Options for the future of Meningococcal B Vaccine (MeNZB™) in the Childhood Immunisation Schedule

Meningococcal Vaccine Strategy Team

July 2007
Executive Summary

While there is good evidence that MeNZB is effective, the epidemic strain is continuing to circulate. It is important to continue to protect the vulnerable birth cohort until there is another vaccine to take the place of MeNZB or the risk to newborns becomes very low, as evidenced by low rates of disease in vaccinated and unvaccinated.

Careful monitoring of disease rates and vaccine breakthroughs needs to continue to inform the decision of whether a booster dose becomes warranted in the under five year age group.

Given a replacement generic vaccine is unlikely to be available within the next two to five years, a set of targets is proposed that could inform future considerations regarding stopping MeNZB vaccination. Of paramount importance is the need to consider the impact on disease rates in the Pacific and Maori populations who have been most affected by this epidemic.

Attention needs to be given to managing the relationship with Novartis so that the vaccine supply chain is not put at risk. This may require the Ministry committing to binding orders (before vaccine may be needed and taking into account the extended shelf life to minimise wastage) to minimise the risk of an interruption to the supply.
Introduction

The MeNZB vaccine was introduced in mid-2004 with the aim of controlling an epidemic of meningococcal disease that had begun in New Zealand in 1991.

The primary focus of the Meningococcal Vaccine Strategy was to implement a programme that achieved high vaccination coverage as quickly as possible, with its imperative epidemic control. At the time the strategy was designed, and as the mass vaccination programme (“the Programme”) was delivered, only limited consideration was given to the length of time the vaccine would continue to be used once the Programme had been completed. Three key scenarios were anticipated:

- The birth cohort would continue to receive the vaccine until there was good evidence that the epidemic had ended, that children were no longer at increased risk of developing disease, and that disease incidence was unlikely to increase if the vaccine was withdrawn e.g., evidenced by low rates of disease in unvaccinated

- A booster dose may be required for the under five year age group, given the rapid waning of SBAs observed during the clinical trials and their likely correlation with reduced protection.

- The birth cohort (with or without a booster dose) would continue to receive the vaccine until there was a generic meningococcal vaccine available.

In was anticipated that the vaccine would continue to be used for some time after the completion of the Programme, and at least through two complete winters after the Programme had ended i.e. through to the end of 2008. There was a reasonable likelihood that the epidemic strain would continue to circulate, with the youngest age groups remaining at increased risk of disease. A period of intensive monitoring was required to assess the Programme’s longer term impact on epidemic strain disease rates, especially those aged under five years. Therefore, the Ministry of Health’s contract with Chiron Vaccines (now Novartis Vaccines and Diagnostics) specified that Chiron would continue to provide vaccine until the middle of 2011 (subject to a binding order from the Ministry of Health) or until an alternative vaccine was available to take its place. To secure vaccine supplies beyond 2011 the Ministry would be required to extend the contract with Novartis.

It is possible a generic group B meningococcal vaccine, and possibly one that also covers group C disease, may become available within the next few years. Generic vaccines are in the process of undergoing Phase 2 clinical trials and there are some promising candidates that include the New Zealand epidemic strain.

Given the uncertainty around timeframes for such vaccine developments, there needs to be consideration of criteria that would assist in the decision to stop using the vaccine for the birth cohort; or implementing a booster dose in those aged under five years.
In order to formulate the policy for the next phase of the programme it is important to review the progress of the epidemic, safety and effectiveness profile of the vaccine, as well as the coverage achieved.

**Vaccine delivery**

The Programme began in Counties Manukau in July 2004 and was gradually introduced across the country over a two year period. A course of three vaccinations was offered to all aged under 20 years and a four dose schedule to infants who begin the course before 6 months of age. From 30 June 2006 (when the Programme ended) to December 2006, the vaccine remained available to all aged under 20 years. The vaccine is currently available for all children aged under five years.

**Epidemic Progress**

The epidemic appeared to reach a 2\textsuperscript{nd} peak in 2001, with some reduction in disease numbers occurring in the two year period prior to the start of the Programme (Appendix Figure 1). As a result, there had been some suggestions that the epidemic was declining and that the decrease in cases following the start of the Programme, was due to natural waning rather than the vaccine. However, over the course of the epidemic fluctuations in disease numbers had been seen previously, with peaks and troughs occurring naturally. Further, a waning in group B meningococcal epidemics usually occurs slowly over a number of years, whereas we have seen a sharp decline in cases since vaccination started, particularly in the Northern region (Figures 2a, 2b). Further evidence that the epidemic was not waning is that while rates of epidemic strain in under fives had decreased between the years 2002 and 2003, they increased again in 2004, the year the Programme started (Figure 3). They then declined rapidly and dramatically in 2005 after the introduction of the vaccine.

We are now in the 17\textsuperscript{th} year of an epidemic that may have continued for up to thirty years without a vaccine intervention. Cuba introduced a combined group B and C vaccine to combat a group B epidemic and they have continued to vaccinate the birth cohort despite the reduction to pre-epidemic levels (0.2/100 000).

**Vaccine safety**

With over 3.1 million doses of MeNZB administered during the Programme the combined safety monitoring activities provided consistent evidence supporting the safety of MeNZB. An emergent issue in late 2006 was a postulated link between the Norwegian parent vaccine, MenBvac, and chronic fatigue syndrome cases in Norway. Investigations are ongoing regarding this issue in Norway, however to date there has been no evidence supporting a causal association.
Vaccine effectiveness

Prior to the epidemic around 50 meningococcal cases occurred each year. The highest annual rate occurred in 2001 with 650 total cases (confirmed and probable) notified (rate of 17/100 000). On average, during the course of the epidemic, 75% of cases were the epidemic strain. The highest rates occurred in Maori and Pacific and those under 18 months.

In the five years prior to the Programme, for those aged under 20 years, there were 215 laboratory confirmed epidemic strain cases and seven deaths per year on average. In 2006 there were 47 cases (a 78% decrease) and two deaths. There has been a significant decrease in rates in Maori and Pacific aged under 20 years since the Programme began (Figure 4).

As at 30 June 2007 there were a total of 40 cases of epidemic strain cases that had occurred in children at least 28 days after receipt of three doses of vaccine (a vaccine breakthrough) (Figure 5).

A Poisson regression model has been developed that considers disease rates in the population of interest using time at risk (person-time data). The rates model facilitates the incorporation of the rollout schedule. It estimates the effects of vaccination, while accounting for potential covariates of region-specific disease rates, deprivation, time, and seasonality. Cases are defined as individuals with the epidemic strain of meningococcal disease. The effect of the vaccine from this model was calculated at 73% (95% CI: 52%-85%) using data to 30 June 2006.

While there can be no doubt that the vaccine is effective, as more time elapses since the Programme ended it is expected that the overall vaccine effectiveness measure will decrease, due to anticipated waning immunity. This may mean that we will see an increasing number of cases in children who have been vaccinated early in the Programme. Therefore it is even more important to continue to offer protection to vulnerable infants, who are at most risk of disease. Consideration should be given to introducing an additional booster for all aged under five years if breakthrough cases increase in this age group.

Vaccine coverage

At the end of the Programme in June 2006, 80% of all those aged under 20 years had completed the three dose MeNZB course. High coverage was achieved in the Pacific population. While Maori coverage was similar to the rest of the population for dose one, compared with other ethnic groups Maori were less likely to complete the course.

From 2007, the vaccine has essentially been offered only to the birth cohort. While the coverage for the first three doses is in line with the routine schedule vaccines, there is some evidence that the coverage for the fourth dose is lower than for other doses. The extent and reasons for this decrease (e.g.
failure to recall children for the 10 month fourth dose) warrant urgent investigation. It should be noted that four vaccine breakthroughs have occurred in young children overdue for their fourth dose.

It is important to note that the poor uptake for any scheduled MeNZB vaccine dose, including the fourth dose, is not a reason to stop vaccinating. Instead the reasons for a drop in coverage should be identified and actively rectified, as for all childhood vaccinations.

Cost Benefit

A cost utility analysis undertaken before the commitment of funding showed the strategy to vaccinate all under 20s to be moderately cost effective. The cost of the Programme was $220 million. Given these significant sunked costs in developing the vaccine and the competitive per dose cost of the available product, the ongoing use of the vaccine in the years subsequent to the end of the Programme (i.e. post 30 June 2006) can only result in a positive cost benefit analysis while there is evidence that epidemic strain disease is still occurring. Purchasing this vaccine now costs no more than IPV which continues to be used even though there is no polio in NZ.

Stopping Criteria

Consideration of stopping MeNZB vaccination before an alternative vaccine becomes available requires that a range of issues be addressed. These would include:

- Establishing acceptable targets for age and ethnic specific rates of disease and consideration of rates of disease in unvaccinated age groups as a indication of disease risk in the absence of vaccine
- Consideration of the length of time required to establish whether lower disease rates have stabilised and are sustainable without vaccination
- Consideration of the ability to re-start MeNZB vaccination if there was resurgence in case numbers following withdrawal of the vaccine, including the ability of Novartis to supply vaccine

Disease rate thresholds

Pre-set disease rate thresholds can act as indicators to support considerations regarding cessation of MeNZB vaccination. Criteria need to consider a range of disease rates in different ages and ethnicities as well as in vaccine and non-vaccine recipients. It is vital that disparities are not increased by withdrawing the vaccine when rates are still disproportionately high in one ethnicity even though rates are much lower overall. A suggested range of indicators is detailed below.

Prior to the epidemic there were 50 cases of meningococcal disease per year of which 60% or 30 cases were B strains, not all of which were the epidemic strain. A target has been set at 20 cases of epidemic strain per year. The
distribution of cases from 1997 to 2003 has been applied to represent the natural age distribution of cases prior to the vaccination intervention. Because this approach means the target for Pacific and Maori will still be higher than for other ethnic groups; the target has been adjusted so that the target rate in Pacific and Maori is the same as for non-Maori, non-Pacific. Note: It is not possible to simply take the pre-epidemic period rates of disease and use these to calculate epidemic strain age and ethnic rates as targets as these data were not available for the pre-1991 periods.

Table 1. Indicators of disease rates before vaccine withdrawal

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Number of cases per year</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of epidemic strain cases in all age groups:</td>
<td>20.</td>
<td>0.49</td>
</tr>
<tr>
<td>Rates of epidemic strain cases in the under 20 year age group:</td>
<td>16</td>
<td>1.35</td>
</tr>
<tr>
<td>Rates of epidemic strain cases in the 15-19 year age group:</td>
<td>3</td>
<td>1.00</td>
</tr>
<tr>
<td>Rates of epidemic strain cases in the 5-14 year age group:</td>
<td>4</td>
<td>0.66</td>
</tr>
<tr>
<td>Rates of epidemic strain cases in the under five year age group:</td>
<td>9</td>
<td>3.21</td>
</tr>
<tr>
<td>Rates of epidemic strain cases in the under one year age group:</td>
<td>3</td>
<td>5.14</td>
</tr>
<tr>
<td>Rate of Pacific epidemic strain cases in the under one year age group:</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Rate of Pacific epidemic strain cases in the under five year age group:</td>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>Rate of Maori epidemic strain cases in the under five year age group:</td>
<td>2</td>
<td>2.99</td>
</tr>
<tr>
<td>Rate of Maori epidemic strain cases in the under one year age group:</td>
<td>1</td>
<td>7.12</td>
</tr>
<tr>
<td>Rate of Maori epidemic strain cases in the under 20 year age group:</td>
<td>3</td>
<td>1.15</td>
</tr>
<tr>
<td>Rate in non vaccinated and partially vaccinated under 20s</td>
<td>8</td>
<td>3.85 (assuming 50% of cases are vaccine breakthroughs)</td>
</tr>
<tr>
<td>Rate in non vaccinated over 20s</td>
<td>4</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Length of time disease rates targets are maintained

The length of time that the pre-determined disease rates are maintained, prior to any vaccine withdrawal, must also be considered, especially given the extended natural length of group B meningococcal epidemics. From the limited experience of meningococcal B epidemics in other countries (particularly Norway) they are characterised as lingering for up to 30 years (or longer) with a number of peaks and troughs occurring throughout their course (Figure 6). The Norwegians experienced a long tail to their epidemic despite
having undertaken an extensive Phase 3 trial in the late 1980s that saw 85% of 13 and 14 year olds vaccinated. It is important to note that Norway re-considered introducing MenBvac in 1999 (in year 27 of their epidemic) as the rates were waning very slowly. Cuba is the country most experienced at delivering group B vaccines in response to an epidemic. They achieved low disease rates following introduction of a combined group B and C vaccine to combat their strain specific group B epidemic and continue to include the vaccine in their infant schedule today.

Given the protracted nature of group B epidemics, it would be prudent once acceptable rates of epidemic strain are reached in New Zealand to allow a further period of time to elapse to ensure that there is no resurgence in disease. We would estimate a minimum period of 24 months should elapse from the end of the 12 month period that all the pre-determined thresholds are first met.

**Ability to restart MeNZB vaccination**

One approach suggested has been to discontinue MeNZB vaccination as soon as pre-determined disease rates that indicate the epidemic has ended are met, and to stockpile sufficient vaccine (and/or Novartis re-establish vaccine manufacturing) so that vaccination can be re-started if disease rates increase. However this option requires consideration of number of issues and risks including:

- Guarantee of vaccine supply (see below)
  - Shelf life of the vaccine
  - Ability and willingness of Novartis to re-start manufacturing of vaccine and the lead time required to contract Novartis to supply vaccine
- Political risk of withdrawing a safe and effective vaccine resulting in an increase in disease rates (see below)
  - Acceptability to the public and health providers to stopping then re-starting the programme
  - A starting threshold would have to be agreed
  - Delay in protection being afforded by the vaccine because of the logistics of restarting MeNZB vaccination e.g. the time required to prepare advice to vaccinators; and the time taken for those vaccinated to become protected with a three dose vaccination series six weeks apart, plus 28 days ie 16 weeks.

**Vaccine supply**

Vaccine supplies are required for the birth cohort for at least two complete winters after the Programme had ended i.e. through to the end of 2008. Such supplies (to the end of 2008) are guaranteed under the existing contract with Novartis (subject to the Ministry placing vaccines orders within the required timeframe). Vaccine supplies beyond June 2011 require that the current contract be extended.
So far the Ministry has only secured vaccine supply till the end of 2008. It is very likely MeNZB vaccination will need to be extended post 2008. Novartis is changing manufacturing site and therefore there is considerable risk that there will be a delay in production and delivery or no vaccine at all post 2008. The Programme managed vaccine supply issues very carefully and proactively to ensure that the risks around production and company commitment falling off were minimised. Consideration must be given to placing orders now for 2009 so that the company know that they are required to continue to supply NZ. The change of site adds complications, such as making sure the vaccine at the new site meets specifications, therefore, continuing liaison with Medsafe is also necessary.

Given the likely continued use of MeNZB and the need to ensure the continued commitment of Novartis it is important to prioritise efforts to complete the assessment of a full consent for MeNZB. Novartis submitted a dossier supporting a full license in the first half of 2006.

Political risk
Consideration needs to be given to the political risks of prematurely halting a successful immunisation programme. Such a step could create a backlash from those in the sector who have been very supportive of The Programme and give additional fodder to the anti-immunisation lobby. The Ministry has enjoyed a positive relationship with Novartis which has led to a spirit of cooperation. Care needs to be taken to ensure this relationship is managed. Variations to the contract and our expectations of vaccine supply must be signalled with Novartis well ahead of production time, taking into account vaccine manufacturers book their manufacturing and bottling plants up two years ahead.

Conclusion
At this point in time there is good evidence that the MeNZB vaccine has met expectations to control the meningococcal disease epidemic. Given the estimated vaccine effectiveness of 73% in the two year period following The Programme’s start, sustaining reduced disease rates in those aged under five years will require that high coverage levels are achieved for the birth cohort.

Given MeNZB is a safe and effective vaccine it is important to take a conservative approach to the withdrawal of the vaccine from the childhood immunisation schedule. The preferred approach would be to wait until a generic vaccine is available. Given such a vaccine is unlikely to be available within the next two to five year period, it is important in the first instance to continue to use MeNZB through to the end of 2008, i.e., through two complete winter periods following the end of the Programme.

The Ministry must intensively monitor disease trends to establish if agreed pre-set thresholds are met that would justify consideration of withdrawal of the
vaccine after the end of 2008. Active monitoring of vaccine breakthroughs needs to continue in order to identify any age groups that would benefit from a booster. Likewise, vaccine coverage must be monitored so that appropriate interventions are put in place to maintain high uptake, particularly in Pacific and Maori, traditionally at most risk of disease.

Vaccine supplies must be guaranteed by providing vaccine forecasts over a period of years and commitments made, in the form of binding orders to guarantee supply. Consideration of the full consent for MeNZB must be given a high priority to ensure the programme can run into the future.

This Programme has achieved outstanding success in delivering an effective vaccine to high-risk groups. The careful management of the final phase of the programme is required so that government priorities regarding disease control and reduction in disparities, as evidenced by their $220 million dollar commitment to the Programme, continue to be met.

**Recommendations**

- The Ministry of Health must proactively monitor for developments of generic Group B meningococcal vaccines.

- The National Immunisation Programme must continue to monitor for vaccine breakthroughs and actively consider the need for a booster in the under five year age group.

- The National Immunisation Programme must continue to monitor coverage and develop and implement strategies e.g. communication strategies to improve the fourth dose uptake.

- The National Immunisation Programme must develop a vaccine forecast for the out years that minimises risks of an interruption to vaccine supply.

- The National Immunisation Programme should begin the process of identifying funding for out years.

- The National Immunisation Programme needs to monitor the age- and ethnic-specific disease rates as specified in this paper

**Prepared by**
Dr Jane O’Hallahan  
Director Meningococcal Vaccine Programme

Yvonne Galloway  
Senior Advisor Effectiveness

Anne McNicholas
Appendix 1

Figure 1. Confirmed and probable notified meningococcal disease cases by year 1990-2006

Figure 2a. Cumulative epidemic strain cases of meningococcal disease, northern region, aged less than 20 years, January 2002 - June 2007
Figure 2b. Cumulative epidemic strain cases of meningococcal disease, New Zealand excluding northern region, aged less than 20 years, January 2002 - June 2007

Figure 3. Epidemic strain rates of meningococcal disease by age group, aged less than 20 years, 2002-2006
Figure 4. Rates of epidemic strain meningococcal disease by year and ethnicity among individuals aged less than 20 years, 2002-2006

Figure 5. Number of cases of epidemic strain meningococcal disease compared with dose three coverage, aged less than 20 years, New Zealand

MeNZB™ vaccine discontinuation options, Ministry of Health
July 2007
Figure 6. Meningococcal disease cases by equivalent year for Norway and New Zealand

MeNZB™ vaccine discontinuation options, Ministry of Health
July 2007