Immunogenicity, Reactogenicity, and Safety of a P1.7b,4 Strain-Specific Serogroup B Meningococcal Vaccine Given to Preteens

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New Zealand (NZ) has experienced a Neisseria meningitidis serogroup B epidemic since 1991. MeNZB, a strain-specific outer membrane vesicle vaccine made using an NZ epidemic strain isolate, NZ98/254 (B:4:P1.7b,4), from two manufacturing sites, the Norwegian Institute of Public Health (NIPH) and Chiron Vaccines (CV; now Novartis), was evaluated for safety, immunogenicity, and reactogenicity in this observer-blind trial with 8- to 12-year-old children. In year 1, cohort A (n = 302) was randomized 4:1 for receipt of NIPH-MeNZB or MenBvac (Norwegian parent vaccine strain 44/76; B:15:P1.7,16). In year 2, cohort B (n = 313) was randomized 4:1 for receipt of CV-MeNZB or NIPH-MeNZB. Participants all received three vaccinations 6 weeks apart. Local and systemic reactions were monitored for 7 days. Seroresponse was defined as a fourfold or greater rise in the serum bactericidal antibody titer from the baseline titer as measured by a serum bactericidal assay. Those with baseline titers of <1:4 required titers of ≥1:8 to seroresponse. Intention-to-treat (ITT) and per protocol (PP) analyses are presented. In cohort A, 74% (ITT) and 73% (PP) of NIPH-MeNZB recipients demonstrated seroresponses against NZ98/254 after three doses, versus 32% (ITT and PP) of MenBvac recipients. In cohort B, seroresponses against NZ98/254 after three doses occurred in 79% (ITT and PP) of CV-MeNZB versus 75% (ITT) and 76% (PP) of NIPH-MeNZB recipients. Vaccines were tolerable, with no vaccine-related serious adverse events. In conclusion, the NZ strain meningococcal B vaccine (MeNZB) from either manufacturing site was immunogenic against New Zealand epidemic vaccine strain meningococci with no safety concerns when given in three doses to these 8- to 12-year-old children.

Meningitis, sepsis, and other serious infections caused by Neisseria meningitidis continue to occur in both developed and developing countries (17). Since 1991, New Zealand (NZ) has experienced an epidemic of serogroup B meningococcal disease, with the B:4:P1.7b,4 strain accounting for 86% of isolates from 1990 to 2003 (10). The incidence peaked in 2001 (17.4 per 100,000). Approximately 80% of diseases occur in those under 20 years old. The highest-risk age group is infants under 1 year old (124.4 per 100,000 in 2003) (10).

Development of a meningococcal serogroup B vaccine has been protracted due to the immunologic cross-reactivity of B polysaccharide with human neural tissue and other concerns (13). Control of serogroup B disease by outer membrane vesicle (OMV) vaccines has been limited. Strain specificity reduces the application of these vaccines. The efficacy in randomized controlled trials of three serogroup B meningococcal OMV vaccines, different from each other in manufacturing process and strain, has been shown in older children and adolescents (3, 7, 26). Strain-specific immunogenicity to these OMV vaccines has been demonstrated in all age groups (27). Limited safety information is available from randomized controlled trials (7, 22, 26). However, serogroup B meningococcal OMV vaccines have received widespread use in Latin America (21).

To address the NZ meningococcal epidemic, the Norwegian Institute of Public Health (NIPH) produced a strain-specific meningococcal B OMV vaccine (NIPH-MeNZB), in collaboration with Chiron Vaccines (CV; now Novartis). The NZ vaccine was manufactured using a selected NZ epidemic strain (B:4:P1.7b,4; NZ98/254) and produced in a manner similar to that for MenBvac, the Norwegian strain parent OMV vaccine (14). Demonstrated physicochemical similarities between MenBvac and MeNZB (19) supported the bridging of preexisting safety information from the parent vaccine. The NZ vaccine was subsequently produced at CV (CV-MeNZB).

The technique of a serum bactericidal-activity assay has been used to measure the serum bactericidal antibody activity responses to serogroup B vaccines and was the primary test of immunogenicity for this trial (7, 18, 20, 21, 23, 24, 27). Correlation between serum bactericidal antibody activity and protection against meningococcal disease was reported in 1969 (15). Subsequently, age groups with comparatively high levels of serum bactericidal antibody activity were found to have higher efficacy after mass vaccination with serogroup B OMV vaccines in Brazil and Chile (7, 21).

Trials were planned in NZ to assess the immunogenicity, reactogenicity, and safety of MeNZB in different age groups prior to application for regulatory approval for widespread use (25). Two phase I/II studies with adults, demonstrating the tolerability and safety of NIPH-MeNZB (28) and CV-MeNZB
TABLE 1. Baseline participant characteristics for the randomized population

| Cohort and vaccine | No. of participants | Mean age (yrs) | No. (%) of female participants | No. (%) of participants of indicated ethnicity |
|--------------------|---------------------|---------------|---------------------------------|-----------------------------------------------|
|                    |                     |               |                                 | NZ European  | Māori  | Pacific  | Other  |
| A                  |                     |               |                                 |                |        |          |        |
| NIPH-MeNZB         | 241                 | 9.5           | 120 (50)                        | 88 (37)       | 57 (24) | 86 (36)  | 10 (3) |
| MenBvac            | 61                  | 9.5           | 22 (36)                         | 20 (33)       | 13 (21) | 22 (36)  | 6 (10) |
| B                  |                     |               |                                 |                |        |          |        |
| CV-MeNZB           | 250                 | 10.0          | 136 (54)                        | 97 (39)       | 80 (32) | 55 (22)  | 18 (7) |
| NIPH-MeNZB         | 63                  | 10.0          | 39 (62)                         | 29 (46)       | 19 (30) | 10 (16)  | 5 (8)  |

MATERIALS AND METHODS

This was a phase II, randomized, controlled, observer-blind trial involving two cohorts of participants. The Auckland Ethics Committee approved this study.

Population. Children 8 to 12 years old from schools in Manurewa and Papakura, Auckland, NZ, were eligible to participate. These were areas with high meningococcal-disease incidence. Forty-two schools were invited to take part, with 39 accepting. Prior to the cohort A trial, 10,500 flyers inviting participation were distributed in these schools, with a further 4,500 distributed prior to the cohort B trial.

For the first year of the study, for cohort A, 1,182 respondents were contacted by telephone; those from schools with the most expressions of interest were approached first. Of those contacted, 337 attended an enrollment appointment, but 35 of them did not satisfy the eligibility criteria; thus, 302 participants were enrolled during October and November 2002. For the second year of the study, for cohort B, 1,518 respondents from schools not involved in cohort A were contacted. Of these, 350 attended an enrollment appointment; 37 of these did not satisfy the eligibility criteria, and thus, 313 participants were enrolled during August and September 2003.

Written informed consent was obtained from parents/legal guardians and written assent from children at the first visit. Children were not eligible if they had previously had a meningococcal disease or recent household contact with a meningococcal disease, had recently received other vaccines, had a history of vaccine hypersensitivity, had had a fever within the past 3 days, had taken systemic antibiotics within the past 14 days, had received blood products in the past 3 days, had a serious chronic disease, or had previously had meningococcal disease or recent household contact with a meningococcal disease.

Vaccination, specimen collection, and laboratory methods. Three vaccines were used, prepared as previously described (28). Each vaccine was from a single manufacturing site, namely, CV-MeNZB and NIPH-MeNZB. Data from this and other studies contributed to licensure of CV-MeNZB as MeNZB with prospective consent in 2004 for use in a mass vaccination program.

(This study was presented in part at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 30 October to 2 November 2004.)
were demonstrated in 14% of cohort A children and 11% of cohort B children. Baseline serum bactericidal antibody titers of \( \geq 1:4 \) against the Norwegian vaccine strain (44/76, B:15; P1.7,16) were demonstrated in 9% of children in cohort A and not evaluated in cohort B.

**Cohort A: comparing NIPH-MeNZB (NZ strain) and MenBvac (Norwegian strain).** (i) NIPH-MeNZB recipients. Seroresponse to the homologous NZ vaccine strain (B:4; P1.7b,4, NZ98/254) was seen in over 70% of MeNZB recipients after three doses. Only 16% showed a seroresponse to the heterologous Norwegian parent vaccine strain (B:15:P1.7,16, 44/76) (Table 2). GMTs against the NZ vaccine strain (NZ98/254) (ITT and PP) were 9 (range, 7 to 11) after two doses and 22 (range, 18 to 27) after three doses, with greater than 90% of recipients achieving serum bactericidal antibody titers of \( \geq 1:4 \) after three doses (Table 3).

(ii) MenBvac recipients. Seroresponse to the homologous Norwegian parent vaccine strain (B:15:P1.7,16, 44/76) occurred in 82% of participants following three vaccine doses. In contrast, seroresponse to the heterologous NZ vaccine strain (B:4; P1.7b,4, NZ98/254) was demonstrated in 32% after three doses (Table 2). GMTs against the Norwegian vaccine strain (44/76) were 8 (range, 5 to 12) after two doses and 22 (range, 18 to 27) after three doses, with greater than 90% of recipients achieving serum bactericidal antibody titers of \( \geq 1:4 \) after three doses (Table 3).

**Cohort B: comparison of NIPH-MeNZB (NZ strain) and CV-MeNZB (NZ strain).** (i) CV-MeNZB recipients. Seroresponse to the homologous NZ vaccine strain (B:4; P1.7b,4, NZ98/254) occurred in 79% of children following three vaccine doses (Table 2). GMTs against the NZ vaccine strain (NZ98/254) were 20 (range, 16 to 24) (ITT and PP) after two doses and 25 (range, 20 to 30) by ITT analysis (24 [range, 20 to 30] by PP) after three doses. The distribution of serum bactericidal antibody titers is shown in Fig. 2. More than 90% demonstrated serum bactericidal antibody titers against NZ98/254 of \( \geq 1:4 \) after three doses (Table 3).

(ii) NIPH-MeNZB recipients. Seroresponse to the homologous Norwegian parent vaccine strain (B:4; P1.7b,4, NZ98/254) occurred in 82% of participants following three vaccine doses. In contrast, seroresponse to the heterologous NZ vaccine strain (B:4; P1.7b,4, NZ98/254) was demonstrated in 54% after three doses (Table 3).

**Cohort A and cohort B NIPH-MeNZB recipients (NZ strain).** The observed difference in response to NIPH-MeNZB between the two cohorts could not be explained by any differences in demographics (sex, ethnicity, age), baseline serum bactericidal titer, or timing of vaccinations or blood draws (Table 2). However, there was a tendency for those with blood draws longer after the time of vaccination to have lower bactericidal titers \( (P = 0.02) \).

**Reactogenicity and safety.** All vaccines were well tolerated. Reactogenicity results were comparable for all four groups. The only reaction showing a statistical difference was swelling in cohort A; however, this could have occurred by chance, given the number of reactions investigated (Table 4). Analgesic use was lower in cohort B than in cohort A.
was provided on request at enrollment in cohort A and only after contacting the study team in cohort B.

More-detailed results are presented for the CV-MeNZB vaccine, which was later used in the mass vaccination program (Table 5). Pain at injection site, most commonly mild, was the most frequent adverse event (Table 4 and Table 5). Other local reactions following CV-MeNZB treatment (≥10-mm diameter) were erythema (25%), swelling (13%), and induration (20%) after at least one of the three vaccine doses (Table 4). Headache was the most common systemic reaction (Table 4). In the CV-MeNZB group, the frequency was most commonly mild (Table 5). Systemic reactions were most frequent on the day following vaccination, mostly lasted less than 3 days, and were most frequently mild. The observed local and systemic reactions either remained similar or decreased slightly across doses. Nine serious adverse events (cohort A, n = 4, and cohort B, n = 5) were reported, none of which were judged to be related to the study vaccines.

**DISCUSSION**

In this study, the NZ strain vaccine (MeNZB) from both manufacturing sites was immunogenic, safe, and tolerable in 8- to 12-year-old children. In the cohort A trial, the first meningococcal B vaccine trial performed with children in NZ, seroresponse against the NZ vaccine strain (B:4:P1.7b,4, NZ98/254) were demonstrated by 74% (ITT) and 73% (PP) of NIPH-MeNZB vaccine recipients 4 to 6 weeks after dose three. CV-MeNZB and NIPH-MeNZB vaccine recipients in cohort B demonstrated similar seroresponse rates after three doses. Significant but tolerable reactogenicity occurred in both candidate and parent vaccine recipients, with comparable results seen in all groups. Almost all participants experienced pain at the injection site, which is similar to previous experience with the parent vaccine (22).

It is difficult to compare the proportion of participants in this

### TABLE 2. Preteens classified as seroresponders to meningococcal group B strains following administration of serogroup B OMV vaccines

| Cohort and vaccine | Dose no. | Type of analysis | No. of participants | No. (%) of seroresponders for indicated strain |
|--------------------|---------|------------------|---------------------|-----------------------------------------------|
|                    |         |                  |                     | B:4:P1.7b,4 (NZ98/254) | B:15:P1.7,16 (44/76) |
| A                  | 2       | ITT              | 221                 | 44 (38–50) | 10 (7–15) |
|                    | PP      |                  | 217                 | 43 (36–50) | 10 (7–15) |
|                    | 3       | ITT              | 220                 | 74 (67–79) | 16 (12–21) |
|                    | PP      |                  | 214                 | 73 (67–79) | 16 (12–21) |
| B                  | 2       | ITT              | 54                  | 28 (18–41) | 44 (32–58) |
|                    | PP      |                  | 53                  | 28 (18–42) | 45 (33–59) |
|                    | 3       | ITT              | 56                  | 32 (21–45) | 82 (70–90) |
|                    | PP      |                  | 56                  | 32 (21–45) | 82 (70–90) |
| A                  | 3       | ITT              | 230                 | 73 (67–78) | ND |
|                    | PP      |                  | 230                 | 73 (67–78) | ND |
|                    | 3       | ITT              | 230                 | 79 (73–84) | ND |
|                    | PP      |                  | 217                 | 79 (73–84) | ND |
| B                  | 2       | ITT              | 55                  | 71 (58–81) | ND |
|                    | PP      |                  | 55                  | 71 (58–81) | ND |
|                    | 3       | ITT              | 55                  | 75 (62–85) | ND |
|                    | PP      |                  | 54                  | 76 (63–85) | ND |

*a* Seroresponders are defined as those showing at least a fourfold increase in serum bactericidal antibody titer compared to the baseline (prevaccination) titer, using interpolated titers. A baseline titer of <1:4 was required to reach a titer of ≥1:8 to be considered a seroresponse.

*b* Serum bactericidal antibody titers were measured following administration of the indicated dose.

*c* Values in parentheses are 95% confidence intervals. ND, test not performed.

### TABLE 3. Preteens with serum bactericidal antibody titers (≥1:4) against New Zealand vaccine strain NZ98/254 (B:4:P1.7b,4) after administration of serogroup B OMV meningococcal vaccines

| Cohort and vaccine | Type of analysis | % of children with serum bactericidal antibody titers of ≥1:4<sup>a</sup> | No. of children | % of children with serum bactericidal antibody titers of ≥1:4<sup>b</sup> | No. of children |
|--------------------|------------------|------------------------|----------------|-----------------------------------------------|----------------|
| A                  | ITT              | 11 (8–16)              | 224            | 92 (88–95)                                   | 224            |
|                    | PP               | 11 (8–16)              | 221            | 93 (88–95)                                   | 214            |
| MenBvac            | ITT              | 23 (14–36)             | 56             | 54 (41–66)                                   | 56             |
|                    | PP               | 23 (14–36)             | 56             | 54 (41–66)                                   | 56             |
| B                  | ITT              | 11 (7–15)              | 236            | 95 (91–97)                                   | 230            |
|                    | PP               | 11 (7–15)              | 236            | 94 (90–97)                                   | 217            |
| NIPH-MeNZB         | ITT              | 11 (5–22)              | 57             | 89 (78–95)                                   | 56             |
|                    | PP               | 11 (5–22)              | 57             | 89 (77–95)                                   | 54             |

<sup>a</sup> Children (age range, 8 to 12 years) received three doses of each vaccine, and serum bactericidal antibody titers were measured before and after vaccination.

<sup>b</sup> Prevaccination titers are considered baseline values.

<sup>c</sup> Postvaccination titers were measured 4 to 6 weeks after administration of the third vaccine dose.

<sup>d</sup> A titer of ≥1:4 has been suggested to be a correlate of protection (5, 6, 18).
study experiencing fourfold rises in serum bactericidal antibody titers with results reported elsewhere in the literature, as there are differences in the definitions of a fourfold rise from a low or undetectable baseline (20). An interlaboratory study involving laboratories from four countries testing the same sera by serum bactericidal assays showed consistency in the percentages attaining fourfold rises in antibody titer, despite variation in the absolute titers achieved (4, 20).

Previous studies have correlated the presence of serum bactericidal antibody activity with protection from meningococcal disease (15, 16) and have correlated a fourfold rise in serum bactericidal antibody titer postvaccination with vaccine efficacy for serogroup B meningococcal disease in particular (7, 21). Norwegian vaccine efficacy (strain B:15:P1.7,16) after 29 months was 57% in a randomized controlled trial of two doses with youth aged 14 to 16 years (3), while efficacy for the first 10 months of the trial was estimated at 87% (23). Given the suggested correlation between the level of seroresponse and vaccine efficacy, MeNZB is likely to be protective against the NZ epidemic strain of serogroup B meningococcus. For serogroup B meningococcal vaccines, unlike for group C vaccines, the correlate of protection is less secure. A titer of /H11350 4 and/or a /H11350 4-fold rise demonstrated by a serum bactericidal-activity assay using human complement has been suggested (5, 6). The decline, at a population level, of serum bactericidal antibody titers below 4 was thought to correlate with breakthrough cases in Norway (18).

Seroresponse after dose two was significantly lower for NIPH-MeNZB vaccine recipients in cohort A than for those in cohort B. The findings of a relationship between time to blood draw and bactericidal titer, while plausible, resulted from a post hoc analysis, so the result needs to be viewed with caution and confirmed in other studies designed to investigate the dynamics of response to this vaccine.
ERYTHEMA, SWELLING, AND INDURATION, AFFECTED AREAS WERE MEASURED AND CLASSIFIED NORMAL DAILY ACTIVITIES; SEVERE, INABILITY TO PERFORM NORMAL DAILY ACTIVITIES. FOR THE VACCINE IN QUESTION. HOWEVER, THERE IS SOME EVIDENCE FROM IN SITUATIONS OTHER THAN EPIDEMICS DOMINATED BY THE STRAIN OF STRAIN AFTER THREE DOSES. THIS FINDING SUGGESTS THAT THERE MAY BE LIMITED APPLICATIONS FOR STRAIN-SPECIFIC MENINGOCOCCAL VACCINES LATER IN THE STUDY POPULATION OF 8-TO 12-YEAR-OLD CHILDREN, WITH NO SAFETY CONCERNS OBSERVED DURING THE TRIAL. AFTER LICENSURE (IN 2004), ME NZB WAS DELIVERED TO CHILDREN AGED 6 WEEKS TO 19 YEARS BY REGION BASED ON THIS AND TRIALS WITH YOUNGER AGE GROUPS (25, 29). EVALUATION OF VACCINE EFFECTIVENESS BY USING DESCRIPTIVE METHODS WILL BE IMPORTANT IN THE ABSENCE OF A PHASE III EFFICACY TRIAL (2). POSTMARKETING SAFETY SURVEILLANCE FOR RARE ADVERSE EVENTS WAS UNDERTAKEN, ACCOMPANYING THE MASS VACCINATION PROGRAM (25).

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