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Group B Meningococcal Disease in New Zealand: Epidemiology and Prevention

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About the Experts

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Dr Stewart Reid

Stewart Reid is a semi-retired GP who has considerable vaccinology experience. With regards to meningococcal disease, he was involved in the New Zealand serogroup B meningococcal vaccine initiative and designed the safety monitoring programme for the rollout of MeNZB™ vaccine. He was involved in the first five editions of the immunisation handbook and has 35 papers on vaccine issues published in peer reviewed journals.

This publication is intended as an educational resource for healthcare professionals. It reviews risk factors, incidence and burden associated with meningococcal disease, focusing on the New Zealand setting. Vaccines available for meningococcal disease in New Zealand are discussed, including an in-depth review of 4CMenB (BEXSERO®), the only vaccine available in this country for group B disease.

Introduction

Meningococcal disease is a bacterial infection caused by *Neisseria meningitidis*.[1] The most common manifestations are meningitis and septicaemia.[1] Meningococcal disease has a case-fatality rate of up to 10% in developed countries, even with rapid treatment.[2] The disease can easily be misdiagnosed and death can occur within 24 hours.[3] All age groups are susceptible to meningococcal disease, however infants are much more likely to be infected compared with the general population.[1,4] Up to 20% of survivors of meningococcal disease have permanent sequelae, including brain damage, hearing loss and limb amputation.[5]

At least 13 different strains of *N. meningitidis* have been identified, with serogroups A, B, C, X, W and Y most likely to cause disease.[2] Patterns of serotype distribution vary across the world.[2] In New Zealand, group B strains are the most prevalent, although isolated outbreaks of groups A and C have occurred, and an increase in group W disease has recently been noted.[6,7]

While vaccines for meningococcal groups A, C, Y and W have been available in New Zealand for a number of years, no vaccine for group B disease has been available here since 2008.[1,6] In July 2018, a multi-component meningococcal group B vaccine (4CMenB; BEXSERO®) was approved for use in New Zealand,[8] following earlier approvals in Europe, the US and Australia, and has been available in New Zealand since October 2018.

Risk factors

Infants have the highest risk of meningococcal disease of any age group, with children aged <5 years and adolescents aged 15-19 years also at increased risk.[1,4,6] During the meningococcal B epidemic that occurred in New Zealand between 1991 and 2007, approximately 80% of cases were in individuals aged 0-19 years, and approximately 50% in children aged <5 years.[9]

In New Zealand, Māori and Pacific peoples remain at increased risk of contracting meningococcal disease compared with other ethnic groups.[1,6,10] Very large ethnic differences in disease rates were noted during the New Zealand meningococcal B epidemic years.[11] The highest rates of meningococcal disease (approximately 70% of all cases) have generally been observed in the northern part of the North Island.[10]

Other risk factors for meningococcal disease include crowded living conditions, exposure to tobacco smoke, and recent or current upper respiratory tract infection.[12] Infants and children who attend early childhood education centres, and adolescents who live in boarding schools, hostels or university residences, are at increased risk of infection.[1,6]

Individuals who have been in close contact of someone with meningococcal disease are at risk.[1,6] This includes health professionals as well as microbiology laboratory staff working with samples from infected patients.[1,6] Individuals who are immunocompromised as a result of immune system disorders, medical treatment or asplenia also have an increased risk of acquiring meningococcal disease.[1,6]

Incidence

In New Zealand, the number of cases of meningococcal disease has been rising since 2014.[7,13] In 2017 and 2018, 112 and 120 cases were notified, respectively.[7] While Group B strains continue to be the most prevalent, there has been a significant increase in cases of the group W strain over this period, including the virulent sequence type ST-11.[13]

Figure 1 shows the number of meningococcal disease cases notified between 1970 and 2018.[7] Between 1970 and 2018, there have been four outbreaks of meningococcal disease in New Zealand. The first occurred between 1985 and 1986 in Auckland, and was caused by the group A serotype.[14] The notification rate during this epidemic was 8.3 cases/100,000 total population (145 cases) and the case-fatality rate was 7%.[14]

Between 1991 and 2007, a second epidemic of meningococcal disease occurred, largely due to the group B subtype B:4:Pa.7b,4.[15] By the end of this period, 6128 cases had been reported, and the case-fatality rate was 4.1%.[11] The highest annual notification rate was 17.4 cases/100,000, recorded in 2001.[11]

To control the epidemic of meningococcal B disease, a national immunisation programme was delivered between 2004 and 2008. The programme used a tailor-made vaccine against the epidemic strain B:4:P1.7b,4 (MeNZB™),

and aimed to vaccinate all under 20-year-olds in New Zealand.[16] A vaccine coverage rate of 81% of eligible individuals was achieved.[17] Effectiveness of the vaccine was estimated to be 73-77%.[17,18] An estimated 210 cases of disease, 6 deaths and 15-30 cases of severe sequelae were avoided between July 2004 and December 2008 as a result of the MeNZB™ vaccine.[17]

A community outbreak of Group C meningococcal disease occurred in Northland in 2011.[19] The notification rate amongst individuals aged <20 years was 27.6 cases/100,000 population (6 cases) in the Whangarei district and 17.6 cases/100,000 population (8 cases) for the Northland District Health Board region.[19] The case-fatality rate was 33%.[19]

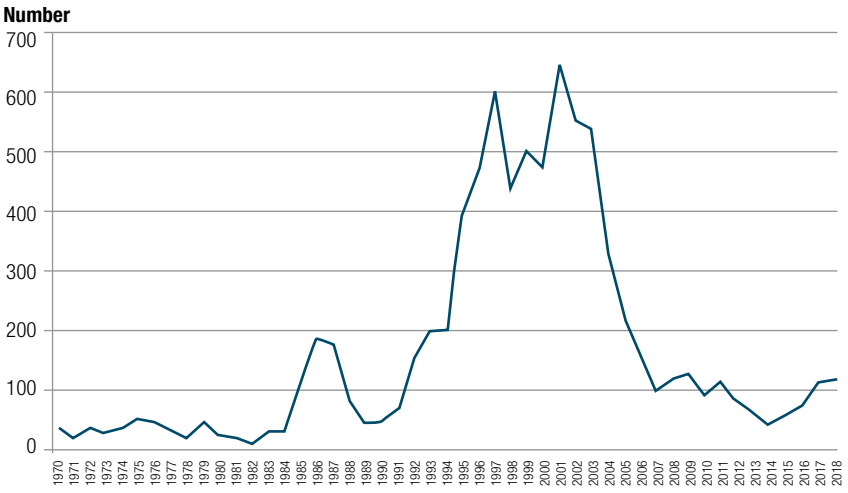


Figure 1. Notified cases of meningococcal disease, 1970-2018 (modified from Ministry of Health Immunisation Handbook 2017 and Institute of Environmental Science Invasive Meningococcal Disease Reports 23 November 2018 and 23 January 2019)[1,7,20]

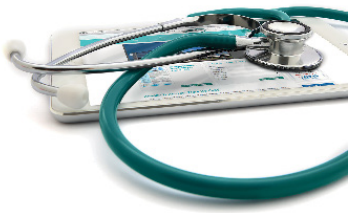
In 2018, 33 laboratory-confirmed cases of group W meningococcal disease were reported, compared with a total of 12 cases in 2017 and 5 in 2016.[20,21] There was notable increase in cases reported in Northland, from 1 case in 2017 to 7 cases in 2018, constituting a community outbreak in that region.[20,22] The national case-fatality rate for group W disease in 2018 was 18.2%.[20]

Burden of disease

Meningococcal disease has the highest fatality rate of any vaccine-preventable disease, except for rabies.[23] The case-fatality rate is up to 10% in developed countries, and even higher in developing countries.[2] Serious sequelae are found in up to 20% of individuals who survive meningococcal disease, including limb loss, cognitive impairment, developmental delays and focal neurological deficits.[5] Hearing loss and psychological disorders, including attention-deficit/hyperactivity disorder, are more common in children who survive meningococcal disease compared with unaffected children.[24]

A recent systematic review of 17 studies conducted in high-income countries (Western Europe, Canada, US, Australia and New Zealand) found that individuals with meningococcal disease had a significantly increased risk of death at hospital discharge, within 2 years of the disease and up to 30 years after the disease.[24] Lower overall quality of life was observed in survivors of meningococcal disease vs controls.[24] A prospective cohort study from Denmark found that child and adolescent survivors of meningococcal disease had lower income at the age of 30 years compared with controls.[25]

In a 2018 global systematic review of 14 studies examining the costs of meningococcal disease, mean costs (in International Dollars) of acute admission ranged from $1629 to $50, 796, with an incremental cost of $16,378.[26] Mean length of hospital stay was 6-18 days.[26] Average costs for readmissions ranged from $7905 to $15,908.[26]



Expert comment: Dr Sharon Wong

Meningococcal disease continues to be a major international public health concern. Early clinical disease can be difficult to differentiate from other more common infectious diseases and the diagnosis should be considered in an unwell individual. Meningococcal disease typically presents as septicaemia and/or meningitis and varies in severity with the age of the case and stage of the illness. Signs and symptoms may be non-specific but the illness has the ability to rapidly advance to include an altered level of consciousness and multi-organ failure.

The majority of cases occur in healthy individuals although certain underlying conditions such as complement deficiencies or hyposplenism predispose to meningococcal disease. Meningococcal disease in New Zealand reflects the pattern of disease seen worldwide, with infants and young children at greatest risk of disease and another peak occurring in adolescents. Most meningococcal disease cases occur throughout the winter and spring seasons each year from June to November. Ethnic disparities are recognised in New Zealand with rates disproportionately higher in Māori and Pacific Peoples. Many infectious diseases are associated with poverty, and both Māori and Pacific ethnicities are additionally over-represented in the lower socio-economic groups. Household crowding is an important modifiable risk factor for meningococcal disease with other risks for children including the receipt of analgesia presumably for recent illness; attendance at social events; household smokers; sharing food, drink or a pacifier; and having a member of the household with prior respiratory symptoms.

Sequelae following meningococcal disease can include hearing loss, neurologic impairment, skin grafting or amputation, and mortality tends to be higher in cases with sepsis. In addition to the costs of initial hospitalisation and treatment of meningococcal disease, there are costs associated with ongoing treatment and rehabilitation as a result of complications, and human costs related to mortality and decreased quality of life.

Expert comment: Dr Stewart Reid

New Zealand epidemiology for invasive meningococcal disease over the last 35 years is very interesting. As with other developed countries, the background incidence is 1-3 cases per 100,000 population per annum and that is where the current rate stands. However, there have been two significant epidemics in this time period: the Group A outbreak, predominately in Auckland in the mid-1970s; and the major epidemic of the strain-specific group B disease from 1991 until 2008. Both of these epidemics led to vaccination campaigns which contributed to the decline in disease incidence. Those of Pacific and Māori ethnicity have an increased incidence of invasive meningococcal disease as noted above. The suggestion is that there is an increased ethnic susceptibility to invasive disease. I do not believe this is the case but consider that ethnicity is a marker for other risk factors such as household crowding. In general, for most infections, lower socioeconomic group status is a marker for increased incidence. I consider this is the reason for the increased incidence in those of Māori and Pacific ethnicity.

Prevention

A multi-component meningococcal group B vaccine (4CMenB; BEXSERO®) is now available in New Zealand for active immunisation in individuals at least 2 months of age, against invasive disease caused by *N. meningitidis* group B strains.[8] 4CMenB contains three surface-exposed recombinant proteins - factor H Binding Protein (fHBP), Neisseria adhesion A protein (NadA), Neisseria Heparin Binding Antigen fusion protein (NHBA) and outer membrane vesicles from the *N. meningitidis* group B strain NZ98/254 (NZ OMV) with PorA 1.4 antigenicity.[8]

No other meningococcal B vaccines are available, after the MeNZB™ vaccine, made for the national meningococcal B immunisation programme of 2004-2008, was withdrawn.[1] Other vaccines available for prevention of invasive meningococcal disease in New Zealand are the quadrivalent meningococcal conjugates MCV_4-D (MENACTRA®) and MCV_4-T (NIMENRIX™) and the meningococcal group C conjugate MenCCV (NEISVAC-C®).[1] MCV_4-D and MCV_4-T protect against groups A, C, Y and W135 disease, and are licensed for individuals aged 9 months to 55 years and 12 months to 55 years, respectively.[27,28] MenCCV is a conjugate meningococcal C vaccine licensed for use in individuals from 8 weeks of age.[29]

Current recommendations and funding for meningococcal vaccines

At present no meningococcal vaccines are included on the National Immunisation Schedule, although a targeted vaccination programme for group W disease was implemented in December 2018 for Northland children aged 9 months to ≤5 years and 13 years to <20 years.[22] In addition, MCV_4-D and MenCCV are funded by Pharmac for use the following cases:

- Children and adults pre/post-splenectomy or with functional asplenia
- HIV-positive individuals
- Individuals with inherited or acquired complement deficiency
- Pre/post solid organ transplantation
- Following stem cell/bone marrow transplantation
- Following immunosuppression lasting >28 days
- Close contact with a meningococcal disease case.[1]

Meningococcal vaccines are also recommended (but not funded) in the following cases:

- Adolescents and young adults living in close proximity to each other (eg. boarding school, university halls of residence, long-term institutional care)
- Travellers to high-risk countries and Hajj pilgrims
- Laboratory workers regularly exposed to meningococcal cultures.[1]

Vaccination should also be considered for non-high risk infants and children aged <5 years, and adolescents aged 15-19 years.[1]

4CMenB

4CMenB was first registered for use in the EU in 2013, and is now licensed for use in more than 41 countries worldwide. 4CMenB is part of the publicly funded national immunisation programme in the UK, Ireland, Italy and South Australia.[30,31]

Immunogenicity

A clinical development programme has demonstrated the immunogenicity and safety of 4CMenB in over 7000 infants, children, adolescents and adults.[32]

A protective response to all 4CMenB antigens was demonstrated in infants after administration of doses at 2, 4 and 6 months or 2, 3 and 4 months of age, allowing for a flexible vaccination schedule.[33] A booster dose in the second year of life increases antibody titres to protective levels.[34] There is some data to suggest a waning of antibody titres to PorA P1.4 and fHBP antigens in children aged 4 years who received the full primary series and booster dose of 4CMenB as infants,[35] however the clinical significance of this observation and the need for additional booster doses to maintain longer term protective immunity has not been established.[8] In infants aged >6 months and children, 4CMenB was immunogenic when administered as a two-dose primary series 2 months apart, with a booster dose recommended for those receiving the primary series <12 months of age.[8]

Concomitant administration of 4CMenB with combined diptheria, tetanus, acellular pertussis, inactivated polio, hepatitis B and *Haemophilus influenzae* type b vaccine (DTaP-HBV-IPV/Hib) and 7-valent pneumococcal glycoconjugate vaccine (PCV7) in infants, and measles-mumps-rubella-varicella vaccine (MMRV) in children aged 12 months, had no impact on the immunogenicity of either 4CMenB or the routine vaccines.[34] 4CMenB has also been administered concomitantly with a meningococcal group ACWY-CRM conjugate vaccine in infants aged 3 months to ≤13 months, and in adults, with no impact on the immunogenicity of either vaccine.[36,37] In addition, 4CMenB may be administered concomitantly with meningococcal group C-CRM conjugate.[8]

In adolescents, 4CMenB was immunogenic when given as a two-dose series at least 1 month apart.[38] Antibody persistence was demonstrated 4 years after the second dose.[39] A recent study demonstrated a decline in antibody titres at 4 and 7.5 years in adolescents and adults who had previously received two doses of 4CMenB, although titres to fHBP, NadA and PorA remained markedly higher than in vaccine-naïve individuals.[40] Response to a booster dose of 4CMenB in previously vaccinated adolescents was more robust than the response to a first dose in vaccine-naïve individuals, indicating effective priming with the two-dose vaccination series.[40]

A recently published phase 3 study confirmed that immunogenicity of 4CMenB is similar in children and adolescents with complement deficiencies, asplenia or splenic dysfunction to immunogenicity seen in healthy children.[41]

Safety

The safety profile of 4CMenB has been well characterised, with injection site pain and fever the most common adverse events in infants, and injection site pain, malaise and headache the most common events in adolescents.[32] Febrile seizures are an uncommon adverse event in infants and children (frequency ≥1/1000 to <1/100), and Kawasaki syndrome is a rare event (frequency ≥1/10,000 to <1/1000).[8,32] Concomitant administration of 4CMenB with routine infant and child vaccines increases reactogenicity to 4CMenB,[34] but this can be reduced by using prophylactic paracetamol.[42]

Postmarketing surveillance of 4CMenB for a 3-year period in Germany found that adverse events were similar to those reported during phase 2/3 trials.[43] Surveillance findings of 4CMenB have also been reported from Canada and the US following vaccination campaigns,[44,45,46] and from the UK following introduction of 4CMenB into the national immunisation programme.[47] No new safety signals have been identified in any of these reports.[44,45,46,47]

Effectiveness

Preliminary data on the effectiveness of 4CMenB are available from an observational cohort study of vaccine-eligible infants in England, conducted after initiation of the national immunisation programme.[48] Vaccine effectiveness was estimated at 82.9% (95% CI 24.1-95.2) after two doses by 6 months of age.[48] Compared with the pre-vaccine period, there was a 50% reduction in the incidence rate ratio of meningococcal B disease in the first 10 months of the immunisation programme (37 cases Sep 2015-June 2016 vs 74 cases average over the previous four Sep-June periods; p=0.0001).[48]

4CMenB has been successfully used to control an increased incidence of meningococcal B disease in a region of Quebec, Canada,[44,45] as well as at university campuses in the US.[46,49] In the Canadian campaign, 82% of the 59,000 targeted residents of the Saguenay-Lac-Saint-Jean region of Quebec aged between 2 months and 20 years were immunised with 4CMenB over an approximate 8-month period in 2014.[44] By the end of 2016, no cases of meningococcal B disease had occurred amongst vaccinated individuals, compared with 2 cases in unvaccinated adult residents and 1 case in an unvaccinated child visiting the region.[44] Multivariate analysis estimated the 4CMenB vaccination campaign significantly reduced the risk of meningococcal B disease (relative risk 0.22; 95% CI 0.05-0.92; p=0.04).[44]

Administration schedule

The recommended administration schedule for 4CMenB (BEXSERO®) is shown in **Table 1.**[8]

Age group	Primary immunisation	Intervals between doses	Booster
Infants 2-5 months*	Three doses of 0.5ml each, with the first dose given at 2 months of age	Not less than 1 month	1 dose in the second year of life with an interval of at least 6 months between the primary series and the booster dose
Infants 6-11 months	Two doses each of 0.5ml	Not less than 2 months	1 dose in the second year of life with an interval of at least 2 months between the primary series and the booster dose
Children 12 months to 10 years	Two doses each of 0.5ml	Not less than 2 months	Need not established
Adolescents (from 11 years) and adults**	Two doses each of 0.5ml	Not less than 1 month	Need not established

Table 1. Recommended 4CMenB (BEXSERO®) administration schedule.[8]

* The safety and efficacy of 4CMenB in infants <8 weeks of age has not yet been established. No data are available.

** The safety and efficacy of 4CMenB in individuals aged >50 years has not been established.

Use of prophylactic paracetamol in children aged <2 years is recommended by the Immunisation Advisory Centre to help manage post-4CMenB fever.[50] Similar recommendations have been made by the Australian Technical Advisory Group on Immunisation and by Public Health England.[51,52]

Expert Comment: Dr Sharon Wong

Primary intervention by vaccination is the most effective medical intervention for epidemic control of infectious diseases, but the availability of an effective vaccine is essential. The major pathogenic *N. meningitidis* serogroups in humans are A, B, C, Y and W135. Polysaccharide and protein conjugate vaccines have been developed against these serogroups with the exception of serogroup B.

The development of serogroup B meningococcal vaccines has been challenging due to the polysaccharide capsule of serogroup B meningococci being poorly immunogenic and being similar to fetal human brain tissue glycoproteins. As a result of these difficulties, innovative techniques have been required for the development of serogroup B vaccines. Outer membrane vesicle (OMV) vaccines have been used in a number of countries, including New Zealand. PorA (class 1) outer membrane proteins of *N. meningitidis* play an important role in the immune response following meningococcal carriage, invasive disease and immunisation by serogroup B OMV vaccines. Following on from this, recombinant meningococcal serogroup B vaccines were developed. 4CMenB, a recombinant quadrivalent vaccine, containing three recombinant serogroup B surface proteins and an inactivated OMV component from the New Zealand group B epidemic strain, covers a broader range of serogroup B subtypes. If introduced into the New Zealand infant immunisation schedule, it has to be noted that trials have been conducted with the vaccine administered at different time points. Additional public education regarding reactogenicity will also be required.

Meningococcal vaccines have typically demonstrated less immunogenicity in infants, the age group in whom the incidence of meningococcal disease is the highest, compared with older children and adults. Immunogenicity often wanes rapidly and in infants a booster dose is required to maintain protection throughout a period that they remain at high risk of disease. Intervention by vaccination will be most effective when given to infants. When meningococcal vaccines are administered concomitantly with routine vaccines in national immunisation schedules, it is important that the response (immunogencity and reactogenicity) to routine antigens is additionally investigated. Meningococcal vaccines against serogroups A, B, C, Y and W are currently available in New Zealand and are recommended for high-risk individuals and in special circumstances.

Expert comment: Dr Stewart Reid

Meningococcal vaccines are generally manufactured using the capsular polysaccharide of the various groups as the target antigen. To enable use in those aged less than 2 years these polysaccharides are conjugated to protein carriers. This means that they are immunogenic in those aged less than 2 years and allow T cell-dependent immune responses resulting in immune memory. Because the group B capsule is very similar to human nervous tissue, the capsular polysaccharide of group B is not a suitable target and instead outer membrane proteins have to be used. These are highly variable but because the New Zealand group B epidemic was dominated by a single subtype it was possible to make an outer membrane protein vaccine specifically against that type, MeNZB™.

To get around the problem of variable outer membrane proteins, the developers of group B vaccines sought target outer membrane proteins which are common to many group B meningococci. This resulted in the quadrivalent vaccine 4CMenB, which is immunogenic against a wide range of group B meningococci. This vaccine includes the New Zealand PorA outer membrane protein in addition to three other more generic proteins. With MeNZB™ the decline in immunogenicity was quite rapid, particularly in those vaccinated in infancy, and so a concern with 4CMenB was that the protection would be relatively short lived. However, with a booster dose in the second year of life, a protective immune response against at least two of the antigens is sustained until at least age 4 years, with some waning seen against PorA P1.4 and fHBP. Data from the UK should help determine whether this waning of antibody is clinically significant – 4CMenB was introduced there in September 2015 in a three-dose schedule at 2, 4 and 12 months of age. We will see whether protection is sustained during the first 5 years of life, when the incidence of meningococcal disease is at its highest.

The protein conjugate polysaccharide vaccines against the other meningococcal groups have clear indications in the NZ handbook as outlined above. Their inclusion in the routine childhood schedule will depend on the incidence of disease in New Zealand and the cost effectiveness of a universal vaccine campaign. Currently it is important that they are used in the specified high-risk groups, and they should be offered to teenagers and young adults who will be living in close proximity to each other. In general for this risk, I would recommend the MCV-D or MCV-T vaccine. Ideally, 4CMenB should be offered as well to give the broadest protection possible.

Clinical studies

Meningococcal B disease epidemic 1991-2007 and immunisation programme[11]

The epidemic of meningococcal B disease in New Zealand between 1991 and 2007 was successfully curbed by a national immunisation programme started in 2004 using a vaccine tailor-made for the epidemic strain, MeNZB™.

A total of 6128 cases of meningococcal disease were notified in New Zealand between 1991 and 2007. This was an excess of 5261 cases over the number that would have occurred had the pre-epidemic average of 51 cases per year (incidence 1.5/100,000) continued. The overall case-fatality rate over the epidemic period was 4.1%. The highest annual notification rate of 17.4 cases/100,000 was recorded in 2001.

Infants consistently had the highest age-specific disease rates during the epidemic period, with a peak rate of 212/100,000 in 1997. Age-standardised rates of disease for Māori and Pacific peoples showed large differences during the epidemic period compared with the rate for Europeans, with peak rate differences of 15.3 for Maori and 58.7 for Pacific peoples in 1997.

In 2001, the peak year of disease incidence, 80.1% of confirmed cases of meningococcal disease able to be strain typed were caused by the epidemic strain. Children aged <5 years, and particularly those aged <1 year, had the highest rates of epidemic strain meningococcal disease. After introduction of MeNZB™, the percentage of confirmed cases with the epidemic strain type decreased from 72.7% in 2004 to 52.2% in 2007 ($p<0.001$).

Age-specific rates of disease were decreased in all age groups ($p<0.001$) between 2004 and 2007, except the 30-39 year age group. Rates of disease were also decreased in all ethnic groups, with particularly marked reductions in Māori and Pacific peoples. A statistical model which controlled for confounding variables demonstrated a significant vaccine effect ($p<0.0001$), with estimated disease rates 3.7 times higher in the unvaccinated group than the vaccinated group, and a vaccine effectiveness of 73% (95% CI 52-85%).

Meningococcal disease in New Zealand; 2018[7,20]

In 2018, 120 cases of meningococcal disease were notified in New Zealand, including 10 deaths. In 2017, a total of 112 cases of meningococcal disease and 9 deaths were reported, and the number of cases has been rising since 2014, when only 45 cases were reported.

Despite a decrease from 67% of all laboratory-confirmed cases in 2017, group B strains of *N. meningitidis* still accounted for the highest proportion of meningococcal disease cases in 2018, at 45% of all cases. However, the proportion of cases attributed to group W strains markedly increased from 11% in 2017 to 29% in 2018. Other laboratory-confirmed cases in 2018 were attributed to group Y strains (14%) and group C strains (8.8%).

For group B notifications, the highest number of cases and rates of disease were reported in children aged ≤5 years and adolescents aged 15-19 years. When assessed by ethnicity, the highest rates of disease occurred in Māori and Pacific peoples. Group B notifications were highest in the Auckland region, with the Waitemata, Auckland and Counties Manukau DHBs reporting a total of 17 cases.

For group W notifications, cases were reported in all age groups except the 10- to 14-year age group. However, in the first half of 2018, 80% of cases occurred in individuals aged >20 years of European/other ethnicity, but from June 2018 only 50% of cases occurred in individuals aged >20 years and only 30% of individuals of European/other ethnicity. Of the 10 deaths reported in 2018,

6 were due to group W disease.

There was a notable increase in the number of group W cases reported in Northland in 2018, to 7 cases, compared with 1 case in 2017. This led to the Northland DHB reporting the highest overall rate of meningococcal disease in 2018, at 7.4 cases/100,000 (13 cases).

Case numbers of group Y disease have remained stable since 2017, after a gradual increase from 2013 to 2017, and continue to occur predominately in older adults of European/other ethnicity. Case numbers of group C disease remained low across all age groups and ethnic groups in 2018.

4CMenB in infants with or without routine vaccines[33]

A phase 2b European randomised controlled trial showed that 4CMenB was immunogenic against reference strains when administered to infants, was generally well tolerated and showed minimal interference with routine vaccines given in the first year of life.

The trial enrolled 1885 healthy infants aged 2 months, and randomised them to four vaccination groups in a 2:2:1:1 ratio according to the following schedule:

- 4CMenB given at 2, 4 and 6 months, together with routine infant vaccines (concomitant)
- 4CMenB given at 2, 4 and 6 months, with routine vaccines given at 3, 5 and 7 months (intercalated)
- 4MenB given at 2, 3 and 4 months, together with routine infant vaccines (accelerated)
- Routine infant vaccines alone, given at 2, 3 and 4 months.

Routine infant vaccines were DTaP-HBV-IPV/Hib and PCV7. All vaccines were administered by intramuscular injection in the anterolateral thigh. When 4CMenB and routine vaccines were given concomitantly they were administered in opposite limbs.

After three vaccinations with 4CMenB, ≥99% of participants had human complement serum bactericidal activity (hSBA) titres ≥5 against strains specific for fHBP and NadA. With the strain specific for PorA P1.4, the proportion of participants with hSBA titres ≥5 was 79% for vaccination at 2, 4 and 6 months with routine vaccines, 86.1% for vaccination at 2, 4 and 6 months without routine vaccines, and 81.7% for vaccination at 2, 3 and 4 months with routine vaccines. Responses to routine vaccines given with 4CMenB were noninferior to responses when given alone for all antigens, except for responses to pertactin and serotype B 6B pneumococcal polysaccharide.

Fever occurred following administration of 26-41% of 4CMenB doses given alone, compared with 23-36% following administration of routine vaccines alone, and 51-61% when 4CMenB and routine vaccines were given at the same time.

4CMenB in infants and children with primary and booster vaccination[34]

The immunogenicity of 4CMenB was confirmed in two phase 3 European trials, which investigated both the primary 4CMenB vaccination schedule in infants, concomitantly with DTaP-HBV-IPV/Hib and PCV7, and a booster dose at 12 months, either alone or concomitantly with MMRV.

A total of 3630 healthy infants aged 2 months were enrolled in the primary vaccination phase study, of whom 2627 were assigned to an immunogenicity substudy and 1003 to a safety substudy. All participants received DTaP-HBV-IPV/Hib and PCV7 at 2, 4 and 6 months. Those in the immunogenicity substudy were randomised to receive routine vaccines alone, or routine vaccines concomitantly with 4CMenB, while those in the safety substudy were randomised to receive 4CMenB or a meningococcal serogroup C conjugate vaccine (MenC). Participants who completed the primary vaccination phase study were enrolled in the booster study at 12 months of age (n=1555), and were randomised to receive a 4CMenB booster dose alone or concomitantly with MMRV.

After three vaccinations with 4CMenB, 100% of participants had hSBA titres ≥5 against strains specific for fHBP and NadA, and 84% had titres ≥5 against a strain specific for PorA P1.4. In a subset of participants, 84% had titres ≥5 against a strain specific for NHBA. At 12 months of age, waning titres were boosted by a fourth 4CMenB dose, leading to hSBA titres ≥5 against all antigens in 95-100% of participants, with or without concomitant MMRV.

Concomitant administration of 4CMenB had little effect on the immunogenicity of routine vaccines, but reactogenicity was increased. A fever of ≥38.5°C was noted in 77% of participants after any 4CMenB dose, compared with 45% after routine vaccines alone and 47% after MenC vaccination.

4CMenB in infants receiving prophylactic paracetamol[42]

Prophylactic paracetamol in infants effectively decreases fever and reactogenicity following concomitant administration of the 4CMenB vaccine and routine vaccines, without compromising immunogenicity, as shown by a European phase 2 randomised controlled trial.

The full trial of 1507 participants included 558 in whom the effect of paracetamol prophylaxis was examined. All participants received routine infant vaccines (DTaP-HBV-IPV/Hib and PC7) at 2, 3 and 4 months. In addition, 188 received concomitant 4CMenB, 184 received 4CMenB + paracetamol, and 186 received the MenC vaccine. At 12 months of age, all participants completing the initial vaccination series were given a booster dose of 4CMenB.

After three vaccinations with 4CMenB, 100% and 99% of participants had hSBA titres ≥5 against fHBP and NadA indicator strains, irrespective of the use of paracetamol. Titres of hSBA ≥5 against the PorA P1.4 indicator strain occurred in 75% and 78% of participants with and without the use of paracetamol, respectively. Immune responses to the booster dose of 4CMenB at 12 months were similar with and without the use of paracetamol. Concomitant use of paracetamol also had no clinically relevant effect on immune responses to routine vaccines, with the largest difference being a 6% lower rate of response to pertactin in the 4CMenB + paracetamol group compared with 4CMenB alone.

In participants who received 4CMenB, the incidence of fever ≥38°C within 3 days of vaccination with any primary dose was markedly reduced with the use of prophylactic paracetamol, from 70.3% to 39.1% of participants. Fever >39.5°C was reduced from 3-5% of participants after any primary dose of 4CMenB to 1.1% with prophylactic paracetamol. The frequency and severity of local reactions to all vaccines was also reduced with prophylactic paracetamol.

4CMenB in adolescents[38]

The 4CMenB vaccine is protective against meningococcal B infection in adolescents when administered as two doses given 1-6 months apart, according to a phase 2b/3 randomised controlled trial from Chile.

The trial enrolled 1631 adolescents aged 11-17 years. In the primary phase, participants received either one dose, two doses 1 month apart, two doses 2 months apart, or 3 doses of 4CMenB, or three doses of placebo. In the second phase at 6 months, participants previously given one or two doses of 4CMenB in the primary phase received either 4CMenB or placebo.

After one dose of 4CMenB, 93-96% of participants had hSBA titres ≥4 against strains specific for fHBP, NadA and PorA P1.4. After two doses of 4CMenB, this percentage increased to >99% of participants ($p<0.0001$ compared with one dose for all antigens), irrespective of the time interval between doses. A third dose of 4CMenB had a small incremental effect on geometric mean titres of hSBA, but did not increase the proportion of participants achieving protective titres. Waning of all antibody titres was evident 2 months after the first dose of 4CMenB, but the second or third dose given at 6 months re-established hSBA titres ≥4 in 99-100% of participants. ELISA testing showed that NHBA had a similar pattern of response to 4CMenB as the other tested antigens.

Overall, there was a higher rate of local and systemic reactions in participants who received 4CMenB compared with placebo, but the reaction rate did not increase with subsequent 4CMenB doses. The most common local reaction was pain, with severe pain occurring after 17% of 4CMenB injections compared with 4% of placebo injections ($p<0.0001$). The most common systemic reactions were malaise and headache, occurring after 51% and 42% of 4CMenB injections, respectively, compared with 30% and 27% of placebo injections (both $p<0.0001$). Fever of ≥38°C occurred after 4% of 4CMenB and 2% of placebo injections ($p<0.0001$).

EXPERT'S CONCLUDING COMMENTS: DR SHARON WONG

Most meningococcal disease worldwide is caused by serogroups A, B and C. Epidemics caused by serogroups A and C have an abrupt onset and tend to last from one to three years. In contrast, outbreaks of meningococcal B disease generally develop gradually with an increase in disease rates over several years and may continue for one to two decades.

Meningococcal disease surveillance, based on compulsory notification coupled with laboratory data, has shown that most meningococcal disease in New Zealand has been caused by serogroup B and to a lesser extent by serogroup C. A serogroup B meningococcal epidemic, dominated by strain B:4:P1.7-2,4, from 1991 to 2007, resulted in more than 6000 cases and approximately 250 deaths. Smaller outbreaks of meningococcal disease have also occurred in localised areas including several serogroup C outbreaks and an outbreak of serogroup A meningococcal disease in Auckland from 1985 to 1986. Ongoing monitoring of the meningococcal epidemiology in New Zealand is imperative. The notified disease rate in New Zealand has been rising since 2014, and is currently higher than rates in the two years prior to the serogroup B epidemic. Is New Zealand heading for another outbreak of meningococcal disease?

The large New Zealand serogroup B meningococcal epidemic led to the development of a meningococcal B OMV vaccine against the epidemic strain. This strain-specific vaccine, MeNZB™, was used in a nationwide vaccination programme from 2004 to 2008 for epidemic control. Other components of disease control have included meningococcal awareness in the community; education of health professionals; parenteral anti-microbial treatment of suspected cases prior to transfer to hospital; and notification to the relevant authorities with contact identification for chemoprophylaxis.

New vaccine technology has been developed since New Zealand's vaccination programme in response to the meningococcal epidemic and having a safe, effective vaccine available is an important tool for meningococcal disease control. Ideally, any vaccine should be given in infancy and funded in order to protect those at highest risk of disease.

EXPERT'S CONCLUDING COMMENTS: DR STEWART REID

The introduction of 4CMenB into the routine schedule presents some challenging issues. Firstly, should two or three doses be offered in the first 6 months of life. The data sheet recommends three doses but the UK schedule is two doses given at 2 and 4 months of age. Secondly, 4CMenB would increase the number of injections per visit to three on some visits. There may be some resistance to this. Whichever schedule is used, a booster dose in the second year of life will be required. Given that there are already four injections at 15 months of age (MMR, Varicella, Hib, PCV) would a fifth injection be acceptable or should another visit be introduced, probably at 12 months of age? The recommendation to give prophylactic paracetamol with 4CMenB differs from the current situation in New Zealand where paracetamol is given only as required. This change would require education and reassurance that there is no significant interference in immune response to any of the antigens.

If the vaccine is not added to the routine immunisation schedule, what is the potential private market for this vaccine? In my view the need for this vaccine is greatest in those aged less than 5 years, with the first doses to be given in infancy. Alas I expect the inverse care law will apply; those most in need are least likely to receive it. Given that those in the lower socioeconomic groups are at highest risk for invasive meningococcal disease they are the least likely to be able to afford the vaccine. As stated above it could be offered to those teenagers and young adults who are going to be living in close contact with others.

In summary, 4CMenB is an important addition to the vaccines available against invasive meningococcal disease.

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