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The New Zealand Meningococcal Vaccine Strategy: A tailor-made vaccine to combat a devastating epidemic

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Abstract

The New Zealand Meningococcal Vaccine Strategy aims to end the devastating 14-year epidemic of B:4:P1.7b,4 group B meningococcal disease in New Zealand through a mass immunisation programme to all under 20 year olds using a tailor-made vaccine (MeNZB™). This paper describes the scientific rationale, development, and key components of the New Zealand Meningococcal Vaccine Strategy. A summary of the efficacy and safety data of existing outer membrane vesicle group B meningococcal vaccines is included as these data critically support the Strategy.

Immunogenicity and reactogenicity data from clinical trials of MeNZB™, the tailor-made vaccine against the New Zealand epidemic strain (B:4:P1.7b,4) of group B meningococcal disease, have recently been reviewed by Medsafe as part of a licensure application under Section 23 of the Medicines Act 1981. Provisional licensure was granted on 8 July 2004, and the epidemic control phase of the Meningococcal Vaccine Strategy commenced on 19 July 2004. This is in the form of a nationwide mass immunisation programme for all aged less than 20 years delivered through public health nursing services and primary care.

The initial lower age limit for immunisation is 6 months of age but this may be lowered in the future when a further trial is completed and immunogenicity and safety data have been assessed by Medsafe. In addition, the vaccine may be introduced into the routine childhood immunisation schedule after the mass immunisation programme has been completed.

The Meningococcal B Immunisation Programme (the Programme) commenced in Counties Manukau District Health Board (DHB) and a geographically defined 'eastern corridor' of Auckland DHB (Glen Innes to Otahuhu), where the disease burden has been greatest, and will be progressively rolled out throughout the country. Extensive vaccine safety monitoring has been in place from the start of the Programme. This depends upon being able to track immunisations through the new National Immunisation Register, which commenced operating on 19 July 2004.

The start of the Programme is the culmination of a search that first began in 1995 to find a way to halt the epidemic of group B meningococcal disease in New Zealand. Assuming vaccine efficacy of 80% and coverage of 90% of the eligible population with three doses of MeNZB™, the Programme aims to reduce cases of B:4:P1.7b,4 meningococcal disease in those aged less than 20 years by over 70%. This strain accounted for an estimated 72% of all meningococcal disease cases in 2003.[1]

Development of the New Zealand Meningococcal Vaccine Strategy

In 1995, a workshop (led by former Public Health Commission staff involving national and international experts) reviewed the epidemiology of and disease control protocols for meningococcal disease, and developed the National Prevention and Control Plan for Meningococcal Disease, as follows:

- Intensified epidemiological surveillance.
- Promoting public awareness to facilitate early medical intervention.
- Promoting professional awareness to encourage early diagnosis and treatment.
- Prevention of secondary cases by notification, contact tracing, and offering prophylactic antibiotics.
- A 3-year case-control study to identify modifiable risk factors.
- A meningococcal vaccine strategy should a vaccine become available.[2]

In 1998, the World Health Organization assisted New Zealand by holding a meeting of national and international advisors and manufacturers that were able and interested in assisting New Zealand to obtain a tailor-made group B meningococcal vaccine. Expressions of interest were then sought from the manufacturers, and after evaluation of the dossiers that were subsequently submitted by interested manufacturers, Chiron Vaccines, working in collaboration with the Norwegian Institute of Public Health (NIPH), was selected to develop and manufacture the vaccine. Following this, the Meningococcal Vaccine Strategy was devised by the Meningococcal Management Team and its advisors, with input from two rounds of international peer review and consultation with key stakeholders and community leaders.

The Strategy is driven by the need to intervene rapidly in this public health emergency. Following the development of a tailor-made vaccine, the key components of the Strategy are:

- Clinical trials to demonstrate immune response to, and initial safety of the new vaccine in several age groups, leading to;
- Provisional consent, under section 23 of the Medicines Act 1981, to immunise children and young people aged less than 20 years in a staged roll out prioritised by disease risk;
- Intensive ‘real-time’ safety monitoring and independent data assessment;
- Careful disease surveillance and appropriate evaluation to enable the post-licensure assessment of vaccine effectiveness.

The application for licensure has been supported by physicochemical evaluation of the parent and candidate vaccines undertaken by the National Institute of Biological Standards and Control in the UK, and bridging of safety data from the large-scale use of the Norwegian parent group B vaccine, MenBvac™ (see below).

Group B meningococcal vaccines

Any vaccine introduced into New Zealand to control the epidemic must have demonstrated the ability to stimulate an adequate immune response against the epidemic strain in the age groups to be vaccinated.

There is currently no commercially available group B meningococcal vaccine against the New Zealand epidemic strain. The polysaccharide capsule of the group B meningococcus is poorly immunogenic and due to antigenic similarities with human tissue glycoproteins, concerns have been raised regarding possible auto-immune reactions following vaccination.[3] Consequently, there has been considerable research into alternative vaccines to prevent group B meningococcal disease. Antibodies to outer membrane proteins (OMPs), that have bactericidal activity, are present in convalescent sera,[4] supporting the logic of vaccine development utilising OMPs.

The serum bactericidal assay (SBA) has been shown to be the most reliable test for the measurement of functional (protective) antibodies following vaccination. This was initially shown for group C meningococcal vaccines where the serum bactericidal activity was directed against the polysaccharide capsule.[5-7] Use of the SBA has been extended to group B meningococcal vaccines which stimulate serum bactericidal antibodies directed against the non-capsular protein surface antigens, particularly class 1 OMP (PorA).[8-12] Recent evidence suggests that class 1 OMPs play a major role in the immune response following meningococcal carriage,[13] invasive disease[4] and immunisation by group B outer membrane vesicle (OMV) meningococcal vaccines.[8-12]

Evaluation of bactericidal antibodies and field efficacy estimates in Brazil and Chile found age groups with high levels of bactericidal antibodies after immunisation had higher efficacy than those with lower, or absent antibody levels,[14,15] although these studies did not define a ‘protective level’. Data from studies using the Norwegian vaccine support the concept that development of serum bactericidal antibodies following immunisation appears to indicate clinical protection.[16]

Efficacy and safety of group B meningococcal vaccines

Literature on the efficacy of group B OMV vaccines is dominated by studies of three vaccines, produced by the Norwegian Institute of Public Health (NIPH) against the Norwegian epidemic strain (B:15:P1.7,16), by the Finlay Institute (FI) against the Cuban epidemic strain (B:4:P1.19,15), and by the Walter Reed Army Institute of Research (WRAIR) against the Chilean epidemic strain (B:15:P1.3). The tailor-made New Zealand vaccine (MeNZB™) is produced using similar technology to that used for the NIPH vaccine (MenBvac™). The results of efficacy studies of the NIPH,[11,16,17] FI,[18,19] and WRAIR[14] vaccines are summarised in Table 1.

In general, the efficacy in population-based studies of these group B OMV vaccines in children, has paralleled immunogenicity, and has been found to be highest in older children and, where studied, poor or absent in the youngest age groups. A randomised controlled trial of the NIPH vaccine in teenagers showed 87% efficacy against group B disease 10 months after a second dose.[11,16] The efficacy dropped to 57% after 29 months, suggesting a further dose and/or booster would confer additional benefit.[16,17]

Table 1. Summary of Efficacy Studies of group B OMV vaccines

Country or region	Vaccine	% of cases in country or region of vaccine strain*	Study type	Sample size (n)	Number of doses given	Time interval under observation	Age group	Efficacy** (%)	95% Confidence Interval (CI)
Norway[11,16,17]	Norwegian (NIPH)		Randomised, double-blind placebo-controlled trial	171,800	2	10 months	Secondary school students	87	62-100%
						29 months		57	21-87%
Cuba[18]	Cuban (FI)	95%[18]	Randomised, double-blind, placebo controlled trial	106,251	2	16 months	10–14 yrs	83	42-95%
Sao Paulo, Brazil[19]	Cuban (FI)	44%[19]	Case-control study	112 cases; 409 controls	2	1989–1991	4–6 yrs	74	16-92%
							2–3 yrs	47	-72-84%
							3 months < 2 yrs	-37	<-100-73%
Iquique, Chile[14]	Chilean (WRAIR)		Randomised, double-blind controlled trial	40,811	2	20 months	5–21 yrs	70	14-91%
							1–4 yrs	-23	<-100-73%

* Where available

** Norway, Cuba, and Sao Paulo – Efficacy against group B disease; Chile – Efficacy against group B disease with serotype15 and/or subtype P1.3 only

A randomised controlled trial in Cuba of their OMV vaccine showed 83% efficacy against group B disease 16 months after the second dose in 10–14 year olds.[18] In a Chilean study, efficacy against group B disease with serotype 15 and/or subtype P1.3 was 70% at 20 months for those aged 5 to 21 years following two doses of the WRAIR vaccine.[14]

As shown in Table 1, the efficacy of OMV vaccines in the youngest and most at-risk age group is as yet unproven—although with continuing routine infant meningococcal vaccination, a low incidence of disease has been maintained for more than 15 years in Cuba.[20] Therefore, an immunogenicity study performed by Tappero et al. in Chile[12] was a landmark because it demonstrated that a high percentage of infants are capable of mounting a strain-specific immune response, as measured by SBA, to a group B OMV vaccine.

In all of the studies presented in Table 1, only two doses of vaccine were given. Infant participants in the Tappero et al. study were given three doses of either the NIPH, or the FI, or a control vaccine.[12] After three doses, 98% and 90% of infants who received the NIPH or FI vaccine, respectively, were seroresponders against their vaccine strain (homologous strain); that is, they demonstrated a fourfold or greater rise in serum bactericidal antibody levels. Seroresponse in infants to strains other than the vaccine (heterologous strain) was poor. Tappero et al. noted that for the FI vaccine recipients, the percentage of seroresponders almost doubled from dose two to dose three, and that had the participants in the Sao Paulo study[19] been given three doses, the efficacy of the vaccine may well have been found to be much higher. The New Zealand clinical trials are being conducted using three doses of vaccine, and the use in younger age groups of a fourth dose (if needed) has not been ruled out.

There is a very large body of applicable safety data on group B OMV vaccines that provides considerable reassurance that an OMV vaccine against the New Zealand strain, although reactogenic, will be safe in all age groups. Approximately 360,000 doses of the NIPH parent vaccine have been administered, to about 180,000 subjects with no serious adverse events attributable to the vaccine occurring.[21,22] Similarly, the FI vaccine has an excellent safety profile, with 60 million doses so far administered in Latin America.[23] Apart from one participant in the WRAIR Chilean randomised controlled trial who developed angioneurotic oedema, no serious adverse events were attributed to the vaccine.[14]

A tailor-made New Zealand vaccine

The continuing high incidence of meningococcal disease, the continuing dominance of the epidemic strain in cases of disease, and the genetic stability of the epidemic strain throughout,[24] supported the logic of developing a tailor-made vaccine. On the basis of the above cited evidence, an OMV-type vaccine was considered a viable option for New Zealand and likely to be safe. However, to elicit protection, a specific vaccine developed from the New Zealand epidemic strain was needed.

In the absence of a commercially available vaccine against the New Zealand epidemic strain, a tailor-made vaccine had to be developed. It was also considered likely that at least three doses would be required to confer protection, possibly four for younger children. The development and manufacture of a New Zealand epidemic strain-specific vaccine (MeNZB™), in sufficient quantities for a nationwide meningococcal B immunisation programme to all aged less than 20 years, has been made possible

through a partnership between the New Zealand Ministry of Health, and Chiron Vaccines working in collaboration with the Norwegian Institute of Public Health (NIPH).

The MeNZB™ clinical trials, sponsored by the Ministry of Health and Chiron Vaccines and undertaken by a University of Auckland research team, are nearing completion. Three doses of MeNZB™ have been administered 6 weeks apart to participants in an adult study, and in studies of children aged 8 to 12 years, 16 to 24 months, and 6 to 8 months. In these studies, seroresponse against the New Zealand epidemic strain has been promising in all age groups and no serious adverse events have been attributed to the vaccine.[22] One further study is underway in children aged 6 to 10 weeks. Alongside assessing immunogenicity and reactogenicity, this study will look for interference with immune responses to routine childhood immunisations. In addition, some participants from the clinical trials are being followed up to monitor the persistence of serum bactericidal antibodies over time and the anamnestic immune response after a fourth dose.

A large randomised controlled trial (to determine the efficacy of MeNZB™ and to further assess the safety of the vaccine) was deemed to be unnecessary for the following reasons:

- There is good evidence that the presence of measurable serum bactericidal antibodies following immunisation with group B OMV vaccines is indicative of vaccine effectiveness;[14,15]
- MeNZB™ will not be used in an age group unless there is satisfactory age-specific immunogenicity data;
- There is a large body of applicable safety data from the use of the NIPH and FI vaccines (described above);
- Blinded safety data has been collected in several clinical trials using OMV vaccines;
- Reactogenicity data will be available from the MeNZB™ clinical trials.

Post-marketing surveillance and evaluation

Vaccines are generally given to a large number of healthy people to prevent disease. Therefore, a very high standard of safety is expected of vaccines. The Meningococcal Vaccine Strategy has been designed to ensure extensive safety monitoring post-licensure of the vaccine. The safety monitoring system has several arms, including real-time hospital monitoring and monitoring of sentinel general practices (see companion article: *Proceedings of the Meningococcal Vaccine Strategy World Health Organization Satellite Meeting, 10 March 2004, Auckland, New Zealand.* URL: http://www.nzma.org.nz/journal/117-1200/1026).[22]

Data from all arms will be presented to an Independent Safety Monitoring Board, set up and managed by the New Zealand Health Research Council. The role of the Board, which has international and national expert members, is to provide advice on whether to cease vaccination because of safety risk, or on the need for further investigation because of a possible safety risk.

The mass immunisation programme will be delivered to those age groups in which MeNZB™ has been shown to be immunogenic. Several observational studies are planned post-licensure to assess the effectiveness of the vaccine. A Poisson regression model will estimate the effect of vaccination by modelling disease rates over time, using data stratified by age, region and time. As vaccination of different regions and ages will occur at different times, the effect of vaccination can be estimated without being confounded by the natural progression of the epidemic.

The analyses will also examine whether the programme has been equally successful in reducing disease rates in high-risk groups, including Maori, Pacific peoples, and those living in more deprived areas. In addition, a population-based case control study may be undertaken which will estimate the 'efficacy' of the vaccine in children aged less than 5 years by determining the odds of exposure to MeNZB™ vaccine in disease cases relative to that in a random sample of similar children in Auckland.

Evaluation of the programme will occur throughout the roll out. Vaccine coverage assessment, along with qualitative evaluation methodologies, will be a key element of this evaluation, focusing on delivery of vaccine to those at highest risk—Maori and Pacific children aged less than 5 years. It is anticipated that the evaluation will allow continual quality improvement in the delivery of vaccine, especially to the highest risk groups.

Conclusion

During 2004, New Zealand entered its 14th year of a widespread epidemic of group B meningococcal disease dominated by a single PorA subtype (P1.7b,4). The extent of the New Zealand epidemic merits a response aimed at producing rapid epidemic control. The Meningococcal Vaccine Strategy aims to achieve this by implementing a nationwide mass immunisation programme to those aged less than 20 years, utilising a tailor-made vaccine.

Rapid epidemic control depends on the development of a vaccine that is efficacious in the most at-risk age groups, on condensing the vaccine licensure timeframe (as permitted by Section 23 of the Medicines Act 1981 in order to address a serious health issue), on effective distribution of the vaccine, and on achieving high coverage in those children in our population who historically have been least likely to be reached by immunisation programmes.

Evidence from international studies of group B OMV vaccines, and the New Zealand-based clinical trials, suggests that MeNZB™ is likely to be efficacious and safe in the population to be immunised. Extensive consultation with, and input from, the health sector, community leaders, and other key stakeholders; new tools such as the National Immunisation Register; and a focus on formative evaluation leading to continual programme improvement provide a sound foundation for the implementation of an equitable and effective immunisation programme.

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