Prevention of group B meningococcal disease by vaccination: a difficult task

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Abstract

New Zealand has embarked on an immunisation program to reduce the incidence of disease caused by serogroup B Neisseria meningitidis. Similar immunisation programs in Norway and South America have shown good efficacy in older vaccinees (ie, persons receiving vaccinations), but variable efficacy in younger vaccinees. Protective efficacy correlates well with the ability of the vaccine to stimulate a fourfold rise in serum bactericidal antibodies. Unfortunately, second and third doses of serogroup B N. meningitidis vaccines do not boost serum bactericidal antibody titres to very high levels; consequently protective efficacy wanes within a few years of immunisation. The overall outcome of the immunisation program will reflect both the immunogenicity of the vaccine and the uptake of the vaccine by the target population. The especially high incidence of meningococcal disease in Pacific and Maori children means that particular efforts will need to be made to reach these groups.

An epidemic of disease due to one strain of serogroup B Neisseria meningitidis began in New Zealand in 1991 and since then has caused almost 5,000 hospitalisations and over 200 deaths.1 A vaccine, based on a similar vaccine developed in response to an epidemic in Norway, has been designed specifically to control this New Zealand epidemic. To achieve this goal, the vaccine will need to prevent disease, and perhaps also carriage—and will need to be delivered to a large majority of the target population. Low vaccine efficacy and or inadequate vaccine delivery will result in a disappointing failure to prevent disease. A wider understanding of the difficulties associated with the development of this vaccine and its delivery may improve the chances of ultimate success in disease prevention.

N. meningitidis is spread in secretions coughed or sneezed by an infected person. After acquisition, by inhalation or by direct contact with infected secretions, the organisms adhere firmly to the epithelial surface of nasopharyngeal cells. Within a few days, the adherent bacteria may manipulate the epithelial cells to transport the bacteria through the cell cytoplasm to then be released into the sub-cellular space2 (Figure 1). From there, the bacteria invade blood vessels and are disseminated in the bloodstream.

In most people, serum antibodies attach to the surface of the bacteria and initiate immune responses, which ensure that the bacteria are killed before they can cause disease. However in people who lack protective antibodies to the invading strain of meningococcus, the organism may survive and proliferate in the blood and from there may invade and multiply in the cerebrospinal fluid. Furthermore, colonisation of the nasopharynx persists for weeks to months providing an ongoing source of infection for others.
Figure 1. After *Neisseria meningitidis* attaches to the surface of nasopharyngeal epithelial cells (A), it is transported through the cytoplasm of these cells to reach the sub-cellular space, from where it invades the bloodstream (B). Persistent colonisation of the epithelial surface of nasopharyngeal cells provides a source of infection for others (C). Eventually the infection of the epithelial surface of the nasopharyngeal cells is eradicated (D) and the person is no longer a source of infection for others.

Most people with *N. meningitidis* colonisation of the nasopharynx do not develop disease—because serum antibodies initiate the immune responses, which rapidly clear the organism from the blood. Antibody bound to the surface of *N. meningitidis* activates serum complement proteins to create channels which disrupt the cytoplasmic membrane of the bacteria and thus kill it. Antibody bound to the surface of the bacteria also enhances phagocytosis by neutrophils and macrophages.

The epidemiology of disease due to *N. meningitidis* is largely a reflection of these central roles of antibody in protection against disease. Newborn infants have high levels of antibody, which has been transported across the placenta from their mother’s blood during the last 6 weeks of pregnancy. This antibody is broken down during the first year of life and is slowly replaced by antibody synthesised by the child’s lymphocytes stimulated by mucosal infection with closely related non-pathogenic organisms. The lowest levels of serum antibody are found in children aged 9 months to 5 years, and it is children in this age group who are at highest risk of meningococcal disease (Figure 2).
Figure 2. The incidence of disease due to *Neisseria meningitidis* (solid line) is greatest between the ages of about 6 months and 5 years when the titre of serum bactericidal antibody (broken line) is lowest.

![Graph showing incidence of disease and titre of serum bactericidal antibody over age](image)

The meningococcus has evolved to evade immune responses.\textsuperscript{4,5} It ‘hides’ within a polysaccharide capsule, which is poorly immunogenic compared with the proteins of the bacterial cell wall and outer membrane (Figure 3).

Figure 3. *Neisseria meningitidis* is surrounded by a polysaccharide capsule, an outer membrane which has a variety of proteins including Por A and Por B inserted into it, a peptidoglycan cell wall, and a cytoplasmic membrane.

![Diagram showing meningococcal structure](image)
Infants produce very weak antibody responses to polysaccharide antigens, and neither infants nor adults generate either immunological memory, or enhanced antibody responses following re-exposure to polysaccharide antigens. The serogroup B meningococcus has further refined this evasion of immune responses by synthesising a polysaccharide capsule, which is composed of the same sugars as those found on the surface of immature neural cells. Lymphocytes with the capacity to produce antibody to these sugars have been deleted in foetal life to avoid the production of harmful auto-antibodies. While infection with other serogroups of *N. meningitidis* (eg, A,C,Y,W135) stimulates antibody responses (albeit weak) against their polysaccharide capsules, infection with serogroup B *N. meningitidis* fails to stimulate an anti-capsular antibody response.

Antibodies to the proteins of the outer membrane, which lies within the polysaccharide capsule, can facilitate complement activation and phagocytosis. Two of these outer membrane proteins (OMPs) are the main components of the serogroup B meningococcal vaccine which will be used in New Zealand. Por A and Por B form clusters that span the outer membrane and provide channels for molecules to gain access to and from the bacterium\(^6\) (Figure 3). The structure of these porin molecules can vary widely between different meningococcal strains. The current New Zealand epidemic has been caused almost exclusively by a strain with porin molecules classified as serotype 4 (based on the predominant Por B molecule) and serosubtype P1.4 (based on the predominant Por A molecule).\(^7\)

The variation in the Por A and Por B molecules produced by different strains of meningococci has the effect that antibodies which bind to the Por A or Por B molecules of one strain may fail to bind to the Por A and Por B molecules of an otherwise similar strain.\(^4,5\) Furthermore, the capsule surrounding the bacteria, and other molecules present in the outer membrane, may mask the Por A and Por B molecules and reduce their accessibility to serum antibodies.\(^8\)

Despite these disadvantages, the OMPs have been the principal antigens in vaccines created to control epidemics of serogroup B meningococcal disease in Cuba, Norway, Brazil, and Chile.\(^9\)\(^–\)\(^13\) While extensive use of a locally produced vaccine appears to have contributed to the disappearance of serogroup B meningococcal disease in Cuba,\(^9\) the experience with similar vaccines in Norway, Brazil, and Chile has been less dramatic, and in none of these latter countries has the vaccine progressed from clinical trials to routine use.\(^10\)\(^–\)\(^13\) Results from clinical trials of these vaccines may help to predict the efficacy of the New Zealand vaccine.

It is probable that the antibody responses to a vaccine derived from the New Zealand epidemic strain will be broadly similar to those found in people immunised with other serogroup B meningococcal vaccines. Seroconversion, defined as a four-fold or greater rise in the titre of serum bactericidal antibody, (ie, antibody which, in the presence of complement, leads to killing of the bacteria) has been found to be a reasonably consistent marker of protection against disease and thus has come to be accepted as a surrogate marker of effective immune responses following vaccination.

Table 1 shows the proportion of vaccinees who seroconverted following two or three doses of a serogroup B meningococcal vaccine and the efficacy of the vaccine in protection against disease during epidemics largely caused by the vaccine strain.\(^10\)\(^–\)\(^16\)
Table 1. Seroconversion rates and vaccine efficacy for serogroup B meningococcal vaccines

<table>
<thead>
<tr>
<th>Vaccine (reference)</th>
<th>Doses</th>
<th>Vaccinees</th>
<th>Rate of seroconversion following immunisation</th>
<th>FU</th>
<th>Vaccine efficacy mean (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwegian (10)</td>
<td>2</td>
<td>Norway 14-16yr n=171,800</td>
<td>NT</td>
<td>29mo</td>
<td>57.2% (27.7% -?)</td>
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<tr>
<td>Norwegian (14)</td>
<td>3</td>
<td>Iceland 18 yr n=153</td>
<td>at 12mo FU 84% at 20mo FU 69%</td>
<td>NT</td>
<td></td>
</tr>
<tr>
<td>Cuban (11)</td>
<td>2</td>
<td>Sao Paulo 3mo-6yr n=2.4 million</td>
<td>NT</td>
<td>&lt;1yr</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6-23mo -37% (≤100-73)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>24-47mo 47% (-72-84)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>≥48mo 74% (16-92)</td>
</tr>
<tr>
<td>Cuban (12)</td>
<td>2</td>
<td>Rio de Janiero 6mo-9yr n=1.6 million</td>
<td>NT</td>
<td>1yr</td>
<td>Age</td>
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<td></td>
<td>6-23mo 47% (≤100-89)</td>
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<td>24-47mo 69% (-45-94)</td>
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<td></td>
<td>≥48mo 82% (40-95)</td>
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<tr>
<td>Vaccine (reference)</td>
<td>Doses</td>
<td>Vaccinees</td>
<td>Rate of seroconversion following immunisation</td>
<td>FU</td>
<td>Vaccine efficacy mean (95% confidence intervals)</td>
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<tr>
<td>Cuban (15)</td>
<td>2</td>
<td>Sao Paulo 3mo-6yr n=210</td>
<td>Age 3-23mo 22% 24-47mo 45% 48-83mo 52%</td>
<td>NT</td>
<td></td>
</tr>
<tr>
<td>USA (13)</td>
<td>2</td>
<td>Iquique, Chile 1-21yr n=40811</td>
<td>Age 1-4yr 12% 5-21yr 65%</td>
<td>20mo</td>
<td>Age 1-4yr -39% (-100-77) 5-21yr 70% (3-93)</td>
</tr>
<tr>
<td>Cuban or Norwegian (16)</td>
<td>3</td>
<td>Santiago, Chile &lt;1-30yr n=543</td>
<td>Age &lt;1yr 90% 2-4yr 78% 17-30yr 67%</td>
<td>NT</td>
<td>Cuban 90% Norwegian 98%</td>
</tr>
</tbody>
</table>

FU=follow up, NT=not tested, wk=weeks, mo=months, yr=years
Figure 4 illustrates the relationship between seroconversion and vaccine efficacy in a more easily assimilated format.

Figure 4. Previous trials of serogroup B meningococcal vaccines have shown a relationship between the proportion of vaccinees who had a $\geq 4X$ rise in serum bactericidal antibody titre following vaccination (horizontal axis) and the protective efficacy of the vaccine (vertical axis). The points shown are for: the Norwegian vaccine given to children aged 14–16yrs (1); the Cuban vaccine given to children in Sao Paulo, Brazil, aged <2yrs (2), 2-4yrs (3), 4–7yrs (4); the Cuban vaccine given to children in Rio de Janeiro, Brazil, aged <2yrs (5), 2-4yrs (6), 4–9yrs (7); and an American vaccine given to children in Iquique, Chile, aged 1–4yrs (8) and 5–21yrs (9).\textsuperscript{10–15}

Tapperro et al found that a high proportion of vaccinees (including those aged less than 1 year) seroconverted following three doses of either the Cuban or the Norwegian vaccine\textsuperscript{16} (Table 1). This suggested that a three dose immunisation program would provide protection against disease for a high proportion of vaccinees.
The initial results from the New Zealand immunogenicity studies are similar to those from the Tapperro study. Seroconversion rates increased with each dose of vaccine and were 100% in adults and 75% in toddlers after three vaccine doses. These results suggest that the New Zealand vaccine should be effective in these age groups.

Unfortunately immunisation with serogroup B meningococcal vaccines does not lead to high levels of serum bactericidal antibody, and the overall effect of giving more doses of vaccine is to increase the proportion of vaccinees who seroconvert rather than to dramatically increase the titres of serum bactericidal antibodies in seroconverters.

Thus, geometric mean titres of serum bactericidal antibody were 1.2–4.6 pre-immunisation and 2.8–30.2 and 9.2–64.6 after the second and third doses of a serogroup B meningococcal vaccine. In contrast, the geometric mean titres of serum bactericidal antibody rose from being undetectable pre-immunisation to 13, 302, and 629 after the first, second, and third doses of a conjugated serogroup C meningococcal vaccine.

The relatively low geometric mean titres of serum bactericidal antibody in people given two or three doses of serogroup B meningococcal vaccines are the probable explanation for the decline in vaccine efficacy which occurs within a year or two of immunisation with these vaccines. Careful observation will be necessary to determine whether initial immunisation will need to be followed by repeat doses at intervals of a year or two.

Vaccines, which produce very high levels of antibody following immunisation, such as the conjugated vaccines against *Haemophilus influenzae* type b, serogroup C meningococcus, and *Streptococcus pneumoniae* reduce asymptomatic nasopharyngeal colonisation as well as invasive disease. Not surprisingly, given the relatively low titres of antibody produced, immunisation with serogroup B meningococcal vaccines does not appear to reduce nasopharyngeal colonisation by the organism and therefore a successful vaccination program may not reduce transmission of infection.

This has important implications for vaccine delivery. Vaccines which prevent carriage reduce the exposure of susceptible persons to the organism and can virtually eliminate disease despite vaccine uptake rates of ‘only’ 90%. In contrast, vaccines which do not prevent carriage do not reduce the exposure of susceptible persons to the organism and therefore disease prevention requires very high levels of vaccine uptake.

The effect of the meningococcal vaccination campaign on the incidence of meningococcal disease in New Zealand largely will depend on the average vaccine efficacy in a fully immunised person and the proportion of the population who are fully immunised. Thus, a vaccine which provides protection against disease in 90% of fully immunised people might be expected to reduce the incidence of disease by about 81% if 90% of the target population are fully immunised.

However, as the vaccine is likely to be less effective in protecting against meningococcal disease due to strains other than the vaccine strain (which comprise about 20% of current New Zealand isolates), and as the vaccine will not be given to people over the age of 20 years (who comprise about 17.6% of notified cases of disease), the overall reduction in disease incidence may be correspondingly less.
There is relatively sparse information about the uptake of childhood immunisations in New Zealand—a situation which should be improved by the introduction (this year) of a national childhood vaccination register. A national survey conducted in 1992 found that less than 60% of all children, and only 42% of Maori children, had been fully immunised by their second birthday.\textsuperscript{22}

A subsequent survey, conducted in 1996 in Auckland and Northland, found that 44.6% of Maori children, 53.1% of Pacific children, and 72.3% of ‘other’ children were fully immunised by their second birthday.\textsuperscript{23} In contrast, a school and public health system-based immunisation program intended to control an epidemic of serogroup A meningococcal disease in Auckland in 1987 and 1988 had an overall uptake of approximately 90%.\textsuperscript{24}

The uptake of any public health intervention is dependent on the perceived benefits and risks of the intervention and on the organisational skill of the health system. The widespread, prolonged epidemic of meningococcal disease in New Zealand over the last 14 years has provided many with close experience of its unpredictable occurrence and often terrifying severity. Fear of the disease, together with parochial support for a local initiative are likely to enhance vaccine uptake, while concerns about less than complete protection and adverse effects following immunisation are likely to reduce vaccine uptake. The need for three doses of vaccine to achieve seroconversion in a high proportion of vaccinees and the goal of immunising all those aged less than 20 years, during a relatively short period, will provide significant tests of the organisational skills of the health system.

The unequal incidence of meningococcal disease (with rates of 28.9, 20.5, 12.1, and 6.8 per 10\textsuperscript{5} population respectively in Pacific, Maori, European and ‘other’ ethnic groups)\textsuperscript{1} will make high rates of vaccine uptake particularly important in Pacific and Maori children. Unfortunately, these groups have had lower rates of vaccine uptake for routine childhood immunisations\textsuperscript{22,23} and, with some exceptions, also had disappointingly low rates of participation in the recent hepatitis B screening program.\textsuperscript{25} Hopefully, lessons learnt from previous public health initiatives will ensure that the vaccine does get delivered to those who might gain the most benefit from it.

Concerns about vaccine safety can have dramatic effects on vaccine uptake. In general, serogroup B meningococcal vaccines cause local symptoms at the injection site—but are safe. Substantial safety data exist for the Norwegian vaccine, on which the New Zealand vaccine is based, and for other similar vaccines. Approximately 345,000 doses of the Norwegian vaccine have been administered in Norway, with approximately 226,000 doses given in controlled trials, mainly to teenagers,\textsuperscript{10}—with no serious adverse events related to the vaccine.\textsuperscript{26}

Further evidence of vaccine safety comes from experience with the Cuban vaccine, of which over 65 million doses have been administered, the American vaccine,\textsuperscript{13} and the Dutch vaccine, which contains six PorA OMPs including that present in the New Zealand strain (P1.4), and which has been given to 103 infants in an English trial.\textsuperscript{27} Although there are excellent reasons to expect that the New Zealand vaccine will be safe, comprehensive post-licensure safety monitoring both by the Centre for Adverse Reaction Monitoring (CARM) and a specifically developed ‘real-time’, hospital based monitoring system will be in place during the epidemic campaign. Furthermore, all
safety data will be assessed by an independent safety monitoring board established by
the Health Research Council.

The New Zealand meningococcal vaccination program is the culmination of years of
effort by many in New Zealand and overseas. It is to be hoped that it will dramatically
reduce the incidence of meningococcal disease and thus repay the approximately
NZ$200 million which the Ministry of Health has committed to this project over the
next 5 years. It is also likely to advance our understanding of this disease and its
prevention in ways that may prove useful to other countries afflicted by similar
epidemics.

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