than the Statistics New Zealand population estimate, then we changed the population estimate to reflect this. This assumption increased the total population estimate by less than 0.1 percent.

Since the available data from the NIR did not include deprivation information for the vaccinated populations, the number vaccinated in each deprivation category had to be estimated. This was done by assuming uniform vaccination coverage over deprivation quintiles. For each demographic-by-time stratum, the proportion of the population in each deprivation quintile was applied to the numbers vaccinated in that stratum.

Statistical methods

Rates models (such as GEE and Poisson regression) are used frequently to model disease rates, and a Poisson regression model was suggested by Ameratunga et al. as the "most appropriate and relevant method to assess the overall effectiveness of the immunisation programme" (16, p. 2232). We considered two types of rates models: Poisson regression, which assumes independence between populations in time and space, and the GEE model, which allows for correlated observations over time. Both models were fit using the SAS statistical package (SAS Institute, Inc., Cary, North Carolina).

All Poisson regression models showed significant underdispersion (deviance to df ratio = 0.42–0.45). Two methods for adjusting for underdispersion were considered: 1) adjusting standard errors with a scale statistic and 2) using a GEE approach. The first method appeared to underestimate the parameter standard errors and to be too liberal in testing the significance of model terms, so a GEE model was adopted. In this model, demographic strata were considered as independent populations that were observed longitudinally at 22 timepoints (the quarter years of the study time period). Thus, the model has temporal, but not spatial, dependencies. As discussed in the article by Liang and Zeger (18), however, the parameter estimates in the GEE models are robust to misspecification of the covariance structure. The GEE model accommodates underdispersion, as well as misspecification in the dependency structure.

Model fitting considered all main effects and all two-way interactions. A backward stepwise procedure was used with the main effects, but a forward stepwise procedure was used with the interactions since the model with all interactions was poorly defined and did not converge. GEE models with district health boards as regional boundaries did not converge. Therefore, the four larger geographic regions were used instead. The deprivation quintile was considered as a categorical and a continuous variable, and as a continuous variable both linear and quadratic terms were investigated. Factors were retained in the model if they were significant at the $\alpha = 0.05$ level.

A sensitivity analysis was done to assess the robustness of the vaccination effect estimate to various data assumptions. First, the effect of Statistics New Zealand growth projections was investigated by fitting the model to three different data sets, using the high, low, and medium population esti-

TABLE 1.   Significant factors in modeling meningococcal disease rates (score statistics) in New Zealand, 2001–2006

Factor	df	Chi-square	*p* value
Region	3	13.68	<0.005
Age	3	30.96	<0.0001
Ethnicity	2	44.76	<0.0001
Deprivation	1	27.22	<0.0001
Year	5	43.01	<0.0001
Quarter	3	59.51	<0.0001
Vaccinated	1	25.67	<0.0001
Deprivation by age	3	9.02	0.03
Age by ethnicity	6	33.49	<0.0001
Region by deprivation	3	10.37	0.02

mates. Second, the effects of including the partially vaccinated cases and populations were investigated, and the protective effect of partial vaccination was estimated. Third, the effect of using different geographic boundaries was investigated by considering both district health boards and regions. Finally, the effect of a nonuniform vaccination coverage distribution across deprivation levels was considered.

RESULTS

There were a total of 1,244 meningococcal cases in the study period with the epidemic strain. Of these, 27 were partially vaccinated and excluded from the analysis, leaving 1,217 cases. There were 24 cases with unknown deprivation values and three cases with unknown ethnicity, which were also excluded, yielding a total of 1,190 cases for study.

Several different models were considered, reflecting different assumptions about the populations studied. We first present the results of the best-fitting model and then discuss the effects of our assumptions and the results of the sensitivity analysis. The best-fitting model includes all covariates as main effects and three interactions: deprivation by age, age by ethnicity, and region by deprivation (table 1). All estimated effects (vaccine and demographic effects) are from the multiple regression model and thus reflect their unique contributions to disease rates after accounting for the effects of other covariates. Finally, we discuss the results of the sensitivity analysis, in which we determine the effect of various assumptions on the vaccine effectiveness estimate.

Estimated vaccine effects

The vaccine effect was highly statistically significant ($p < 0.0001$), with 3.7 times higher meningococcal disease rates in the unvaccinated group than in the vaccinated group (95 percent confidence interval: 2.1, 6.8). This yields a vaccine effectiveness of 73 percent (95 percent confidence interval: 52, 85).

In total, there were 905,507 person-years vaccinated through June 2006 and 20 vaccinated cases. If this population were not vaccinated, we would expect 3.7 times higher rates
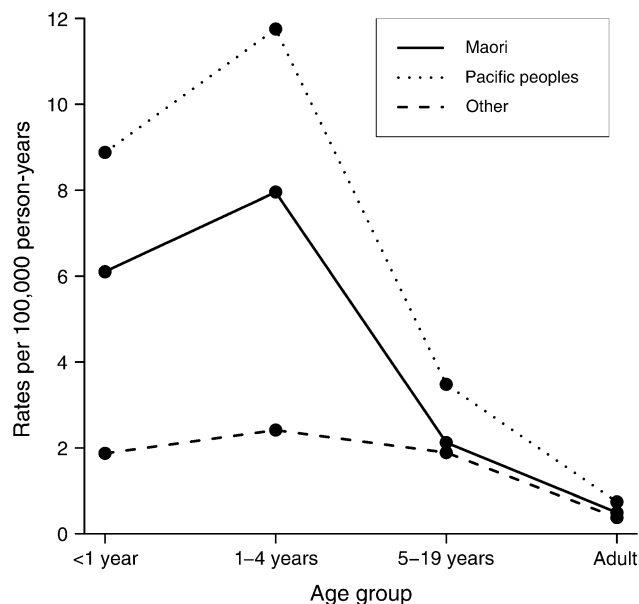
FIGURE 1. Estimated meningococcal rates in New Zealand (cases per 100,000 person-years) for each age and ethnic group of the reference group (unvaccinated persons in the lowest deprivation quintile in the fourth quarter of 2006).
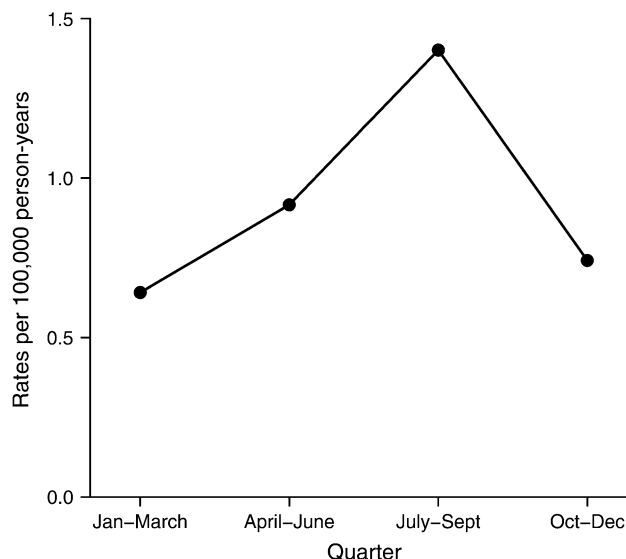

FIGURE 2. Estimated meningococcal rates in New Zealand (cases per 100,000 person-years) for each season for the reference group (unvaccinated adults in the lowest deprivation group of European or other ethnicity in 2006). Jan, January; Sept, September; Oct, October; Dec, December.

or an expected 74 (rather than 20) cases. Thus, an estimated 54 epidemic strain, laboratory-confirmed meningococcal cases were prevented by the Programme (95 percent confidence interval assuming a fixed population size: 22, 115 cases). Multiplying the age-specific mortality rates by the number of prevented cases estimated in each age group yielded an estimated 1.7 fatalities that were prevented.

Age and ethnicity effects

In each ethnic group, children had significantly higher disease rates than adults ($p < 0.0001$). Pacific peoples had the highest rates of meningococcal disease, and this rate was especially high for young children (figure 1). The relative rates across age groups were very similar in the Maori and the Pacific people populations: The incidence of disease was 16 times higher for children aged 1–4 years, 12 times higher for children aged 0–<1 year, and 4–5 times higher for children and youth aged 5–19 years than for adults. In the European and other ethnic populations, there were smaller differences in rates among the three youngest age groups: Meningococcal rates were six times higher in children aged 1–4 years and five times higher in children aged 0–<1 year and children and youth aged 5–19 years than for adults.

Deprivation effects

Higher levels of deprivation led to significantly higher meningococcal rates overall ($p < 0.001$), although the effects of deprivation differed in the different age categories as well as in the different geographic regions. The effects of

deprivation were significantly worse for babies: for children aged 0–<1 year, meningococcal rates increased 1.8 times for each quintile of deprivation (a significantly higher increase per quintile than for adults; $p < 0.01$); for children aged 1–4 years and from 5 years to adult, meningococcal rates increased 1.4 times for each quintile of deprivation (these two age groups were not significantly different). The effects of deprivation were the greatest in the Southern region, where meningococcal rates increased 1.4 times for each quintile of deprivation, compared with 1.2 times in the Northern region, 1.0 times in the Midland region, and 1.1 times in the Central region.

Seasonal effects

Meningococcal rates were highest in the July–September season and lowest in the January–March season (figure 2).

Time effects

Overall, meningococcal rates decreased over time (figure 3). Importantly, rates were decreasing before the Programme began. The average decrease in disease rates from 2001 to 2006 was 18 percent per year.

Sensitivity analysis

Using Statistics New Zealand low- or high-growth population estimates yielded a model with the same factors and similar parameter estimates as the medium-growth estimates.
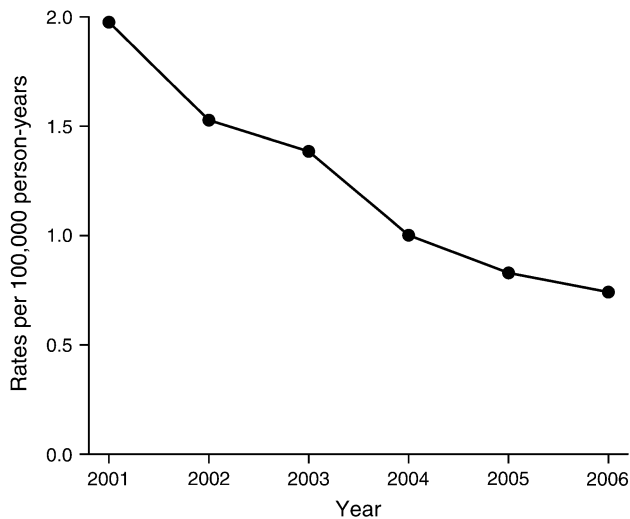
FIGURE 3. Estimated meningococcal rates in New Zealand (cases per 100,000 person-years) in the fourth quarter of the years 2001–2006 for the reference group (unvaccinated adults in the lowest deprivation group of European or other ethnicity).

For the low-growth population estimates, the estimated vaccine effect was a risk ratio of 3.8 and a vaccine effectiveness of 74 percent. For the high-growth population estimates, the estimated vaccine effect was a risk ratio of 3.4 and a vaccine effectiveness of 71 percent.

Including the partially vaccinated cases and populations in the model had little effect on the estimated vaccine effect: The estimated risk ratio for full vaccination was 3.6, and the vaccine effectiveness was 72 percent. The model indicates a significant protective effect of partial vaccination ($p = 0.02$), although the effect is much lower than for full vaccination. Unvaccinated subjects were 1.6 times as likely (95 percent confidence interval: 1.1, 2.4) to contract the disease as subjects who received one or two doses of the vaccine.

A Poisson regression model with geographic regions defined by the 21 district health boards instead of the four larger regions resulted in an estimated vaccine risk ratio of 3.8 and a vaccine effectiveness of 74 percent.

Although information on vaccination coverage over deprivation quintiles was not available for each demographic-by-time stratum, it was available for the overall population. The proportions of the population that were fully vaccinated by June 2006 were 85 percent, 80 percent, 76 percent, 78 percent, and 82 percent for the five deprivation quintiles, respectively. For the sensitivity analysis, two nonuniform vaccination coverage distributions were considered: 1) a decreasing distribution (coverage probabilities of 88 percent, 84 percent, 80 percent, 76 percent, 72 percent) and 2) a U-shaped distribution (coverage probabilities set to equal the observed proportions above). The estimated vaccine effect for the decreasing distribution was 3.6 with a vaccine effectiveness of 72 percent, and the estimated vaccine effect for the U-shaped distribution was 3.8 with a vaccine effectiveness of 74 percent.

DISCUSSION

In this study, we investigated the effectiveness of a new group B strain-specific meningococcal vaccine (MeNZB) in a prospective observational study following a nationwide vaccination program in New Zealand. The urgent need to control the epidemic rendered a randomized controlled efficacy trial unethical, putting individuals in the control arm of the study at risk unnecessarily (Ministry of Health, Chiron Corporation, University of Auckland, unpublished manuscript). Although randomized controlled trials are generally considered to be the "gold standard" for evaluation, in situations such as this, they may be unethical, impossible, or unnecessary to assess the efficacy of certain vaccines (19, 20). Furthermore, observational studies can have the advantages of demonstrating effectiveness in broader populations and more realistic settings and providing information on adverse events and risks (20–22). Recently, Benson and Hartz (23) found similar estimates of treatment effects in a comparison of observational studies and randomized controlled trials, contrary to early studies, and attribute this to an improvement in the design and analysis of observational data. A well-designed observational study considers and adjusts for potential confounding variables through statistical methods such as regression (24).

The multiple regression model allowed for the adjustment of potential confounders such as age, ethnicity, season, region, socioeconomic status, and the natural progression of the disease over time—an important factor since the epidemic was waning prior to the start of the Programme. Interactions between geographic region and time were not significant in the rates model, indicating that differing patterns of disease progression in different regions were unlikely to confound the results. The effects of demographic variables, such as ethnicity, age, and deprivation, were similar to those reported elsewhere (2). Ethnicity may be a proxy for overcrowding, which is a known risk factor for meningococcal disease (25).

We found no statistically significant interactions between any demographic variable and the vaccine effect, even though a comparison of crude disease rates indicated a potentially lower vaccine effect for babies than for other age categories (in 2005, the risk ratio for children aged 0–<1 year was 0.9, for children aged 1–4 years was 11.3, and for children and youth aged 5–19 years was 2.9). With the limited data on this age group, we were unable to determine if this was a spurious effect or a real effect that our data set had insufficient power to detect. In January 2006, however, on the basis of immunogenicity data from clinical trials, a fourth dose of vaccine was licensed for infants who received their first dose before 6 months of age. A fourth dose of MeNZB administered at 10 months of age was found to induce immune responses similar to those seen in older age groups after three doses (26).

This study demonstrated that the MeNZB vaccine significantly decreased the likelihood of contracting the epidemic strain of meningococcal disease. Vaccinated individuals decreased their risk by almost fourfold (95 percent confidence interval: 2.1, 6.8), and the vaccine had an effectiveness of 73 percent (95 percent confidence interval: 52, 85). This

percentage is likely to be an underestimate of the true effectiveness of the vaccine, given that several conservative assumptions were made in the analysis.

Meningococcal cases with unknown deprivation (24 cases) or ethnicity (three cases) were excluded from analysis. All 27 excluded cases contracted the disease prior to 2004 and were thus unvaccinated, so their exclusion underestimated (slightly) the meningococcal disease rates in the unvaccinated population and yielded a conservative estimate of the vaccine effect. (The data quality of the demographic information on cases improved over time.)

In a sensitivity analysis, the estimates proved to be robust to data and modeling assumptions. Estimates of the risk ratio ranged between 3.4 and 3.8, and estimates of the vaccine effectiveness ranged between 71 and 74 percent. We found a significant protective effect of partial vaccination ($p < 0.005$). Interpreting the risk ratio or vaccine effectiveness for partial vaccination is problematic, however, because it is based on individuals who received one or two doses of the vaccine and it doesn't separate out the effects of one dose and two doses.

An estimated 54 epidemic strain, laboratory-confirmed meningococcal cases were prevented in the 2 years since the Programme began (95 percent confidence interval assuming a fixed population size: 22, 115), and an estimated 1.7 deaths were prevented. These values are also likely to underestimate the true number of meningococcal cases prevented, since we would expect that a similar proportion of unconfirmed (or "probable") cases would also be prevented.

A remaining question of interest regards the long-term effectiveness of the vaccine. In the United Kingdom, the meningococcal serogroup C vaccination program demonstrated lower effectiveness after 1 year for children vaccinated at 2–4 months of age, although the effectiveness remained high 4 years after vaccination for children vaccinated from 5 months to 18 years of age (27). In Norway, a randomized controlled trial of two doses of a vaccine referred to as "MenBvac" developed by the Norwegian Institute of Public Health in teenagers showed a drop in efficacy from 87 percent after 10 months to 57 percent after 29 months (10). Further observation is needed to determine whether the three-dose New Zealand vaccine, MeNZB, will provide longer lasting protection. At the conclusion of the Programme at the end of June 2006, there were still significant unvaccinated populations, since no adults were vaccinated and approximately 20 percent of children remained unvaccinated or partially vaccinated. Thus, the long-term effects of the vaccine can continue to be studied.

REFERENCES

1. Sexton K, Lennon D, Oster P, et al. The New Zealand meningococcal vaccine strategy: a tailor-made vaccine to combat a devastating epidemic. N Z Med J 2004;117:1–9.
2. Martin D, Lopez L, McDowell R. The epidemiology of meningococcal disease in New Zealand in 2004. A report prepared for the Ministry of Health by the Institute of Environmental Science and Research Limited (ESR). Wellington, New Zealand: ESR, 2005. (www.moh.govt.nz/moh.nsf/238fd5fb4fd051844c256669006aed57/47914a3170b2449bcc2570290010e66c?OpenDocument).
3. Martin D, McDowell R. The epidemiology of meningococcal disease in New Zealand in 2003. A report prepared for the Ministry of Health by the Institute of Environmental Science and Research Limited (ESR). Wellington, New Zealand: ESR, 2004. (www.moh.govt.nz/moh.nsf/238fd5fb4fd051844c256669006aed57/c088f437895d6dc8cc256ed1000b2539?OpenDocument).
4. Martin D, Walker S, Baker M, et al. New Zealand epidemic of meningococcal disease identified by a strain with phenotype B:4:P1.4. J Infect Dis 1998;177:497–500.
5. Holst J, Aaberge IS, Oster P, et al. A 'tailor made' vaccine trialled as part of public health response to group B meningococcal epidemic in New Zealand. Euro Surveill 2003;7:030724. (http://www.eurosurveillance.org/ew/2003/030724.asp#5).
6. Bovre K, Holten E, Vik-Mo H, et al. *Neisseria meningitidis* infections in northern Norway: an epidemic in 1974–1975 due mainly to group B organisms. J Infect Dis 1977;135:669–72.
7. Fredriksen JH, Rosenqvist E, Wedege E, et al. Production, characterization and control of MenB-vaccine "Folkehelsa": an outer membrane vesicle vaccine against group B meningococcal disease. NIPH Ann 1991;14:67–79.
8. Oster P, Lennon D, O'Hallahan J, et al. MeNZB™: a safe and highly immunogenic tailor-made vaccine against the New Zealand *Neisseria meningitidis* serogroup B disease epidemic strain. Vaccine 2005;23:2191–6.
9. Wong SH, Jackson CM, Martin DM, et al. Safety and immunogenicity of New Zealand strain meningococcal serogroup B outer membrane vesicle vaccine in healthy 16–24 months old toddlers. (Abstract). In: Apicella MA, Seifert H, eds. Fourteenth International Pathogenic *Neisseria* Conference, Milwaukee, Wisconsin, 2004:8.
10. Sierra GVG, Campa HC, Varcacel NM, et al. Vaccine against group B *Neisseria meningitidis*: protection trial and mass vaccination results in Cuba. NIPH Ann 1991;14:195–207.

11. Holst J, Feiring B, Fuglesang JE, et al. Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against *Neisseria meningitidis* serogroup B disease. Vaccine 2003;21:734–7.
12. Balmer P, Borrow R. Serological correlates of protection for evaluating the response to meningococcal vaccines. Expert Rev Vaccines 2004;3:77–87.
13. Bjune G, Høiby EA, Grønnesby JK, et al. Effect of outer membrane vesicle vaccine against serogroup B meningococcal disease in Norway. Lancet 1991;338:1093–6.
14. Rosenqvist E, Høiby EA, Wedege E, et al. Human antibody responses to meningococcal outer membrane antigens after three doses of the Norwegian group B meningococcal vaccine. Infect Immun 1995;12:4642–52.
15. Tappero JW, Lagos R, Ballesteros AM, et al. Immunogenicity of 2 serogroup B outer-membrane protein meningococcal vaccines: a randomized controlled trial in Chile. JAMA 1999;281:1520–7.
16. Ameratunga S, Macmillan A, Stewart J, et al. Evaluating the post-licensure effectiveness of a group B meningococcal vaccine in New Zealand: a multi-faceted strategy. Vaccine 2005; 23:2231–4.
17. Salmond C, Crampton P. NZDep2001 index of deprivation. Wellington, New Zealand: Ministry of Health, 2002.
18. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
19. Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ 1996;312:1215–18.
20. Rochon PA, Gurwitz JH, Sykora K, et al. Readers guide to critical appraisal of cohort studies. 1. Role and design. BMJ 2005;330:895–7.
21. Orenstein WA, Bernier RH, Dondero TJ, et al. Field evaluation of vaccine efficacy. Bull World Health Organ 1985;63: 1055–68.
22. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field: further observations. Epidemiol Rev 1988; 10:212–41.
23. Benson K, Hartz A. A comparison of observational studies and randomized, controlled clinical trials. N Engl J Med 2000;342: 1878–86.
24. Normand SLT, Sykora K, Li P, et al. Readers guide to critical appraisal of cohort studies. 3. Analytical strategies to reduce confounding. BMJ 2005;330:1021–3.
25. Baker M, McNicholas A, Garrett N, et al. Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. Pediatr Infect Dis J 2000;19: 983–90.
26. Meningococcal Management Team. Meningococcal B immunisation programme. Supplement—February 2006. Wellington, New Zealand: New Zealand Ministry of Health, 2006. (http://www.immunise.moh.govt.nz/documents/Supplement-toProgrammeGuideFeb06edited.doc).
27. Trotter C, Andrews N, Kaczmarski E, et al. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 2004;364:365–7.