Antibody persistence following MeNZB vaccination of adults and children and response to a fourth dose in toddlers

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ABSTRACT
Background A New Zealand serogroup B meningococcal epidemic prompted trials of a strain-specific (B:4:P1.7-2,4) outer membrane vesicle vaccine (MeNZB).

Methods Adults, school children, and infants provided serum after three MeNZB doses to evaluate antibody persistence via serum bactericidal assay. Toddler (16–24 months) non-responders and responders received a fourth MeNZB dose 11 and 17 months after dose three respectively. Response was a ≥4-fold rise in bactericidal titre to a titre of ≥8.

Results Geometric mean bactericidal titres (GMTs), with 95% CI, after dose 3: adults: 27 (14–52), 5 (3–11), and 7 (3–15) at 1, 10, and 22 months; school children: 18 (13–25) and 4 (3–6) at 1 and 4 months; infants: 27 (19–39) and 2 (2–3) at 1 and 7 months. The titre achieved after priming significantly influenced persistence. Toddler non-responder GMTs were 4 (3–5) and 1 (1–1) at 1 and 11 months after dose 3 and 69 (46–106) 1 month after dose 4. Responder GMTs were 24 (19–30) and 3 (2–4) at 1 and 17 months after dose 3 and 259 (184–363) 1 month after dose 4. Dose 4 had no safety concerns.

Conclusions Immune response to MeNZB was most sustained in adults. In infants, bactericidal titres decayed almost to baseline by 7 months after dose 3. Toddlers showed marked immune response following a fourth dose suggesting memory. Persisting antibody is likely to be necessary for ongoing protection, as seen with serogroup C meningococci.

INTRODUCTION
In 2002, with a view to controlling a New Zealand (NZ) serogroup B meningococcal epidemic which had started in 1991, a series of NZ-based trials of a tailor-made vaccine targeting the epidemic strain (B:4:P1.7-2,4), MeNZB, were conducted.1–6 Following MeNZB licensure in mid-2004, the Ministry of Health instigated a mass vaccination programme offering three 25 μg MeNZB doses to those aged 6 months to 19 years. In 2005 this programme was expanded to include infants from 6 weeks of age, with a change in 2006 to a four-dose priming series in infants receiving the first dose of MeNZB prior to age 6 months.5 Similar mass vaccination programmes for epidemic serogroup B meningococcal disease using different outer membrane vesicle (OMV) vaccines were undertaken in 1989–1990 in Sao Paulo (Brazil) and Cuba.7 8 In Cuba, VA-MENGOC-BC was subsequently introduced into the national immunisation programme in 1991 with two 50 μg doses given at 3 and 5 months of age.8

During the NZ epidemic, the rate of all meningococcal disease cases rose from 1.5 per 100 000 persons in 1990 to a peak of 17.4 per 100 000 persons in 2001.9 The highest rates were seen in infants less than 1 year old, indigenous Māori and Pacific people and those living in the most socio-economically deprived areas. During the period 1995–2003, the epidemic strain accounted for approximately 85% of meningococcal disease cases.9 During 2007–2009 there was an annual average of 44 epidemic strain cases compared with an annual average of 507 epidemic strain cases during 2001–2003.10

MeNZB was developed via collaboration between the NZ Ministry of Health, Chiron Vaccines (now Novartis) and the Norwegian Institute of Public Health (NIPH). Clinical trials were conducted in adults, school children (3–12...
years), toddlers (16–24 months) and infants (6–8 months and 6–10 weeks). In the absence of a clear correlate of protection, the primary immunogenicity outcome measure of these trials was seroresponse defined as a fourfold rise in the serum bactericidal antibody titre compared with the prevaccination baseline; or for those with a baseline titre <4, a titre ≥8. High seroresponse rates of 74% or greater at 1 month after a third dose of MeNZB were demonstrated in adults, school children, toddlers and 6–8-month-old infants. Infants aged 6–10 weeks when commencing vaccination required four doses to achieve similar seroresponse rates.

When MeNZB was licensed the expected duration of protection against the epidemic strain was unknown. Limited data were available regarding the decay of antibody response following vaccination, particularly in young children and infants. In addition, limited data were available regarding the safety and immunogenicity of a fourth dose in young children, and the effect of a fourth dose in children who had not responded to three doses was unknown. As a consequence, an extension study in a cohort of adults and children who took part in the primary MeNZB studies was undertaken in order to investigate the persistence of immune response and the safety and immunogenicity of a fourth dose of MeNZB in toddlers.

METHODS

This study comprised two parts: the persistence study and the booster study. Originally, the persistence study planned to invite all children who had received three doses of MeNZB in the primary trials to participate at one of two time points. However, decay of bactericidal antibodies occurred sooner than anticipated and the second time point was abandoned. Approval to conduct this study was granted by Auckland Regional Ethics Committee.

Participants

Persistence study

All participants had previously received three doses of MeNZB administered on a 0–6–12-week schedule. Healthy adults (n=47) who had received either 25 or 50 μg doses of MeNZB in 2002 were invited and enrolled in June 2003 following written informed consent and a health check. Blood was drawn at 10, 16 and 22 months after the third MeNZB dose. Approximately 350 healthy children who received 25 μg doses of MeNZB at age 6–12 years (Trial A: 2002, Trial B: 2003) or at 6–8 months (2005) were invited to participate. Trial A in school children compared NIPH-manufactured MeNZB with the parent vaccine MenB vac, with both vaccines manufactured at the NIPH in Oslo, Norway; while Trial B compared NIPH-manufactured MeNZB with Chiron-manufactured MeNZB, manufactured at Chiron Vaccines, Siena, Italy. Enrolment of children into the persistence study occurred in March/April 2004 following written informed consent from a parent/legal guardian and a health check. Blood was drawn at 4 months (Trial B), 7 months (infants) or 14 months (Trial A) after the third MeNZB dose. Exclusion criteria were a bleeding diathesis, previous serogroup B meningococcal disease or recent household exposure to serogroup B meningococcal disease, or receipt of any vaccination (50 days), systemic antibiotic (6 days) or blood product (12 weeks) prior to enrolment.

Booster study in 16–24-month-old toddlers

Healthy toddlers who received three 25 μg MeNZB doses given 6 weeks apart at age 16–24 months (2003) were invited to participate in one of two separate protocols, responders (n=82) and non-responders (n=63) with seroresponse defined above. Enrolment occurred following written informed consent from a parent/legal guardian and a health check. In addition to the exclusion criteria listed for the persistence study, children were ineligible if they had an acute or chronic illness, a fever of ≥38°C in the past 3 days or previous hypersensitivity to any vaccine.

On enrolment in April 2004, both groups provided a serum sample (11 months after dose 3) and non-responders received a fourth dose of MeNZB. In October 2004, responders returned for a second blood draw (17 months after dose 3) and received a fourth dose of MeNZB. In addition, a serum sample was obtained 4–6 weeks after dose 4 in both groups.

Vaccine, vaccine administration and safety evaluation

Toddlers in the booster study received 25 μg MeNZB as their fourth dose by intramuscular injection into the deltoid. MeNZB was manufactured by Novartis, Siena, Italy as previously described. Safety monitoring was conducted as in the primary study. Injection site tenderness, erythema, swelling and induration, axillary temperature, irritability, sleepiness, rash, diarrhoea, vomiting, changing eating habits and analgesia/antipyretic use were recorded daily for 7 days postvaccination.

Serologic evaluation

For each study, blood samples were collected at the time points described by venipuncture into serum separating tubes and handled as in previous trials. Bactericidal titres were determined by serum bactericidal assay (SBA) against the vaccine strain, NZ98/254, using a single human complement source. When an individual serum sample is tested on different occasions, the resulting titres can vary. Therefore, for each participant, bactericidal titres analysed in the same batch are reported. In the persistence study titres determined in the same batch were (1) the 1-month postdose 3 titre and the first follow-up titre and (2) the 16- and 22-month postdose 3 titres in adults. In the booster study these were (1) the baseline and 1-month postdose 3 titre and (2) the titres immediately prior to and 1-month postdose 4. For this reason, and because the participants in this trial represent a sample of the original studies, the results reported here may vary from those reported previously.

Titres were reported as the reciprocal of the dilution of serum at the point where the antibody curve intersected the 50% survival/kill line. Titres of less than 2 were assigned a value of 1 when calculating geometric mean titres (GMTs).

Statistical methods

The analysis of this study was descriptive. No power calculations were undertaken as the sample size was determined by the number of participants who received three MeNZB doses in the primary studies. Percentages are quoted with 95% CIs (adjusted Wald method). GMTs are followed by the 95% CIs of the GMT.

To investigate whether the antibody titre at 1 month after the third MeNZB dose influenced the titre at the first subsequent follow-up time point, a general linear model was used. This model used the log of the first subsequent follow-up
bactericidal titre as the outcome and time interval from dose 3 to first follow-up, age group, log of the titre at 1 month after dose 3 and its interaction with age group as explanatory variables. Where the interaction was significant the data were analysed separately for each age group.

**RESULTS**

The extension study enrolled 309 participants; 38 adults, 153 school children, 40 infants and 78 toddlers. A summary of recruitment and retention along with participant demographics is shown in table 1. Serum bactericidal antibody titre results are shown in table 2.

**Persistence study**

Persistence of serum bactericidal antibodies against the epidemic strain was most sustained in adults and was similar irrespective of the vaccine dose (50 or 25 μg) (table 2). In both groups of adults bactericidal antibody titres had decreased by 10 months and there was little change in the GMT or the proportion with a titre ≥4 or ≥8 at subsequent time points.

Persistence of serum bactericidal antibodies against the epidemic strain was most sustained in adults and was similar irrespective of the vaccine dose (50 or 25 μg) (table 2). In both groups of adults bactericidal antibody titres had decreased by 10 months and there was little change in the GMT or the proportion with a titre ≥4 or ≥8 at subsequent time points.

**Table 1** Recruitment, demographics and retention summary for MeNZB vaccine extension study

<table>
<thead>
<tr>
<th>Primary study</th>
<th>Persistence study (after three doses MeNZB)</th>
<th>Booster study (fourth dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolment period</td>
<td>Adults 25 μg</td>
<td>Adults 50 μg</td>
</tr>
<tr>
<td>Potential subjects</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Not eligible for invitation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>No postvaccination serology</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>No baseline serology</td>
<td>(1)</td>
<td>(1)</td>
</tr>
</tbody>
</table>

**Extension study**

<table>
<thead>
<tr>
<th>Enrolment period</th>
<th>Invited*</th>
<th>Declined</th>
<th>Lost to follow-up</th>
<th>Out of region</th>
<th>Not eligible</th>
<th>Taking antibiotics</th>
<th>Enrolled in another trial</th>
<th>Recent vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults 25 μg</td>
<td>24</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>(3)</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>Adults 50 μg</td>
<td>23</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>8–12 years (A)</td>
<td>113</td>
<td>25</td>
<td>25</td>
<td>1</td>
<td>2</td>
<td>(3)</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>8–12 years (B)</td>
<td>145</td>
<td>35</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>6–8 months</td>
<td>91</td>
<td>35</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>16–24 months NR</td>
<td>40</td>
<td>35</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
</tr>
</tbody>
</table>

**Demography**

| Males (n (%)) | 8 (40) | 4 (22) | 33 (53) | 45 (49) | 21 (53) | 16 (53) | 20 (42) |
| Mean age at baseline† | 38.5 years | 38.0 years | 9.8 years | 10.5 years | 7.0 months | 1.6 years | 1.7 years |
| Mean age at follow-up | 39.6 years | 39.0 years | 11.2 years | 11.0 years | 16.7 months | 2.8 years | 2.9 and 3.4 years |
| European (n (%)) | 17 (85) | 17 (94) | 20 (32) | 46 (51) | 23 (58) | 18 (60) | 38 (79) |
| Indigenous Maori (n (%)) | 2 (10) | 1 (6) | 17 (27) | 25 (27) | 5 (13) | 4 (27) | 4 (8) |
| Pacific Island (n (%)) | 1 (5) | 0 (0) | 22 (38) | 15 (17) | 7 (18) | 8 (13) | 4 (8) |
| Asian (n (%)) | 0 (0) | 0 (0) | 2 (3) | 5 (5) | 5 (13) | 0 (0) | 2 (4) |
| African (n (%)) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

**Extension study retention**

| Withdrew | 2 | 2 | 2 | 1 | 0 | 0 | 3 |
| Withdrew consent | (1) | (1) | (1) | (1) | (1) | (1) |
| Moved out of region | (1) | (2) | (2) | (2) | (2) | (2) | (2) |
| Completed study (n (%)) | 18 (90) | 16 (89) | 62 (100) | 90 (99) | 40 (100) | 30 (100) | 45 (94) |
| Excluded from analysis | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

Response was defined as a fourfold or greater rise in serum bactericidal antibody titre against the vaccine strain (NZ98/254) from prevaccination baseline to a titre of at least 8.

*Approximately half of all MeNZB recipients in the children’s trials were considered for the extension study.

†Baseline: Prior to a three-dose primary series of MeNZB.

A and B, two trials conducted in school children; NR, non-responders to three doses of MeNZB; R, responders to three doses of MeNZB with follow-up at two time points.
DISCUSSION

Following three doses of MeNZB, a tailor-made vaccine targeting the NZ serogroup B epidemic strain, adults demonstrated the most sustained immune response; almost half still had a bactericidal antibody titre ≥8 at 22 months after their third vaccination irrespective of the dose (25 or 50 μg). Infants immunised at age 6–8-months old showed the greatest decline in bactericidal antibodies and only 13% had a bactericidal antibody titre ≥8 at 7 months. Individuals with a higher titre at 1 month after the third dose were more likely to have a higher titre at first subsequent follow-up irrespective of age group and timing of follow-up. A fourth dose of MeNZB given to toddlers at 11 or 17 months after dose 3 resulted in significantly higher bactericidal antibody titres against the NZ epidemic strain than have previously been reported for MeNZB.2–6

MeNZB has previously been reported to be reactogenic, with the frequency of injection site reactions, particularly pain, increasing with increasing age in NZ trials.3–5 Infants who received MeNZB with routine immunisations reported more systemic reactions than those who received routine immunisations alone; and a fourth dose in young infants given at 10 months of age was associated with higher rates of injection site reactions, irritability, sleepiness and fever than observed in infants who received their first MeNZB dose at 6–8 months.6 In our booster study, the frequency of local and systemic reactions was similar across the four doses, with the exception of injection site tenderness which occurred more frequently after the fourth dose. Despite the reactogenicity of MeNZB, retention in the vaccine trials was high (94–99%), and during the 2004–2006 vaccination programme 83% of NZ children received three vaccine doses.3–6

at the first subsequent follow-up time point. For example, all of those whose 1-month postdose 3 titre was ≥128 had a titre of ≥4 at the first subsequent follow-up time point irrespective of the timing of the follow-up serology, age group or vaccine dose. Of note, only a few participants achieved a bactericidal titre ≥128 postdose 3, and the proportion varied by age group. In adults 13.5% (95% CI 5.6% to 28.6%) achieved a titre ≥128 following three doses of MeNZB, as did 11.3% (95% CI 7.1% to 17.5%) of school children and 5.1% (95% CI 0.6% to 18.0%) of 6–8-month-old infants.

**Booster study in 16–24-month-old toddlers**

Non-responders received a fourth dose of MeNZB 11 months after dose 3 at an average age of 2.8 years. The GMT was 4 at 1 month after dose 3 and 69 at 1 month after dose 4 (table 2). Immediately prior to the fourth dose only one child had a titre ≥4 (none had a titre ≥8); however, at 1 month after dose 4 all children had a titre ≥8.

Seroresponders received a fourth dose of MeNZB 17 months after dose 3 at an average age of 3.4 years. The GMT was 24 at 1 month after dose 3 and 259 at 1 month after dose 4. At 1 month after dose 3 all had a titre both ≥4 and ≥8. By 10 months after dose 3 the proportion with a titre ≥4 had declined to 20%. Immediately prior to the fourth dose 34% had a titre ≥4; however, at 1 month after dose 4 all children had a titre ≥8.

No vaccine-related serious adverse events occurred. Local and systemic reactions were similar across all four doses for both responders and non-responders (table 3). In both groups injection site tenderness was reported more frequently following the fourth dose than the preceding doses.

**Table 2** Persistence of immune response following three doses of MeNZB by age group and immune response to a fourth dose in toddlers

<table>
<thead>
<tr>
<th>Vaccine dose</th>
<th>Age group</th>
<th>Months after dose 3</th>
<th>GMT (95% CI)</th>
<th>Titre ≥4 (95% CI)</th>
<th>Titre ≥8 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 μg</td>
<td>Adults</td>
<td>1</td>
<td>25 (15 to 43)</td>
<td>94.1 (70.7 to 100.0)</td>
<td>94.1 (70.7 to 100.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>6 (3 to 11)</td>
<td>64.7 (41.1 to 82.7)</td>
<td>47.1 (26.3 to 69.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>10 (4 to 23)</td>
<td>73.3 (47.5 to 89.3)</td>
<td>60.0 (35.7 to 80.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>9 (4 to 19)</td>
<td>66.7 (41.5 to 84.8)</td>
<td>53.3 (30.2 to 75.1)</td>
</tr>
<tr>
<td>25 μg</td>
<td>Adults</td>
<td>1</td>
<td>27 (14 to 52)</td>
<td>95.0 (74.3 to 100.0)</td>
<td>80.0 (57.7 to 92.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>5 (3 to 11)</td>
<td>50.0 (30.0 to 70.0)</td>
<td>40.0 (21.9 to 61.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>8 (3 to 17)</td>
<td>61.1 (38.5 to 79.6)</td>
<td>44.4 (24.6 to 66.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>7 (3 to 15)</td>
<td>61.1 (38.5 to 79.6)</td>
<td>38.9 (20.4 to 61.5)</td>
</tr>
<tr>
<td>25 μg</td>
<td>School children trial A</td>
<td>1</td>
<td>18 (12 to 26)</td>
<td>88.5 (77.4 to 96.8)</td>
<td>72.1 (59.7 to 81.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>3 (2 to 4)</td>
<td>35.5 (24.8 to 48.0)</td>
<td>25.8 (15.6 to 38.0)</td>
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<tr>
<td>25 μg</td>
<td>School children trial B</td>
<td>1</td>
<td>18 (13 to 25)</td>
<td>85.6 (76.6 to 91.4)</td>
<td>74.4 (64.5 to 82.3)</td>
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<td></td>
<td></td>
<td>4</td>
<td>4 (3 to 6)</td>
<td>44.4 (34.6 to 54.7)</td>
<td>26.7 (18.6 to 36.7)</td>
</tr>
<tr>
<td>25 μg</td>
<td>Infants</td>
<td>1</td>
<td>27 (19 to 39)</td>
<td>97.4 (85.4 to 100.0)</td>
<td>92.3 (78.8 to 98.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>2 (2 to 3)</td>
<td>27.5 (16.1 to 43.0)</td>
<td>12.5 (5.1 to 26.7)</td>
</tr>
<tr>
<td>25 μg</td>
<td>Toddler non-responders</td>
<td>1</td>
<td>4 (3 to 5)</td>
<td>63.3 (45.4 to 78.1)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>1 (1 to 1)</td>
<td>3.3 (0.0 to 18.4)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 t</td>
<td>69 (46 to 106)</td>
<td>100.0 (86.2 to 100.0)</td>
<td>100.0 (86.2 to 100.0)</td>
</tr>
<tr>
<td>25 μg</td>
<td>Toddler responders</td>
<td>1</td>
<td>24 (19 to 30)</td>
<td>100.0 (90.4 to 100.0)</td>
<td>100.0 (90.4 to 100.0)</td>
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<td></td>
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<td>11</td>
<td>2 (1 to 2)</td>
<td>20.0 (10.8 to 34.1)</td>
<td>6.7 (1.7 to 18.7)</td>
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<td></td>
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<td>17 t</td>
<td>3 (2 to 4)</td>
<td>34.1 (21.6 to 49.5)</td>
<td>17.1 (8.3 to 31.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 t</td>
<td>259 (184 to 363)</td>
<td>100.0 (89.8 to 100.0)</td>
<td>100.0 (89.8 to 100.0)</td>
</tr>
</tbody>
</table>

Serum bactericidal antibody titres were against the vaccine strain (NZ98/254). Responders were those with a fourfold or greater rise in serum bactericidal antibody titre against the vaccine strain from prevaccination baseline, or for those with baseline <4 to a titre of at least 8.

*Time fourth dose was administered.

†4–6 weeks after dose 4.

GMT, geometric mean titre.

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An increased immunologic response to a serogroup B OMV vaccine booster dose, compared with the response to a primary series, has been demonstrated previously in adults and adolescents in studies using MenBvac or MeNZB.12 14–18 Only one study in Norwegian adults did not show evidence of increased immunogenicity following a booster dose of MeNZB administered 12 months after a three-dose priming series.19 A marked immune response to a fourth dose of MeNZB was observed in our study in toddlers irrespective of previous response status, suggesting immune memory. In addition, significantly higher
 titled were achieved following the booster dose than following the three-dose priming series. This finding supports the use of a booster dose as this and other studies have demonstrated that higher antibody titres persist for longer periods. Evidence of increased antibody avidity following a fourth dose of OMV vaccine in infants further supports the potential benefits of boosting. Booster doses of meningococcal vaccines, for both serogroup B and C, have been used to simulate disease exposure in vaccinated individuals allowing the examination of immune response kinetics. In each study, no substantial increase in bactericidal antibodies was observed until 5 days after booster administration, with the peak occurring 2–4 weeks postbooster. The kinetics of the response to a booster dose, and the persistence of antibody following a fourth dose of MeNZB in infants and young children, remains unknown.

SBA is recognised as the primary assay for assessing serogroup B meningococcal vaccine immunogenicity and inter- and intralaboratory investigations standardised the SBA for use in NZ. Although a variation in absolute bactericidal titres between laboratories was demonstrated, the proportion with a bactericidal antibody titre ≥1.4 remained relatively constant. Bacterial antibody decay in adults and adolescents in this study is similar to that demonstrated following three doses of the NIPH vaccine MenBvac. Following MenBvac, a titre ≥4 was demonstrated in 57% of English adults and 50% of Norwegian adults 12 months after three doses, and in 28% of Norwegian adolescents 10 months after three doses. Other experience using MeNZB demonstrated similar results in Norwegian adults of whom 60% had a titre ≥4 twelve months after three doses. No studies demonstrating persistence of immune response following three doses of an OMV serogroup B meningococcal vaccine in young children were identified.

Several authors have described a relationship between bacte- ricidal antibody titres and OMV vaccine efficacy. Two studies report vaccine efficacy over time following vaccination in populations in which bactericidal antibody titres have been measured postvaccination (table 4). Vaccine efficacy in the first 12 months following vaccination was high in NZ children aged 6 months to 4 years (82–89%) and in Norwegian adolescents (87%). However, efficacy was dramatically reduced in the second 12-month period after vaccination, coinciding with a rapid decay in circulating bactericidal antibody titres. Epidemic strain disease cases in children fully immunised with MeNZB began to be reported within 12 months of the start of the immunisation programme, with the highest rate of vaccine breakthrough reported in infants aged less than 1 year old. Earlier modelling of MeNZB efficacy was unable to demonstrate efficacy in infants aged less than 1 year old, the age group most at risk of disease during the NZ epidemic.

A rapid decline in vaccine efficacy has been demonstrated in infants vaccinated from 2 months of age with meningococcal serogroup C conjugate vaccination in the UK and Spain. In the UK infants, vaccine efficacy in the first 12 months following vaccination was 93%, with no evidence of efficacy demonstrated beyond this time. This decline in efficacy mirrored a rapid decline in circulating bactericidal antibodies. A similar decline in SBA titres was observed in toddlers following a meningococcal serogroup C conjugate booster vaccination given in the second year of life. In contrast, no significant decline in vaccine efficacy was observed over time in older children and adolescents in whom persistence of bactericidal antibodies was much greater (SBA titres ≥8 in 79–88% after 4–5 years). Waning vaccine efficacy paralleling falling antibodies after vaccination in young infants has also been observed following Haemophilus influenzae type b vaccination.

This and other UK studies have given rise to the suggestion that immune memory in the absence of circulating bactericidal antibody is insufficient for protection against meningococcal serogroup C disease. It is postulated that immune memory alone may not provide a sufficiently rapid response to meningococcal infection, because of a delay in antibody rise, and therefore the presence of circulating antibody may provide an important first defence from disease. The extension of these hypotheses to serogroup B disease are supported by this and other MeNZB studies which demonstrate a rapid decline in circulating antibody following OMV vaccination, a concurrent decline in vaccine efficacy, and a delay in immune response following ‘exposure’ to a booster MeNZB dose. That higher antibody titres persist for longer has been demonstrated for both meningococcal serogroup B and C vaccines. In a recent study in infants vaccinated from 2 months old, investigating a recombinant serogroup B vaccine (rMenB) with and without OMV, only the rMenB with OMV induced bactericidal titres against the NZ epidemic strain. In infants receiving rMenB+OMV, bactericidal titres after the fourth dose were almost identical to those observed in the MeNZB young infants study, and were not of the magnitude observed following the fourth MeNZB dose in toddlers. This suggests that this new meningococcal serogroup B vaccine will not be superior to MeNZB for control of disease caused by the NZ epidemic strain.
This study suggests that children vaccinated during the NZ mass vaccination programme during 2004–2006 were unlikely to have persisting antibody protection against the epidemic strain when the programme was reviewed in 2008 given the rapid decay observed. While a four-dose priming series continued to be offered to infants from 6 weeks of age beyond the end of the vaccination programme, coverage was poor (50–60%). Despite low levels of circulating antibody in older children and poor vaccine coverage in infants, epidemic strain disease continued to wane. Routine infant MeNZB vaccination was stopped in June 2008 with ongoing active schedules (altered spacing of vaccinations or additional doses) beyond the end of the vaccination programme, coverage was given the rapid decay observed. While a four-dose priming series continued to be offered to infants from 6 weeks of age beyond the end of the vaccination programme, coverage was poor (50–60%).

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Bactericidal antibody titres are needed to extend the duration of control of endemic disease is still under investigation. Higher bactericidal antibody titres are needed to extend the duration of control of endemic disease is still under investigation. Higher

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