

15 Meningococcal Invasive Disease

15.1 Introduction

Meningococcal disease is caused by *Neisseria meningitidis*, a gram-negative intracellular diplococcus typically seen within leucocytes. It causes both endemic and epidemic disease. The first epidemic was probably reported by Willin in 1661, but Weiselbaum did not identify the organism until 1887. Vieusseux published the first definitive description of meningococcal meningitis in 1905.

At least 13 serogroups of meningococci can be differentiated based on the chemical and immunological properties of the capsular polysaccharides. Most human disease is caused by serogroups A, B, C, W135 and Y, and these strains are responsible for nearly all outbreaks of disease. Meningococci can be further subdivided on the basis of the class 2 or 3 outer membrane protein (serotype) and class 1 outer membrane protein subtype and lipopolysaccharide (immunotype). Standard nomenclature lists serogroup, serotype, serosubtype and immunotype (eg, B:4:P1.7-2,4). Meningococci have the capacity to exchange genes and switch serogroups.

Group A is the most common epidemic strain throughout the world and was responsible for the 1985/86 Auckland epidemic. Since 1991 there has been a New Zealand wide epidemic of serogroup B disease with the B:4:P1.7b,4 strain (see 'New Zealand epidemiology' below). This long lasting epidemic has led to New Zealand working with vaccine manufacturers to produce a strain specific group B meningococcal outer membrane vesicle (OMV) vaccine (MeNZB™, Chiron) specific to the New Zealand strain, in order to combat the epidemic. Following immunogenicity, safety and reactogenicity trials in 2003/04, the vaccine was progressively introduced through the country in a programme for children and young adults aged 0–19 years (see 15.4C).

15.2 The illness

Infection with the meningococcus results in a wide range of presentations, but most commonly meningitis and/or septicaemia (meningococcaemia). Meningococcal invasive disease usually has a sudden onset with fever, malaise, prostration and a variety of other possible symptoms including nausea, vomiting and headache. Approximately two-thirds of cases have a rash, which may be petechial, purpuric or (less commonly) maculopapular and urticarial. The presence of a petechial or purpuric (haemorrhagic) rash must be taken very seriously. Those particularly at risk of meningococcal disease are children under five years of age, although all age groups may be infected and there is a higher case fatality rate in adults. The presentation may be non-specific in young infants.

In fulminant cases, disseminated intravascular coagulation, shock, coma and death can occur in a few hours despite appropriate treatment. The signs and symptoms of meningococcal meningitis do not differ from those caused by *Haemophilus*

influenzae type b (Hib) or *Streptococcus pneumoniae*, although petechiae or purpura are rare with these aetiologies. Invasive meningococcal infection can also give rise to arthritis, myocarditis, pericarditis, endophthalmitis and pneumonia. Other presentations include primary pneumonia, occult bacteraemia, conjunctivitis and chronic meningococcaemia. Patients with a deficiency of terminal complement components (C5–9) are at special risk of invasive infection and recurrent meningococcal disease. Therefore, individuals with illness caused by an uncommon serogroup, a second episode of meningococcal disease or a vaccine failure should be investigated for an immune deficiency.

A definitive diagnosis depends on culture or positive PCR (polymerase chain reaction) test of the bacteria from blood, cerebrospinal fluid or another usually sterile site. Bacteria may be observed intracellularly after gram staining cerebrospinal fluid specimens or aspirates from purpuric lesions. In those who have received prior antibiotics, 3–5 mL of blood should be taken in an EDTA tube for meningococcal PCR studies, and a throat swab (including the posterior nasopharynx), which may allow isolation of the organism. Acute and convalescent sera should also be taken for serum bacteriocidal antibodies assay (see Appendix 9).

Because of the fulminant nature of this disease, antibiotics should be administered on suspicion of diagnosis and before transferring the patient to hospital. The patients for whom this recommendation particularly applies are those who are obviously ill and deteriorating quickly, and those with delirium, coma or a haemorrhagic rash. These patients may or may not have neck stiffness.

Patients should receive:

- adults: benzylpenicillin 1.2 g (2 megaunits) IV (or IM); or amoxycillin 1–2 g IV (or IM)
- children: benzylpenicillin 25–50 mg/kg IV (or IM); or amoxycillin 50–100 mg/kg IV (or IM)
- or any other available parenteral antibiotic.

For more detail, see Appendix 9.

15.3 Epidemiology

Asymptomatic *N. meningitidis* colonisation of the upper respiratory tract occurs in 5–15 percent of individuals. Smoking, passive smoking, crowding, and viral or mycoplasma infections increase carriage. Spread from person to person is by respiratory droplets and from contact with respiratory secretions (eg, kissing or sharing a glass). Infants and young children under five years of age are the most susceptible to the disease, with peak incidence occurring in the 6–12 months age group.

Close contacts of primary cases of meningococcal infection are at increased risk of developing disease, particularly within families, early childhood services, semi-closed communities, schools and military recruit camps. Students in their first year of tertiary education living in hostel accommodation are also at higher risk.^{1,2} Household contacts are estimated to have 500–800 times increased risk of contracting the disease compared with the risk for the general population.³

It is not possible to calculate the incubation period for meningococcal disease for sporadic cases. Those contacts of cases of meningococcal disease who develop the disease usually do so within four days, but it can be up to 10 days. Patients may be considered to be no longer infectious after 24 hours of antibiotic therapy, although rifampicin, ceftriaxone or ciprofloxacin is necessary to reliably clear nasopharyngeal carriage (see ‘Chemoprophylaxis’, in section 15.8).

The annual incidence of meningococcal disease is about 1–3 per 100,000 in developed countries, and 10–25 per 100,000 in some developing countries. Serogroup A can cause massive outbreaks of disease, such as the regular epidemics in the sub-Saharan Africa meningitis belt, where attack rates may approach one to two cases per 100 people per year. The polysaccharide group A vaccine may be used to control these epidemics. There have been outbreaks of group A disease, and more recently group W135 disease, associated with the Haj pilgrimage, and meningococcal vaccination is required before participation.^{4,5} Meningococcal disease appears to have increased in developed countries over the past decade or so.

Notification rates in Australia increased from less than 1 per 100,000 in 1986 to 1.9 in 1991, and 2.7 (499 notifications) in 1997.⁶ An increase in group C disease led to meningococcal C conjugate vaccine being introduced into the Australian infant schedule in 2004, with a catch up programme for all children and young adults aged 6 weeks to 20 years. Before the programme began, there were 162 cases of group C disease in 2002 (from a total of 393 isolates), which decreased to 71 in 2004.^{7,8}

In the United States (US), there has been an increase in localised outbreaks, often in school aged children and young adults, particularly of group Y disease.⁹ In Canada an increased incidence of group C meningococcal disease led to several community based immunisation programmes¹⁰ with the group C polysaccharide vaccine. This has been followed by the introduction of meningococcal group C conjugate vaccine onto the routine infant immunisation schedule in Canada.

In the United Kingdom (UK), outbreaks of group C disease in young adults and an increased rate of disease in infants led in 1999 to the introduction of a group C conjugate vaccine into the infant immunisation schedule and a mass immunisation campaign for all children, adolescents and young adults up to 20 years of age. Four years after introduction the reported efficacy was at least 83 percent in children who had received the conjugate vaccine from five months of age to 18 years. However, in infants who were immunised in the first six months of life, the vaccine offered little protection one year after the last dose.¹¹ A booster dose in the second year of life may help to address this waning immunity.

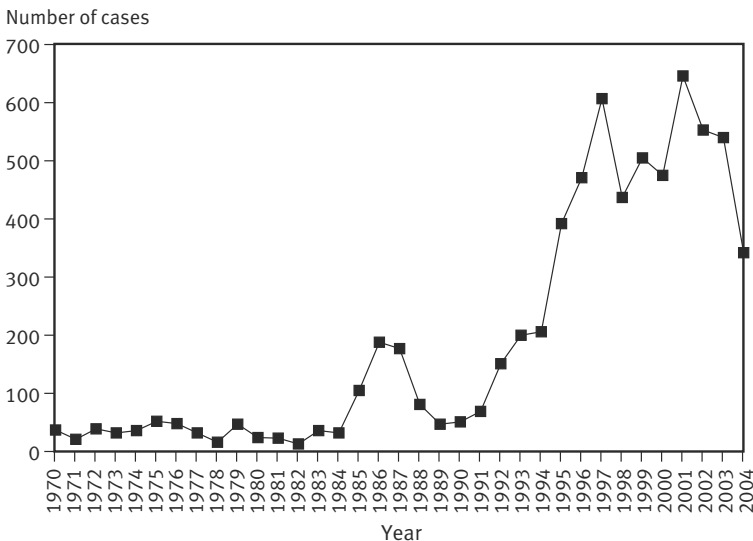
Epidemics of group A or group C meningococcal disease usually resolve in one to three years. Polysaccharide vaccines against these strains are effective in adults and to a variable degree in children. In contrast, strain specific group B disease epidemics start slowly and may persist for 5–10 years or longer, as seen in Norway and Chile.^{12,13} A higher proportion of group B disease cases occur in children under five years of age, and at the start of an epidemic there may be an age shift towards higher rates in older children and adolescents. The serogroup B polysaccharide is poorly immunogenic in humans. Instead, vaccines using other bacterial components – especially preparations of outer membrane proteins (OMP) – have been developed. The protection provided by these vaccines is expected to be sero-subtype specific, especially in younger age groups.

New Zealand epidemiology

Since 1991 there has been a persistently elevated rate of meningococcal disease in New Zealand, increasing from 53 cases recorded in 1990 to a peak of 648 cases in 2001. Since 2001 there has been a gradual decline in the number of cases reported, with 344 cases reported in 2004. This annual rate in 2004 was 9.2 cases per 100,000, compared with the rate of 1.5 per 100,000 in the non-epidemic years 1989/90 and a rate of 17.4 per 100,000 in 2001 (see Figure 15.1).

A workshop to discuss meningococcal disease control was held in 1995, where it was recommended that a case control study to investigate risk factors for the disease be undertaken.¹⁴ The case control study found household crowding to be an important risk factor independent of ethnicity.¹⁵

Figure 15.1: Notified cases of meningococcal invasive disease, 1970–2004



Historically, in New Zealand the dominant serogroup has been serogroup B, except for a large outbreak of serogroup A in Auckland in 1985/86, and small group C outbreaks in south Wellington and Taranaki during 1994, Otago in 2002 and 2003, and Huntly in 2005. A mass immunisation programme using a group A polysaccharide vaccine controlled the group A outbreak in Auckland. In response to the group C outbreaks, quadrivalent vaccine was given to geographically defined populations two to four years of age in Wellington, and two to nine years of age in Taranaki. In response to the Otago outbreaks, staff and school students were given quadrivalent polysaccharide vaccine in one outbreak, and students in hostel accommodation were offered the quadrivalent vaccine in the second outbreak. The meningococcal conjugate group C vaccine was offered to school students in the Huntly outbreak in 2005.

The proportion of isolates from *N. meningitidis* serogroup B disease rose from 47.8 percent in 1990 to 88.4 percent (282 out of 319 isolates) in 2001, and 87.3 percent (220 of 252 isolates) in 2004. The increase in disease rate in all years is mostly from the epidemic strain B:4:P1.7b,4. In 2001, 262 of the 319 isolates (88.4 percent) and in 2004, 184 of the 252 isolates (73 percent) were of this sero-subtype. During this epidemic, disease rates have been higher in the winter months and consistently higher in Auckland and the northern region of New Zealand. The rate of disease in 2004 was 11.6 per 100,000 total population in the northern region compared with 9.7 per 100,000 in the midland region, and 7.0 per 100,000 in both the central and southern regions. In 2004, 273 of the 342 total cases (79.8 percent) were laboratory confirmed cases, with the remainder diagnosed on clinical grounds. Rates of disease are highest in infants under one year of age, and in children between one to four years of age (see Table 15.1).

Table 15.1: Numbers and age-specific rates of cases of meningococcal disease, under 20 years of age, 2001 and 2004

Age group (years)	Number of cases		Age specific rate per 100,000	
	2001	2004	2001	2004
< 1	110	46	201.3	84.2
1–4	176	96	81.4	44.4
5–9	76	43	26.6	15.0
10–14	69	35	23.7	12.0
15–19	96	40	36.2	15.1
Total all ages	648	342	17.3	9.2

Rates are consistently higher in Māori and Pacific children compared with the total population. The rate in 2004 for Māori children one to four years of age was 85.9 per 100,000 and in Pacific children 93.9 per 100,000, compared with the total population rate of 44.4 per 100,000 for children one to four years of age. Similar increases of a lesser magnitude of serogroup B disease have been reported by other comparable countries, including Norway, the Netherlands, Oregon (US) and the UK.

15.4 Vaccines

Please note that:

- sections 15.4A, 15.5A, 15.6A and 15.7A refer to meningococcal polysaccharide vaccines
- sections 15.4B, 15.5B, 15.6B and 15.7B refer to protein conjugate meningococcal vaccines
- sections 15.4C, 15.5C, 15.6C and 15.7C refer to group B vaccines.

Table 15.2: Indications for meningococcal vaccines

Vaccine	Licensure	Funded for	Recommended for	See section(s)
Meningococcal A	Y, NA	Nil	Nil	15.4A–7A
Meningococcal B Outer Membrane vesicle (MenZB™)	Special programme	Current programme: all children aged 6 weeks to 19 years, plus other specified groups. Programme from July 1 2006: <ul style="list-style-type: none"> · infants aged 6 weeks, and 3, 5 and 10 months · adults and children pre- or post-splenectomy · microbiologists and laboratory workers exposed to N. meningitidis isolates · others as notified by the Ministry of Health. 	NA	15.4C–7C
Meningococcal C conjugate	Y	May be funded for a community programme to control an outbreak	1.Young adults in their first year of residence in hostel accommodation 2.Close contacts of cases of meningococcal C disease (as an alternative to meningococcal A, C, Y, W135 polysaccharide vaccine)	15.4B–7B
Meningococcal C polysaccharide	Y, NA	Nil	Nil	15.4A

Vaccine	Licensure	Funded for	Recommended for	See section(s)
Meningococcal A, C, Y, W135 conjugate	N as at 31.12.2005	NA	NA	15.4B
Meningococcal A, C, Y, W135 polysaccharide	Y	<p>1. Adults and children pre- or post-splenectomy.</p> <p>2. May be funded for a community programme to control an outbreak.</p>	<p>1. Young adults in their first year of residence in hostel accommodation.</p> <p>2. Close contacts of cases of meningococcal C disease (an alternative for those in 1 and 2 is meningococcal C conjugate vaccine).</p> <p>3. Individuals at high risk of invasive disease, including those with:</p> <ul style="list-style-type: none"> · sickle cell anaemia · deficiencies of terminal complement components · HIV infection. <p>4. Other groups at higher risk are:</p> <ul style="list-style-type: none"> · military recruits · microbiologists and laboratory workers exposed to <i>N. meningitidis</i> isolates · travellers to sub-saharan Africa and Haj pilgrims 	15.4A–7A

Key: Y: yes licensed in New Zealand, N: no, not licensed in New Zealand, NA: not available in New Zealand.

15.4A Meningococcal polysaccharide vaccines: group A, C, Y and W135 vaccines

There are four meningococcal polysaccharide vaccines with consent for distribution in New Zealand: a monovalent group A vaccine (Menomune-A, Aventis Pasteur, used during the Auckland epidemic and no longer available); a bivalent vaccine containing groups A and C (Mencevax AC, GSK, no longer available); and two quadrivalent vaccines containing groups A, C, Y, and W135 (MENCEVAX ACWY, GSK; Menomune™ ACYW-135, Sanofi Pasteur), containing 50 µg of each antigen. Normally the quadrivalent vaccine is administered.

The meningococcal vaccines are a purified, heat stable, lyophilised extract from the polysaccharide outer capsule of *N. meningitidis*. Like other unconjugated polysaccharide vaccines, they are less effective in children under two years of age and are licensed for use only in children over this age. The exception is group A antigen, which is immunogenic and may be efficacious in infants three months of age and older if given in two doses, three months apart. Group C polysaccharide vaccine, as available in the group A, C, Y and W135 vaccines, should be avoided in children under two years of age because it is not immunogenic in this age group.^{16,17,18,19}

For a consideration of the role of conjugate group C vaccine which is immunogenic in children under two years see 15.4B.

Efficacy of group A, C, Y and W135 vaccines

The efficacy against groups A and C has been shown in outbreaks to be 85 to 100 percent in older children and adults.²⁰ There is no similar data for groups Y and W135, but they are immunogenic in those who are two years of age and over. The antibody responses to each of the four polysaccharides in the quadrivalent vaccine are serogroup specific.

Protective levels of antibody are usually achieved within 7–10 days after vaccination. Immunity lasts approximately three years, although in younger children there may be a more rapid decline in antibody levels. The decline in efficacy of the group A vaccine is age dependent. In a three-year study, efficacy declined from more than 90 percent to less than 10 percent among children under four years of age when vaccinated, compared to a decline to 67 percent in children older than four years.²¹ In the 1985/86 outbreak in Auckland the estimated efficacy of group A vaccine was 100 percent after two doses of vaccine for children between three and 23 months of age, and after one dose for children from two years of age.²²

About 1.6 million doses of the tetravalent polysaccharide vaccine were administered in Canada to people between six months and 20 years of age in response to an epidemic of meningococcus group C in the early 1990s. The overall field efficacy of the vaccine was 79 percent (higher in teenagers and lower in children under five years of age).²³ The epidemic waned both in provinces that vaccinated and in those that did not.²⁴ A subsequent case control study found a good level of protection

(77 percent) was provided over a five-year period by a single dose of the polysaccharide vaccine in individuals aged six years and over, but in those aged two to five years only short term protection was achieved.²⁵

Dosage of polysaccharide vaccines

For those two years of age and over the vaccine is administered as a single dose of 0.5 mL, given by subcutaneous injection. (See section 2.3 for needle sites and sizes.) In an epidemic the group A antigen may be considered for those under two years of age, and two doses will be required. Specific recommendations will be made depending on the situation.

Revaccination

There is little information available to determine the need for revaccination. Revaccination may be indicated for people at high risk of infection (eg, who are remaining in areas in which the disease is epidemic), particularly children who were first vaccinated when they were under four years of age; such children should be considered for revaccination after two to three years if they remain at high risk. Although the need for revaccination of older children and adults has not been determined, antibody levels decline rapidly over two to three years, and if there are still indications for immunisation, revaccination should be considered. Reimmunisation of adults before five years after initial immunisation does not seem to be necessary. Serological studies have reported that multiple doses of serogroup A and C polysaccharide vaccines may cause immune hyporesponsiveness to the antigens, although the clinical relevance of the phenomenon is unknown.^{26,27}

15.4B Protein conjugate meningococcal group C vaccines

The conjugation of the serogroup C oligosaccharide to a protein carrier, such as tetanus toxoid, facilitates T-cell help and converts the immune response from a T-cell independent to a T-cell dependent one. This allows an effective primary immune response following vaccination in all ages, including infancy, and rapid anamnestic antibody responses with an increased avidity index on subsequent antigen exposure consistent with the development of immunological memory. In addition, conjugate vaccines reduce nasopharyngeal colonisation of meningococcus serogroup C, thereby protecting unvaccinated individuals by a herd immunity effect.

The UK was the first country to introduce a national immunisation programme for conjugate meningococcal group C vaccines.²⁸ Protein conjugate meningococcal group C vaccine, using the same technology as conjugate Hib vaccines, was introduced to the UK immunisation schedule in 1999 as three doses for infants, and a single dose to children from the age of one year to young adults up to and including 20 years of age. Initial results show the disease has decreased and the vaccine is effective in the vaccinated group.²⁹ The vaccines were introduced in response to increasing rates of serogroup C disease (~3 per 100,000) that occurred during the 1990s, which were associated in particular with outbreaks in universities

and accompanied by high fatality rates. Licensure was not based on efficacy trials, but instead on safety and immunogenicity data, including extrapolation of serological correlates of protection from older children and adults who had received group C polysaccharide vaccines.

Pre-licensure studies had shown that conjugate meningococcal group C vaccines were well tolerated and induced bactericidal antibodies and immunological memory in UK toddlers after one dose,³⁰ justifying a single dose catch up schedule for children aged one to 18 years. Similarly, the conjugate vaccines were immunogenic following a primary two-, three- and four-month series during infancy, and immunological memory persisted four years later when subjects were rechallenged with meningococcus serogroup C polysaccharide.^{31,32} Consequently, no booster doses have been given following the primary accelerated immunisation series during infancy.³³ Of importance, infants in both the UK and Africa who received a primary series with conjugate meningococcal group C vaccines may have subsequent anamnestic responses attenuated by repeated doses of meningococcal polysaccharide group C vaccine.^{34,35}

Protein conjugate meningococcal group C vaccine has also been introduced to the routine childhood schedule in Australia. The protein conjugate meningococcal group C vaccine Meningitec® (Wyeth) and protein conjugate meningococcal group A and C vaccine Menjugate are now licensed in New Zealand.

Combination protein conjugate meningococcal vaccines

Other conjugate meningococcal vaccines, such as a conjugate vaccine active against groups A and C, have been developed. The conjugate vaccine Menjugate is now licensed in New Zealand.

A conjugate quadrivalent meningococcal vaccine effective against groups A, C, Y and W135 meningococcal disease (Menactra®, Sanofi Pasteur) is licensed in the US, but not in New Zealand at the time of writing, for individuals 11 to 55 years. Immunisation against meningococcal disease with this quadrivalent conjugate vaccine is now recommended in the US at the age of 11 years,³⁶ or if missed it is given at age 15 years. A quadrivalent vaccine is also recommended before college entry. Post-licensure reports of five cases of Guillain-Barré syndrome³⁷ in young adults aged 17–18 years, 14 to 31 days after the Menactra® vaccine led to an investigation. The manufacturer has advised medical practitioners of the association of Guillain-Barré syndrome with the vaccine, and the Centers for Disease Control have advised that parents and students should be warned of the association. To date there is insufficient information to conclude there is a causal relationship, and there is continuing follow up.

Efficacy of protein conjugate meningococcal group C vaccines

Since the introduction of the national meningococcal group C immunisation programme in the UK, coverage has exceeded 80 percent in all targeted age groups

younger than 19 years. During the first two years of the campaign the cases of serogroup C disease decreased by 86.7 percent, with short term vaccine efficacy of 97 percent in teenagers and 92 percent among toddlers.³⁸ There was a concomitant decrease in deaths due to serogroup C from 67 in 1999 to five in 2001. By the end of 2001 there were 26 vaccine failures. More recent estimates place overall vaccine efficacy at 90.4 percent after four years.³⁹ The vaccines have been well tolerated without serious adverse effects. Low grade fever was detected in 5 percent and mild local reactions were reported in about 40 percent of recipients.^{40,41,42}

Protective efficacy against carriage of serogroup C by adolescents one year after the immunisation campaign was estimated at 69 percent, with the vaccines providing induced mucosal immunity in 63 percent of those who had been immunised.⁴³ At the same time there was no increase in colonisation by the other meningococcal serogroups. Consistent with the reduction in meningococcal carriage rates there has been a 67 percent reduction in serogroup C disease among unvaccinated children within the target age groups and a reduction of 35 percent of cases in adults over the age of 25 years.⁴⁴ At the same time there is no evidence of capsular switching or an increase in disease by serogroup B strains.⁴⁵

Although at four years of follow up the vaccine's effectiveness remained at 90 percent, a significant trend for waning effectiveness after one year was observed, particularly among infants.⁴⁶ Similarly, measures of seroprotection are absent in the majority of infants and toddlers within two to three years of their last vaccination after either the single valent group C vaccine or the quadrivalent conjugate vaccine.^{47,48} Even though the conjugate vaccines induce an anamnestic response, it is not clear whether circulating protective antibodies are also required to prevent meningococcal disease. If invasive disease develops within hours or days of acquisition and colonisation of the nasopharynx, it is unlikely there will be sufficient time to mount a memory response and produce protective serum antibody levels. Current protection from meningococcal disease is likely to require a combination of reducing the likelihood of exposure to disease and reduced carriage, immunological memory and circulating antibodies.⁴⁹

Despite these considerations, the meningococcal C vaccine has had a major impact on the epidemiology of meningococcal C disease in the UK. Further work may provide information on the persistence of mucosal and serological protective antibody responses and the effects of further boosting.

Dosage of protein conjugate meningococcal group C vaccines

Each 0.5 mL dose of Meningitec® (Wyeth) contains 10 µg *N. meningitidis* group C oligosaccharide (MnCO) conjugated to approximately 15 µg *Corynebacterium diphtheriae* CRM₁₉₇ protein, given by intramuscular injection. (See section 2.3 for needle sites and sizes.)

The recommended dose of Meningitec® vaccine for infants is three doses of vaccine at six- to eight-week intervals. For children over the age of one year, along with adolescents and adults, one dose is recommended.

15.4C Group B meningococcal vaccines

Group B vaccines are not commercially available. Vaccines derived from group B polysaccharides are poorly immunogenic, and therefore research has concentrated on the outer membrane protein (OMP) and in particular the outer membrane vesicle (OMV). Vaccines based on the OMP/OMV induce serum bactericidal antibodies. Any estimation of their clinical efficacy is limited by the quality of the available data.

The two most evaluated OMP vaccines are those produced in Norway in response to an epidemic with the strain B:15:P1.7.16, and a vaccine produced in Cuba in response to a B:4:P1.19.15 strain epidemic. The Norwegian vaccine was given as two doses to 13 to 14 year old school children and showed an efficacy of 57 percent at 29 months in a randomised controlled trial.⁵⁰ A later evaluation estimated that the vaccine efficacy at 10 months after the introduction of the vaccine was 87 percent.⁵¹ The vaccine was not introduced nationally because the epidemic declined and the efficacy of 57 percent was judged insufficient.

The Cuban vaccine, a combined group C polysaccharide vaccine with the group B OMP vaccine, had an efficacy of around 80 percent in a randomised trial among adolescents.⁵² Vaccination of all Cubans under 20 years of age, and ongoing routine vaccination of all infants with two doses of the vaccine, had contributed to the continuing control of the disease in Cuba.

The Cuban vaccine was also used in mass immunisation campaigns in some Latin American countries experiencing outbreaks of meningococcal group B disease caused by varying proportions of the same strain as Cuba. Studies showed that two doses of the Cuban vaccine were effective in older children, but in children under four years of age results varied from showing no effect to a moderate effect. However, it was observed that if vaccination led to a rise in serum bactericidal antibody levels this was suggestive of vaccine efficacy. Vaccine efficacy appeared to be higher when the vaccine strain was similar to the outbreak strain.

A study in Chile, using both the Norwegian and the Cuban vaccines, compared the antibody response in infants, children and adults. Following three doses, over 95 percent of infants sustained a four-fold rise in serum bactericidal antibody against the vaccine strains.⁵³ This suggests that three doses of an OMV vaccine could provide clinical protection in this age group.

New Zealand Meningococcal B Immunisation Programme

Development and manufacture of a vaccine specific to the New Zealand epidemic strain (MeNZB™) in sufficient quantities for the nationwide immunisation programme was possible because of a partnership between the Ministry of Health

and Chiron Vaccines, working in collaboration with the Norwegian Institute of Public Health. The MeNZB™ clinical trials to determine immunogenicity, safety and reactogenicity were led by a research team from the University of Auckland. Three doses of MeNZB™ were administered six weeks apart, in an adult study and in studies of children aged 8–12 years, 16–24 months and 6–8 months. In an infant study, the MeNZB™ was administered together with the usual childhood schedule vaccines to infants starting at 6–10 weeks old.

The benchmark⁵⁴ used in the clinical trials to indicate protection was a four-fold increase in serum bactericidal assay titre from a baseline titre of two. This test is the most reliable available measure of functional antibodies following vaccination. International experience with other similar vaccines indicates that the percentage of those who achieve a four-fold rise by serum bactericidal assay following vaccination may underestimate the percentage that will be protected from disease. For some individuals an immune response is seen but it fails to reach the four-fold rise cut off. Further information for medical practitioners on the MeNZB™ vaccine is available in the *Meningococcal B Immunisation Programme: Programme Guidelines for Health Professionals* (see www.moh.govt.nz).

Results from the MeNZB™ clinical trials

Clinical trials, using a schedule of three doses of MeNZB™ given concurrently with the routine schedule for young infants and with an interval of six weeks for older age groups, demonstrated that 55 percent of infants (aged 6–10 weeks), 74 percent of older infants (aged 6–8 months), 75 percent of toddlers (aged 16–24 months), 76 percent of children (aged 8–12 years), and 93 percent of adults developed a four-fold rise (compared with pre-vaccination values) in serum bactericidal assay titres four to six weeks after the third dose.

The successful trials in those age six months to 19 years led to licensure with provisional consent to vaccinate children and young people aged from six months to 19 years of age from 8 July 2004 and infants from 6 weeks of age on from 3 February 2005.

Additional data showed an improvement in the response rate (to 69 percent) after a fourth dose of MeNZB™ was given to infants at the age of ten months (43 weeks) and licensure with provisional consent for a fourth (further) dose of MeNZB™ vaccine for all infants who started their MeNZB™ course under six months of age, was granted on 16 January 2006. For infants who received the third dose of MeNZB™ vaccine at five to six months of age (21–26 weeks), the fourth dose should be given at ten months (43 weeks) of age. For babies who received the third dose of MeNZB™ vaccine at six months (26 weeks) of age or older, the fourth dose is given four months (17 weeks) after the third dose of MeNZB™ vaccine.

For babies who received the third dose of MeNZB™ vaccine before the age of five months (21 weeks), the fourth dose is recommended to be given nine weeks after the third dose to improve protection.

The necessity for further doses in other age groups has not been established.

The Meningococcal B Immunisation Programme commenced in July 2004 in the Counties Manukau District Health Board (DHB) area, followed by the greater Auckland and Northland DHB areas in November 2004. From late January 2005 the programme was extended DHB by DHB across the North Island and from Southland through to Nelson–Marlborough in the South Island, the latter beginning their programme in July 2005.

Children under five years of age, children not attending school and young people who had left school were immunised by primary care and outreach immunisation services.

Children and young people who were attending primary, intermediate and secondary school, were immunised at school by Public Health Nurse services.

The Meningococcal B Immunisation Programme finishes on 30 June 2006, although immunisation of babies from the age of six weeks, and for certain groups (see 15.5C) will continue until it is clear that the epidemic is controlled. MeNZB™ will also be available until the end of December 2006 for children and young adults to complete their three dose vaccine course.

The epidemiology of the disease will continue to be monitored so that vaccine efficacy may be assessed and the bacteria studied to detect any capsular change or emergence of different subtypes. Post-licensure vaccine efficacy and safety evaluations will be assessed and be sent to Medsafe as part of a full licence application.

Comprehensive safety monitoring

A comprehensive system of post-licensure safety monitoring is a key component of the Meningococcal B Immunisation Programme, and is designed to:

- detect serious adverse events following vaccination
- assess whether such events have a causal or coincidental relationship to vaccination
- increase public confidence in the immunisation programme, thereby helping to maintain coverage by alleviating unsubstantiated fears of vaccine reactions.

Dosage of group B vaccines

Each 0.5 mL dose of the MeNZB™ vaccine contains 25 µg of *N. meningitidis* group B OMV, and is given by deep intramuscular injection, preferably in the anterolateral thigh in infants/toddlers and in the deltoid region of the non dominant arm in toddlers, older children, adolescents and adults. (See section 2.3 for needle sites and sizes.)

The vaccine can be administered concomitantly with routine immunisation vaccines, using separate injection sites.

15.5 Recommended immunisation schedule

15.5A Recommended immunisation: group A, C, Y, W135 polysaccharide vaccines

Routine immunisation with meningococcal polysaccharide vaccine is not recommended because the usual risk of vaccine preventable meningococcal disease is very low. The vaccine is not recommended under two years of age because of the poor immune response, but may be used in outbreak situations in younger age groups (eg, a group A polysaccharide vaccine was used in Auckland and a group C vaccine was used in Canada).

Funded immunisation schedule for individuals pre- and post-splenectomy: meningococcal group A, C, Y, W135 vaccine (upon the recommendation of a secondary care specialist)

The quadrivalent polysaccharide meningococcal vaccine (Menomune™ ACYW-135, Sanofi Pasteur) is recommended, and from 2006 will be publicly funded, for the following individuals at high risk of invasive meningococcal disease:

- adults pre- and post-splenectomy, and children pre- and post-splenectomy or with functional asplenia – individuals scheduled for splenectomy should be immunised at least two weeks before the operation (see section 1.8).

A booster of the quadrivalent vaccine is also funded for individuals considered at special risk.

Note: From 2006, for individuals pre- and post-splenectomy the quadrivalent meningococcal vaccine (ACYW135), the meningococcal B vaccine MeNZB™ (while the vaccine is available in New Zealand), Hib vaccine and pneumococcal polysaccharide vaccine are publicly funded (both the vaccine and administration) (see section 1.8 and individual vaccine chapters).

Organisation and community based outbreaks

The quadrivalent meningococcal vaccine or the conjugate group C vaccine is recommended and publicly funded in an outbreak for the following groups:

- organisation and community based outbreaks, defined as three primary cases of invasive meningococcal disease caused by strains in the quadrivalent polysaccharide vaccine (A, C, Y and W135) within a three-month period, giving a primary attack rate of ≥ 10 cases per 100,000 population (See section 15.8).

Recommended immunisation for other individuals at increased risk of invasive meningococcal disease (not currently funded)

Individuals with a high risk of invasive meningococcal infection should be offered the quadrivalent polysaccharide meningococcal vaccine. Neither the vaccine nor the administration of the vaccine is currently funded. For children, see the schedules for use of the conjugate group C meningococcal vaccine in section 15.5B.

The quadrivalent polysaccharide meningococcal vaccine is recommended but not publicly funded for those with:

- sickle cell anaemia
- deficiencies of the terminal complement components
- individuals with human immunodeficiency virus (HIV) infection, who may be safely immunised with meningococcal polysaccharide vaccines.

The vaccine has been shown to be immunogenic in these groups, but there is no data on clinical protection.

Close contacts

Close contacts of cases of meningococcal disease are at increased risk of developing the disease over subsequent months, despite appropriate chemoprophylaxis. Immediate family or close contacts of cases of proven invasive meningococcal disease (if the disease is due to a group included in the vaccine) should be offered meningococcal vaccine as well as chemoprophylaxis.

Other groups

The quadrivalent meningococcal vaccine or the conjugate group C vaccine is recommended, but not publicly funded, for the following groups:

- young adults entering hostel accommodation (see section 15.5B)
- military recruits
- microbiologists and laboratory workers routinely exposed to *N. meningitidis* isolates
- travellers to countries during meningococcal epidemics, as in the sub-Saharan ‘meningitis belt’ during the annual Haj (see below).

Before travel

There are areas of the world where the risk of acquiring meningococcal infection is increased. Nevertheless, the risk to travellers to the developing world as a whole has been estimated as being less than one in a million per month. Recurrent epidemics of meningococcal disease occur in the sub-Saharan ‘meningitis belt’, from Senegal in the west to Ethiopia in the east, usually during the dry season (December to June). Epidemics are occasionally identified in other parts of the world and occurred

recently in Saudi Arabia (during a Haj pilgrimage), Kenya, Tanzania, Burundi, Mongolia and Nepal. For website sources for information about meningococcal vaccines for travellers, see Appendix 11.

15.5B Recommended immunisation: group C meningococcal conjugate vaccine

The vaccine is not on the New Zealand National Immunisation Schedule. It is recommended, but not publicly funded, for the following groups.

- Protein conjugate meningococcal group C vaccine may be offered, as an alternative to the quadrivalent polysaccharide vaccine, to young adults who will be resident in hostel type accommodation, particularly in their first year.
- The group C conjugate vaccine may be used to control an outbreak of meningococcal disease caused by group C⁵⁵ (see section 15.8).

15.5C Special programme for MeNZB™ vaccine: schedule recommendations and funding

Until 30 June 2006, MeNZB™ is offered to all children and young people aged 0–19 years as three doses of vaccine. For infants aged six weeks to five months the vaccine is given at the same time as the usual infant schedule at age six weeks, and at three and five months, plus a fourth dose (offered since January 2006) at age ten months. From the age of six months to 19 years three doses of the vaccine are given six weeks apart. The Meningococcal B Immunisation Programme will be completed at the end of June 2006, except for infants starting the usual childhood schedule. From 1 July 2006, providing the provisional licensure is extended, MeNZB™ will be available and funded for the following groups.

- Infants will continue to be offered four doses of MeNZB™ with the infant schedule vaccines at age six weeks, at three and five months, and a fourth dose at ten months.
- Other children under the age of five years (three doses of MeNZB™ vaccine at six-week intervals).
- Children and young people aged 5–19 years who started a course of MeNZB™ vaccine before 30 June 2006 have until 31 December 2006 to complete the course.
- Microbiologists and laboratory workers routinely exposed to *N. meningitidis* isolates (three doses of MeNZB™ vaccines at six-week intervals).

- Individuals of any age with a high risk of invasive meningococcal infection and specific conditions (three doses of MeNZB™ vaccines at six-week intervals)
These include:
 - i. Actual or functional asplenia – individuals scheduled for MeNZB™ vaccine pre-splenectomy, will need to have completed their MeNZB™ vaccine course (all three doses) at least four weeks prior to the scheduled operation date
 - ii. Sickle cell anaemia
 - iii. Deficiencies of the terminal complement components
 - iv. Individuals with HIV infection, who may be safely immunised with meningococcal polysaccharide vaccines.

Practitioners will be informed if there are other recommendations and funding for MeNZB™ vaccine.

Premature babies

Preterm infants and other infants with low birthweight should be immunised at the usual chronological age with the usual vaccine dosage, as for other routine childhood vaccines. For infants still in hospital at six weeks of age, provided the infant is well, MeNZB™ should be given concurrently with other routine childhood vaccines, whether given at six weeks or prior to discharge.

Ongoing programme monitoring

The effects of the programme will continue to be monitored. This will include ongoing analysis of the epidemiology of meningococcal disease, investigation of vaccine failures, and reporting of adverse events. These results will be reviewed at six-monthly intervals and practitioners will be informed of any changes to the programme and when MeNZB™ vaccination will cease.

15.6 Expected responses and adverse events following immunisation (AEFI)

15.6A Meningococcal polysaccharide vaccines

Expected responses

Generalised reactions to meningococcal vaccine are rare, but are more common in children than in adults. Reactions include fever, malaise and chills. In the Auckland epidemic, 130,000 Auckland children were immunised with group A vaccine, and there were 546 reports of unusual clinical events by parents and practitioners.⁵⁶ These events included 152 reports of fever; 85 of rash and local reactions; 63 of headache, stiff neck and myalgia; and 92 of apparent peripheral nerve involvement. None were permanent. An independent panel of experts examined the data and concluded that there was no evidence of permanent sequelae caused by the vaccine.

Up to 80 percent of recipients will have some local reaction, but most are minor.⁵⁷ Approximately 10 percent will develop local reactions at the injection site within 24 hours of the injection.

Adverse events following immunisation

The Canadian campaign delivered over a million doses of tetravalent polysaccharide vaccine, with reported allergic reactions in 9.2 per 100,000 doses, anaphylaxis in 0.1 per 100,000 doses, and neurologic reactions in 0.5 per 100,000 doses; there were no reports of long term sequelae or of encephalopathy, meningitis or encephalitis.⁵⁸

Any severe or unexpected reactions should be reported to CARM, PO Box 913, Dunedin, using the prepaid postcard HP3442 (see section 2.4) or via online reporting at <http://carm.otago.ac.nz>. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

15.6B Group C meningococcal conjugate vaccine

Expected responses

The most frequent response to the meningococcal C vaccine in the UK school programme was transient headache in 12 percent of students in the first three days after vaccination. Mild to moderate local reactions at the injection site consisting of pain, tenderness and occasional redness were also reported. These were maximal on the third day after the vaccine and resolved within a day.

Adverse events following immunisation

Adverse events were rare. Anaphylaxis was reported at a rate of 1 per 500,000 doses distributed.⁵⁹

Any severe or unexpected reactions should be reported to CARM, PO Box 913, Dunedin, using the prepaid postcard HP3442 (see section 2.4) or via online reporting at <http://carm.otago.ac.nz>. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

15.6C MeNZB™

Expected responses and adverse events following immunisation

Clinical trial adverse reactions reported across all age groups are provided in Tables 15.3–15.5 below. The age groups are infants 6–10 weeks old (523 doses), infants/toddlers 6–24 months old (1472 doses), children 8–12 years old (1606 doses), and

adults over 18 years old (103 doses). Note that the following categories of frequency have been defined:

- very common (≥ 10 percent)
- common (≥ 1 percent and < 10 percent)
- uncommon (≥ 0.1 percent and < 1 percent)
- rare (≥ 0.01 percent and < 0.1 percent)
- very rare (< 0.01 percent).

Adverse reactions were collected on the day of vaccination and each day following for up to seven days. The majority of reactions were self limiting and resolved within the follow up period. The full MeNZB™ data sheet is available at www.medsafe.govt.nz.

In all age groups, injection site reactions (tenderness/pain, redness, swelling and induration) were very common, but mild or moderate in intensity, with tenderness/pain being the most common. Most injection site reactions settled within two to three days, with those persisting for more than seven days being uncommon.

Crying (infants), irritability, sleepiness, change in eating habits, diarrhoea and vomiting, and fever of at least 38.0°C (infants, toddlers) were very common after vaccination, and most of these occurred at a similar rate in the control vaccine groups, where studied. Pyrexia greater than 38.0°C, six hours after vaccination, was observed in up to 20 percent of all infants aged 6–10 weeks receiving MeNZB™. However, most were apyrexial within 48 hours of vaccination.

After the fourth dose of MeNZB™ vaccine, there was an increase in the local reactions of erythema, induration and swelling. There was no increase in severe local reactions or systemic reactions.

In children and adults, very commonly reported adverse reactions include headache, malaise, nausea and myalgia.

Any severe or unexpected reactions should be reported to CARM, PO Box 913, Dunedin, using the prepaid postcard HP3442 (see section 2.4) or via online reporting at <http://carm.otago.ac.nz>. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

Table 15.3: Adverse reactions to MeNZB™ reported within seven days, all age groups

General disorders		Fever ≥ 38.0°C axillary
Very common	Infants	20%
	Infants/toddlers	13%
		Fever ≥ 38.5°C sublingual
Common	Children	3%
	Adults	0%

Injection site reactions		Redness	Swelling	Induration	Tenderness/pain
Very common	Infants	9%	4%	10%	47%
	Infants/toddlers	44%	25%	51%	56%
	Children	11%	7%	10%	78%
	Adults	16%	9%	17%	95%

Table 15.4: Additional reactions to MeNZB™ reported in infants (first year of life) and toddlers (second year of life) over all doses given

General disorders		Irritability	Change in eating habits	Impaired sleeping	Unusual crying
Very common	Infants	80%	35%	54%	44%
	Infants/toddlers	45%	21%	18%	1%

Gastrointestinal disorders		Diarrhoea	Vomiting
Very common	Infants	17%	13%
	Infants/toddlers	11%	8%

Table 15.5: Additional reactions to MeNZB™ reported in older children and adults over all doses given

General disorders		Malaise	Headache
Very common	Children	18%	23%
	Adults	21%	26%

Musculoskeletal, connective and bone disorders		Myalgia	Arthralgia
Common	Children	9%	6%
	Adults	19%	2%

Gastrointestinal disorders		Nausea
Common	Children	9%
	Adults	13%

15.7 Contraindications

15.7A Meningococcal polysaccharide vaccines contraindications

See section 1.9 for general contraindications for all vaccines.

The available data does not suggest that giving meningococcal vaccine to pregnant women causes any adverse effects. Nevertheless, as with any vaccine in pregnancy, careful consideration of the risks and benefits of immunisation to the mother and fetus is needed. Maternal antibodies will protect the newborn for the first few months, and the subsequent response to the vaccine is not altered.⁶⁰

15.7B Group C meningococcal conjugate vaccine contraindications

Anaphylaxis to a previous dose of the vaccine or any of the components is a contraindication to a further dose.

15.7C MeNZB™ contraindications

Hypersensitivity to any component of the vaccine or persons having shown signs of hypersensitivity after previous administration of MeNZB™ vaccine.

As with other vaccines, administration of MeNZB™ vaccine should usually be postponed in persons with an acute febrile illness (fever > 38.0 °C).

15.8 Control measures

All cases of invasive meningococcal infection should be notified immediately on suspicion to the local medical officer of health.

Adults and children in close contact with primary cases of invasive meningococcal infection should receive antibiotic prophylaxis, preferably within 24 hours of the initial diagnosis, but prophylaxis is recommended up to 10 days after contact. Those at particular risk include:

- household contacts (ie, people who have eaten or slept in the same house during the seven days prior to the onset of disease in the index case)
- early childhood service contacts
- those living in close contact in semi-closed communities and institutions
- individuals who have had contact with the patient's oral secretions through kissing or sharing food and beverages.

Prophylaxis is not routinely recommended for health care personnel unless there has been intimate contact with oral secretions (eg, as a result of performing mouth to mouth resuscitation or suctioning of the case, before antibiotic therapy has started).

Chemoprophylaxis

The drug of choice for chemoprophylaxis is rifampicin. The recommended dose is 10 mg/kg (maximum dose 600 mg) every 12 hours, for two days. Some experts recommend four doses of 5 mg/kg per day over two days for infants under one month of age. Rifampicin causes orange discoloration of urine, sputum and tears, and staining of soft contact lenses. The colour change in body secretions is harmless, but patients should be warned and advised not to wear soft contact lenses. Rifampicin increases the hepatic metabolism of oral contraceptives, and women on these should be reminded of the seven-day rule (ie, extra contraceptive precautions during the antibiotic course and for seven consecutive days while taking the active pills after completion of the antibiotic course).

A single dose of intramuscular ceftriaxone (125 mg for children under 12 years of age and 250 mg for older children and adults) has been found to have an efficacy equal to that of rifampicin in eradicating the meningococcal group A carrier state. Ceftriaxone is the drug of choice in a pregnant woman because rifampicin is contraindicated in pregnancy. Ceftriaxone may be reconstituted with lignocaine (according to the manufacturer's instructions) to reduce the pain of injection. A New Zealand study demonstrated that ceftriaxone and rifampicin were equivalent in eliminating naso-pharyngeal carriage of *N. meningitidis* serogroup B.⁶¹

Ciprofloxacin given as a single oral dose of 500 mg is also effective at eradicating carriage. Ciprofloxacin is not generally recommended for individuals under 18 years of age or for pregnant and lactating women because the drug causes cartilage damage in immature laboratory animals. However, an international consensus report concluded that ciprofloxacin could be used for chemoprophylaxis of children when no other acceptable alternative therapy is available.⁶²

Use of group C meningococcal vaccines for close contacts

Close contacts of cases of group C meningococcal disease should be offered a group C containing meningococcal vaccine (see recommendations for the polysaccharide A, C, Y, W135 vaccine and for the conjugate vaccine). (See below for the use of the vaccines in the control of outbreaks.)

Other vaccine serogroups

The group B meningococcal vaccine, MeNZB™, is not used in outbreak control. The requirement for multiple doses means the vaccine offers no benefit in preventing early disease. Group A vaccines have been used in control. (See section 15.3.)

Outbreak control

When there is an outbreak of meningococcal disease of a vaccine serogroup, the medical officer of health and Ministry of Health assess the epidemiology of the cases. When there are three or more confirmed or probable cases of meningococcal disease of the same serogroup in a community or institution within a three-month period, and the overall rate reaches or exceeds 10 cases per 100,000, then an immunisation programme may be recommended to a defined population.⁶³ The population in a community outbreak is the smallest geographically defined region in which the cases live, and the size of the population is determined from census data. The cases should not be close contacts or linked by common affiliation; that is, they should all be primary cases. In an institutional outbreak, a vaccine programme may be considered if two cases are identified in a three-month period.

For more details on control measures, refer to the *Control of Communicable Diseases Manual*.⁶⁴

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