

2012 Antigen Review for the New Zealand National Immunisation Schedule: Meningococcal B and C

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Executive summary

Neisseria meningitidis is the causative agent of meningococcal disease. The organism is only found in humans and is a commensal carried in the nasopharynx of approximately 10% of the population although this is age-dependent. The meningococcal population is highly diverse and isolates from invasive meningococcal disease represent only a small sub-set of this overall population. The polysaccharide capsule of invasive meningococci is the major virulence factor and is used both to serotype the organism and as a vaccine antigen. The traditional polysaccharide vaccines are poor immunogens in infants under two years old, which stimulated the development of conjugate vaccines in the 1990s. Conjugate vaccines have been developed for four (A, C, W135 and Y) of the five major serogroups. Group B vaccines based on outer membrane surface proteins are currently in development and being trialled with one under approval processes in a number of countries as of early 2013.

The objectives for this review have been informed by the general specifications and the specific specification for the 2012 antigen review. Information about the epidemiology in NZ is derived from annual reports from ESR.

This report summarises the some of the key data for meningococcal vaccines and vaccination published between 2009 and 2012.

Epidemiology in New Zealand

Since 2008, the number of invasive meningococcal disease cases has remained above the level prior to the meningococcal B epidemic. The majority of cases occurred in the northern regions of the North Island, with high rates in Northland due to a community outbreak of group C in that region. Infants aged less than one year have the highest rates of disease, with a secondary peak occurring in the 15–19 year old age group. Māori and Pacific Peoples have higher rates compared with the European or Other ethnic group, and this is most marked in infants under one year of age group. Meningococcal disease rates are higher in the most socioeconomically deprived group compared with less socioeconomically deprived groups.

Group B strains are still the most prevalent, causing over 60% of the cases. In 2011, the epidemic B:P1.7-2,4, was responsible for 37% of all meningococcal disease. The number of cases of meningococcal disease caused by group C strains has increased since 2007, largely due to the increase in one particular strain, C:P1.5-1,10-8. Vaccination with the C conjugate vaccine can protect against all C strains and has been used to control community outbreaks of meningococcal disease.

Safety

The polysaccharide vaccines have been in use for many decades and there are no new issues arising concerning their reactogenicity profiles or associated adverse events. However, as with the pneumococcal polysaccharide vaccines, the polysaccharide vaccines have been associated with irreversible hyporesponsiveness.

The group C conjugate vaccines have not been associated with any new safety concerns over the past four years. Studies evaluating their concomitant use with other scheduled vaccines have not identified any safety concerns in any age groups. A Cuban BC vaccine used widely in the Americas appears to have an acceptable safety profile in all age groups.

There is now a group B vaccine (4CMenB) with large scale clinical trial data to support its use and licensure has recently been granted in Europe. Safety data for the 4CMenB vaccine (Bexsero®) suggests that compared with some other childhood vaccines, it is relatively locally reactogenic and possibly more pyrogenic. No concerns about serious adverse events (SAE) have been identified. However, febrile seizures have occurred in temporal association with this vaccine. While these simple febrile seizures usually resolve without complications, this is an issue that will need to be monitored should this vaccine be considered for use in NZ and consideration given to additional communication with health professionals and parents.

Immunogenicity, efficacy and effectiveness

The irreversible hyporesponsiveness associated with polysaccharide vaccines has resulted in the cessation of their use as booster vaccines in clinical trials assessing anamnestic immune responses. All three internationally licensed conjugate vaccines demonstrate adequate immunogenicity in infants with either two dose or three dose primary schedules. The magnitude and persistence of antibodies following tetanus toxoid (TT) conjugated vaccine appears to be superior to those observed following diphtheria toxoid (D) or CRM₁₉₇ conjugates. However, all vaccines show adequate immunogenicity responses and differences in immunogenicity have not been shown, to date, in effectiveness.

The decline over time since vaccination in protective antibody levels is dependent on the age at which the vaccine was received, except in infants immunised at a young age where a rapid decline over time in antibody levels is seen. There is generally a higher response to group C vaccine when given as a monovalent vaccine as opposed to a quadrivalent vaccine.

In cases of vaccine failure, it is assumed to be due to the rapidity of disease progression due to low serum antibody levels rather than a lack of immunological memory indicating that booster doses are required to maintain individual protection. There is no evidence available for efficacy of conjugate vaccines in older adults.

Conjugate vaccines provide excellent herd immunity. The conjugate group C vaccines demonstrate a significant effect on carriage, which has been shown consistently in populations who have introduced these vaccines, and disease has been effectively controlled in many countries. Despite falls in serum antibodies, over time, the impact of conjugate vaccines on the incidence of disease suggests the reduction in carriage is a major determinant of the overall vaccine effectiveness. The duration of protection provided to the population receiving conjugate vaccines is based on a combination of herd immunity and individual levels of serum bactericidal antibody (SBA).

The Cuban BC polysaccharide-OMV vaccine has been widely used internationally since the 1980s in the Americas, and its implementation has resulted in excellent control of meningococcal disease. Herd immunity has also been demonstrated to be associated with its use.

Late-phase trials have investigated the immunogenicity profile for the group B 4CMenB vaccine Bexsero® and shown that protective levels of serum bactericidal antibodies are induced against a wide panel of group B serotypes in most vaccinees. There is not yet any effectiveness data for this vaccine.

Age-specific issues

The main burden of meningococcal disease in NZ is caused by group B and group C organisms. The under-one year olds are disproportionately affected by the disease, primarily, due to a lack of SBAs against meningococci. The 15-19 year olds also experience an increased risk of disease. Successful campaigns against group C meningococcal disease have been based on infant schedule vaccination associated with a mass catch-up campaign in children, adolescents and young adults.

Vaccinations against group C meningococci, in those aged below one year old, induce protective antibody responses, but the titres fall rapidly over time. A booster dose at 12 months induces protective antibody levels, but again the titres fall. Protection of this age group may be most effective by the use of herd immunity, as shown in those countries implementing a single dose schedule at 12 months old alongside a mass catch-up campaign.

Only conjugate vaccines can be effectively used in the infant age group. Polysaccharide vaccines may still be effective in the adult population for short term protection, although, hyporesponsiveness is a concern. Conjugate vaccines should be considered in preference to polysaccharide vaccines for all age groups in general as they overall elicit a better antibody response without hyporesponsiveness. No data on the efficacy of the conjugate vaccines in the over 65 year olds have been reported.

The 4CMenB vaccine has been evaluated in infants, children, adolescents and young adults groups and is immunogenic against the NZ epidemic strain of group C.

Options for scheduling

Based on NZ epidemiology, where the greatest burden of disease is in infants and young children and the second burden is on adolescents, there are three general options for the scheduling of group C vaccines:

1. An infant primary series (two or three dose) with or without a booster in the second year of life alongside a catch-up campaign.
2. A single dose at one year old (with or without booster) alongside a catch-up campaign.
3. Either of the above options with an early adolescent dose booster for longer term adolescent protection.

The option taken will be dependent on the local epidemiology of group C disease and a cost-benefit analysis.

Factors that may support not using a group C vaccine as a primary course in the early infant schedule include the relatively low incidence of group C disease in NZ, the superior immunogenicity of conjugate vaccines observed when administered to older infants and children and the associated reduced number of doses required. The herd immunity resulting from such a schedule may protect the younger infant age group. Given these issues, it may be pragmatic to use one or two doses of meningococcal C vaccine later in the first year of life or during the second year of life alongside a mass campaign to all children, adolescents and young adults to obtain herd immunity. Additional boosters for early adolescents may be also considered to offer on-going protection to this age group.

The larger burden of disease caused by group B, particularly in infants, supports that the best placement of a group B vaccine would be on the infant schedule, initially, at least until herd immunity is observed. At which time, moving it to an older age with fewer doses may be pragmatic and cost effective. The 4CMenB vaccine has been assessed for concomitant use with the other infant vaccines, including pneumococcal vaccine.

Implementation issues

If NZ moves to replace the use of polysaccharide vaccines with conjugate vaccines in high risk groups, consideration should be given to the communication required to providers for whom many there is still significant confusion about the different types of vaccine. Any increase in the number of separate injections may require consideration in terms of vaccinator education and possible schedule visits. Should a vaccine be considered for the adolescent programme, consideration needs to be given to resourcing issues for the school-based programmes.

The post implementation monitoring of both vaccine effectiveness and safety has been highlighted as vital part of a vaccination programme against meningococcal disease, and more so, should a group B vaccine be introduced. NZ already has in place excellent systems and infrastructure for monitoring the epidemiology of disease and vaccine safety.

Northland recently implemented a mass immunisation programme to control a community outbreak of group C and there are lessons on the factors that both enable and posed challenges for this campaign.

Communication is a vital issue and likely to be of particular relevance to outbreak control and any use of a group B vaccine. The 4CMenB vaccine appears to be more reactogenic than the current routine childhood vaccines and co-administration has the potential to affect perception of all childhood vaccines should significant febrile events occur frequently. Managing health professional and parental expectations around vaccine reactions will need to be considered carefully.

There are many countries that have included vaccination against meningococcal disease on their routine immunisation schedules, including the United States (US), Australia, United Kingdom (UK) and Canada. The next focus for meningococcal vaccines and vaccination is for group B.

2012 Antigen Review for the New Zealand National Immunisation Schedule: Meningococcal B and C

Prepared as part of a Ministry of Health contract

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This review is one of a series of 18 antigen reviews presented in 15 individual reports.

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Abbreviations

4-MCV	Quadrivalent meningococcal conjugate vaccine
ACIP	Advisory Committee on Immunisation Practices
AEFI	Adverse Event Following Immunisation
C-MCV	Group C meningococcal conjugate vaccine
D	Diphtheria toxoid
ESPID	European Society for Paediatric Infectious Diseases
GMT	Geometric mean titre
HBV	Hepatitis B vaccine
MCV	Meningococcal conjugate vaccine
MPV	Meningococcal polysaccharide vaccine
NP	Nasopharyngeal
NZ	New Zealand
OM	Otitis media
OMV	Outer Membrane Vesicle
SAE	Serious Adverse Event
TT	Tetanus toxoid
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization
WSPID	World Society for Paediatric Infectious Disease

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1. Background – meningococcal disease and vaccination

Neisseria meningitidis is a Gram-negative diplococcus only found in the nasopharynx of humans and is carried by approximately 10% of the population. The polysaccharide capsule is an important virulence factor and 13 serologically distinct groups of meningococci have been identified. The vast majority of disease is caused by five serogroups (A, B, C, W135 and Y). Vaccines to prevent meningococcal disease were originally based on the capsular polysaccharide, although some vaccines including the NZ-specific MeNZB™ vaccine and recombinant vaccines have used surface protein antigens as vaccine targets.

Vaccines which use just the capsular polysaccharide as immunogens are available for use in NZ (Mencevax® and Menomune®). Both vaccines cover meningococcal groups A, C, W135 and Y. These polysaccharide-only vaccines have a range of limitations, and to address those limitations, a number of vaccines have the polysaccharide (or oligosaccharide) chemically conjugated to an immunogenic protein such as tetanus toxoid (TT) or diphtheria toxoid (D). Menactra® is licensed for use in NZ and covers serogroups A, C, Y and W135, whereas, the vaccines Meningitec® and NeisVac-C® cover group C only. None of the meningococcal vaccines are currently on the immunisation schedule as of early 2013; however, vaccines are funded for at-risk groups, such as pre or post-splenectomy patients and for community outbreaks.

A meningococcal group B polysaccharide vaccine is not available, because the polysaccharide is poorly immunogenic and may result in cross-reactive antibodies. Like polysaccharide vaccines for other diseases, the meningococcal quadrivalent polysaccharide vaccines are less effective in children under two years of age as they do not induce memory nor do they provide sufficient protection against disease. For this reason, polysaccharide vaccines are not licensed for use in children less than two years of age.

A number of meningococcal vaccines are in development. These include tetravalent conjugate vaccines, using alternative proteins for conjugation (TT or a mutant form of diphtheria toxoid known as cross reactive material or CRM₁₉₇), group B vaccines based on surface antigens plus or minus outer membrane vesicles (OMV), and group C vaccines with alternative conjugate proteins (CRM₁₉₇).

The NZ meningococcal epidemic, which began in 1991, led to the development and implementation of a novel vaccine based on the NZ-specific epidemic strain B:4:P1,7-2,4. The decline in the epidemic, limited duration of immunity in infants and relatively low uptake led to the withdrawal of the vaccine in 2008, but the development of the MeNZB™ vaccine provided important data for the use of OMV in group B meningococcal vaccines.

Compared with the progress in vaccine development for many other diseases, the progress in the development of effective vaccines against meningococcal diseases has been relatively slow; meningococcus was first isolated well over 100 years ago and it is around 100 years since the first trials of whole-cell vaccines (1).

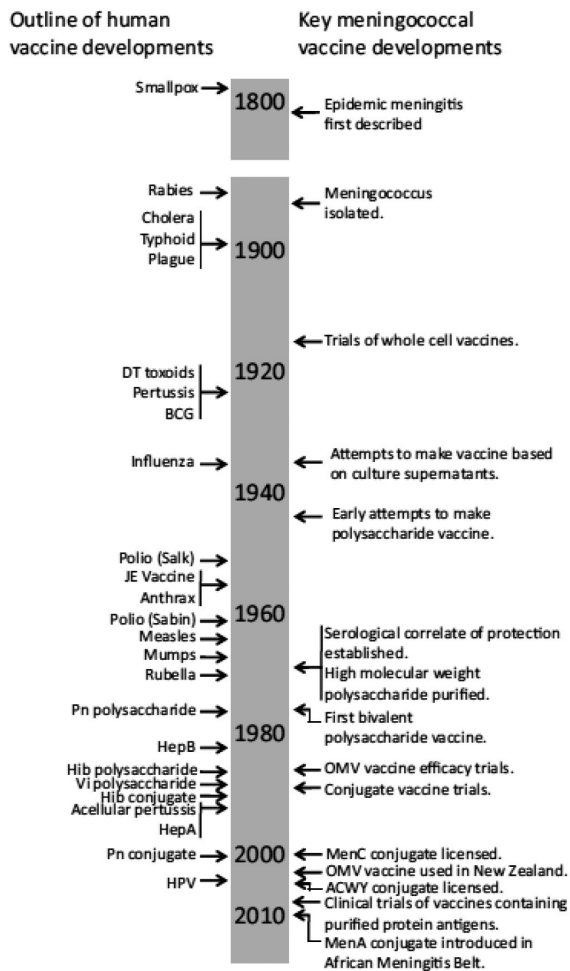


Figure 1. Outline of the development of meningococcal vaccines juxtaposed with key developments of human vaccines against other diseases, with permission from Vipond et al. (1).

The aim of this report is to summarise some of the key literature on meningococcal vaccines and vaccination that has been published within the past four years (2009 – 2012). During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.

2. Methodology for review

2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2012 NZ antigen review and the specific specifications for meningococcal vaccines. These are listed below. The dates for publication are from 2009 to 2012, according to the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around meningococcal vaccines for NZ.

- General specifications
 - Safety
 - Effectiveness
 - Implementation issues (practicality and possible impact on uptake)
 - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination
 - Different options of placement on the schedule, based on international findings and best practice
 - Different vaccine options and comparisons between the options
- Specific specifications for meningococcal
 - Summary of different schedule options as described in the literature.
 - Evidence for administering the vaccine programme as a universal programme and evidence for administering it as a targeted programme (for targeted programmes, evidence of which groups should be targeted).
 - Investigation of options for outbreak control.
 - Evidence for providing boosters.
 - Investigation of where an additional injection would be included in the schedule.
 - Eligibility considerations for at risk groups – for example young people living in halls of residence, crowded housing (Deprivation Index rating 9-10), chronic illness patients.
 - Duration of protection provided by vaccines.

Excluded in the scope of this review is literature published prior to 2009, cost benefit evaluations and recommendations for policy makers.

2.2 New Zealand Epidemiology

The NZ epidemiological information presented is based on national notification and laboratory-based surveillance. Notification data from 2007 - 2011 presented in this report has been updated to reflect those in EpiSurv as at 21 February 2012. The data in the report is derived from the 2011 annual report for Meningococcal Disease by ESR (2).

2.3 Literature search strategy

The points below have formed the focus of the literature search

1. Safety
 - a. Safety of meningococcal vaccine B and/ or C in infants.
 - b. Safety in older adults.
 - c. Anything new in safety over the past few years.
2. Effectiveness in disease control.
 - a. Children.
 - b. Adults.
 - c. Evidence of effectiveness in older adults.
 - d. Indirect effects/herd immunity.
 - e. Duration of protection.
3. Implementation issues (practicality of and possible impact on uptake).
 - a. Value of a catch-up/supplementary dose in infant schedule.
4. Differences that need to be considered for each age-group, for example the variable severity of disease and immunisation concerns that differ with age.
 - a. At-risk groups such as young people living in halls of residences.
 - b. Crowded housing (Deprivation Index rating 9-10).
 - c. Chronic illness patients.

Continued...

5. Different options for placement on the schedule, based on international findings and best practice.
6. Different vaccine options for each disease and comparison between the options.
7. Current international research and evidence around use of vaccines.
 - a. Consider this point covered in 1-6.

Other areas of special interest

- Different schedule options as described in the literature
- Evidence for administering the vaccine programme as a universal programme and evidence for administering it as a targeted programme (for targeted programmes, evidence of which groups should be targeted)
- Investigation of options for outbreak control
- Investigation of whether a booster dose would be included in the programme and if so, international evidence for when this should be administered
- Eligibility considerations for at-risk groups - for example young people living in halls of residences, crowded housing (Deprivation Index rating 9-10), chronic illness patients
- Duration of protection provided by vaccines

2.3.1 Medline search terms and strategy

MeSH term: Meningococcal Vaccines

1420

Limit to Humans, English, 2009 – current

354

NOT parent, physician, survey, interview, qualitative

336

MeSH term: Adverse Effects

101

Match 336 against 101

37

Safety as keyword

27 (keep and view)

MeSH term: Effectiveness

31 (keep and view)

2.3.2 Cochrane Library search terms and strategy

Search term meningococcal Vaccin*

Limit to Cochrane Reviews, Other Reviews, Trials
2009-present

1 result (keep and view)

2.3.3 Scopus search terms and strategy

Meningococcal AND Vaccin* Published 2011 – present
4629

Limit to: Medicine, humans, vaccination,
pneumococcus vaccine, journals

381

Exclude Letter, Short survey, editorial and erratum
173 (keep and view)

Reject social science articles. Delete duplicates

Endnote library 117

2.3.4 Grey literature

Conference abstracts were sought to include data that has not yet been published, particularly from the key infectious diseases conferences for 2011 and 2012 – European Society for Paediatric Infectious Diseases (ESPID) and the World Society for Paediatric Infectious Diseases (WSPID). No conference abstracts and posters were used as the pertinent studies were published by January 2013 and included in the review.

2.3.5 Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. A further 118 articles were accessed.

2.3.6 Final library

The final library includes 235 references. Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.

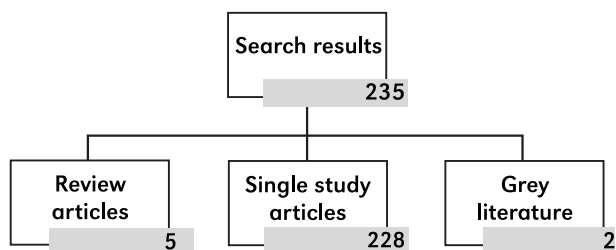


Figure 2. Flow of selection of articles for review

2.4 Participants/populations

The population considered for a universal programme are infants and children under two years of age, school aged children and adolescents. High risk age groups are infants and children under five years of age and adolescents 11 - 18. Catch-up programmes consider ages under 20 years.

Other high risk persons identified from the literature include:

- HIV-infected persons in the above age group.
- Persons aged two - 55 years with persistent complement component deficiency (such as C5–C9, properdin or factor D) or functional or anatomical asplenia.
- Persons aged two - 55 years with prolonged increased risk for exposure (microbiologists routinely working with *N. meningitidis* and travellers to or residents of countries where meningococcal disease is hyperendemic or epidemic.).
- College students and military personnel.

2.5 Interventions

The interventions included are:

- Meningococcal polysaccharide vaccines (MPV).
- Meningococcal conjugate vaccines (MCV).
- Other protein-based meningococcal vaccines.

The controls are placebo or another meningococcal vaccine. Some studies have used an unrelated vaccine or concomitantly administered vaccines.

2.5.1 Meningococcal polysaccharide vaccines

2.5.1.1 Mencevax® ACWY

Mencevax® A, C, W-135 and Y (GlaxoSmithKline) is a quadrivalent lyophilized preparation of purified polysaccharides from *N. meningitidis* groups A, C, W-135 and Y. Each dose contains 50µg of each of the polysaccharides. Excipients are sucrose, trometamol, sodium chloride and water for injection.

2.5.1.2 Menomune® ACYW-135

Menomune® ACW-135 and Y (sanofi pasteur Inc.) is a quadrivalent freeze-dried preparation of purified polysaccharides from *N. meningitidis* groups A, C, W-135 and Y. Each dose contains 50µg of each of the polysaccharides. Each dose in isotonic sodium chloride also contains 2.5-5.0mg of lactose.

2.5.2 Meningococcal conjugate vaccines

2.5.2.1 Meningitec® (group C conjugate vaccine using CRM₁₉₇ as the conjugate)

Meningitec® (Pfizer) is a conjugate vaccine against *N. meningitidis* serogroup C oligosaccharide conjugated to *Corynebacterium diphtheriae* CRM₁₉₇ protein. CRM₁₉₇ is a non-toxic variant of diphtheria toxin isolated from cultures of *C. diphtheriae* strain C7 (β 197). Each 0.5mL dose contains 10µg *N. meningitidis* serogroup C oligosaccharide conjugated to approximately 15µg *C. diphtheriae* CRM₁₉₇ carrier protein, aluminium phosphate as adjuvant, sodium chloride and water for injection.

2.5.2.2 NeisVac-C® (group C conjugate vaccine using tetanus toxoid as the conjugate)

NeisVac-C® (Baxter Healthcare Corporation) is a conjugate vaccine against *N. meningitidis* serogroup C conjugated to 10 to 20µg of tetanus toxoid protein, adsorbed to aluminium hydroxide as adjuvant. Each dose contains aluminium hydroxide (1.4mg, equivalent to 0.5mg aluminium), sodium chloride (4.1mg) and water for injection to 0.5mL. No preservative is added to the formulation.

2.5.2.3 Menactra® (group ACW135Y conjugate vaccine using diphtheria toxoid as the conjugate)

Menactra® (sanofi pasteur) is a conjugate vaccine against *N. meningitidis* serogroup C conjugated to 48µg of D protein. Each dose contains 4.0µg of each of the polysaccharide groups conjugated to formalin-detoxified D. Also included in each dose is sodium chloride 4.35mg (within 0.85% Physiological Saline and 0.5M Phosphate Buffered Saline, pH 6.8), Sodium phosphate – dibasic anhydrous 0.348mg (within 0.5M Phosphate Buffered Saline, pH6.8), Sodium phosphate – monobasic 0.352mg (within 0.5M Phosphate Buffered Saline, pH6.8). There is no preservative or adjuvant.

2.5.2.4 Hib - Group C vaccine (Menitorix®)

Hib-MenC-TT (Menitorix®, GlaxoSmithKline) is a *Haemophilus influenzae* type b polyribose ribitol phosphate and group C meningococcal polysaccharide conjugate vaccine. Each dose contains *H. influenzae* type b polyribose ribitol phosphate (5µg) conjugated to TT as carrier protein (12.5µg) and Group C Meningococcal polysaccharide (5µg), conjugated to TT as carrier protein (5µg). The powder for reconstitution contains the excipients, trometamol and sucrose. The diluent contains 0.9% sodium chloride in water for injections.

2.5.3 Group B vaccines

A number of group B vaccines are currently in development. The majority of these vaccines are based on the use of meningococcal surface antigens which have been shown to induce a bactericidal antibody response. One group of vaccines is based on the surface protein porA and uses OMV to present the protein in the vaccine (for example MenZB™). A second group of vaccines uses three surface proteins, factor H binding protein (fHbp), Neisserial heparin-binding antigen (NHBA), and Neisserial adhesin A (NadA) as immunogens in the vaccine. Two additional proteins, identified in earlier studies as being immunogenic (GNA1030 and GNA2091), were used to create fusion proteins with fHbp and NHBA (fHbp-GNA1030 and NHBA-GNA2091).

2.5.3.1 Recombinant meningococcal vaccine (rMenB)

rMenB (Novartis, investigational vaccine) contains 50µg each of fHbp (fused with genome derived Neisserial antigen 2091) NHBA (fused with genome derived Neisserial antigen 1030) and NadA. Fusion proteins were formed to increase the immunogenicity of the antigens. Each dose of rMenB also includes 1.5mg aluminium hydroxide, 3.25mg NaCl 10 mmol/L histidine and water for injection.

2.5.3.2 rMenB+OMVNW and 4CMenB (Bexsero®)

The rMenB+OMVNW investigational formulation (Novartis) is as per rMenB above with the addition of 25µg of OMV from serogroup B strain 44/76.

4CMenB, Bexsero® (Novartis), contains the rMenB with 25µg OMV from strain NZ98/254: rMenB plus 25µg detoxified OMV from the NZ epidemic strain NZ98/254.

2.5.3.2 Recombinant lipoprotein 2086 (rLP2086)

This investigational vaccine (Pfizer) consisted of equal amounts of the lipidated recombinant lipoprotein 2086 proteins (subfamily A, A05 variant and subfamily B, B01 variant) expressed in *Escherichia coli*; 60µg, 120µg, or 200µg of protein is suspended in 0.5mL of solution per dose. Each dose is formulated with 250µg aluminium phosphate as a stabiliser, 150 mmol/L sodium chloride, 0.0012–0.0058% Polysorbate 80 and 10 mmol/L histidine at pH 6.0.

2.5.4 Other protein-based vaccines

2.5.4.1 Group B-C vaccine (VA-MENGOC-BC®)

Meningococcal BC vaccine, VA-MENGOC-BC® (Finlay Institute, Havana, Cuba), is a meningococcal C polysaccharide-OMV vaccine which is available on the global market. The group C polysaccharide is formulated with a group B OMV which gives it the immunological stimulating properties of a protein-based vaccine. Each dose contains 50µg of OMV protein, 50µg of capsular polysaccharide from group C, 2mg of aluminium hydroxide gel, 0.05mg of thiomersal, 4.25mg of sodium chloride, 0.05mg phosphates and water for injection.

Table 1. Meningococcal vaccines either already available or likely to be available in NZ as of early 2013

Coverage	Vaccine	Polysaccharide	Protein-based
A, C, W135, Y	Mencevax® (GSK)	*	
A, C, W135, Y	Menomune® (sanofi)	*	
A, C, W135, Y	Menactra® (sanofi)		*(D)
C	Meningitec® (Pfizer)		*(CRM)
C	NeisVac® (Baxter)		*(TT)
C (and Hib)	Menitorix® (GSK)		*(TT)
C (and B:4:P1.19,15:L3,7,9)	VA-MENGOC-BC® (Finlay Institute)		*
B	Bexsero® (Novartis)		*

D = Diphtheria toxoid; CRM = CRM₁₉₇, a non-toxic recombinant variant of diphtheria toxin; TT = Tetanus toxoid

Highlighted vaccine currently available in NZ

Highlighted vaccine currently available in other countries

Highlighted vaccine currently recently licenced/undergoing licensure in several countries.

2.6 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching. Conference abstracts have also been added.

3. Recent New Zealand epidemiology

3.1 Overview of epidemiology

The 2012 annual report data was not available from ESR at the time of this report in early 2013.

A large epidemic of meningococcal disease occurred in NZ during 1991 - 2007. The majority of cases during the epidemic were caused by a single strain of meningococcus, defined by the serogroup type and sub-type as B:P1.7-2,4. The rate of disease at the height of the epidemic reached 17.4 per 100,000 population. A multi-agency collaboration led to the development of an outer membrane protein-derived vaccine, MeNZB™, specific for the NZ epidemic strain. The decline in the epidemic led to the withdrawal of the vaccine in 2008.

Since 2008, the number of meningococcal disease cases has remained above the pre-epidemic level. In 2011, the rate was 2.7 cases per 100,000 population with a total of 119 cases notified (108 confirmed) as shown in Table 2. Thirteen fatalities occurred in 2011, giving a case-fatality rate of 10.9% for meningococcal disease in 2011, which was slightly higher than in previous years. Three fatalities were due to group B strains (two, epidemic strain) and 10 were due to group C strains (9, C:P1.5-1,10-8).

Table 2. Notified cases and rate of meningococcal disease, 2007-2011 (2)

Year	No.	Rate
2007	104	2.5
2008	122	2.9
2009	133	3.1
2010	97	2.2
2011	119	2.7
Rate per 100,000 population		

3.1.1 Age specific rates

The highest age-specific disease rate was among those aged less than one (38.5 per 100,000) and one-four years (12.7 per 100,000), see Figure 3 (3).

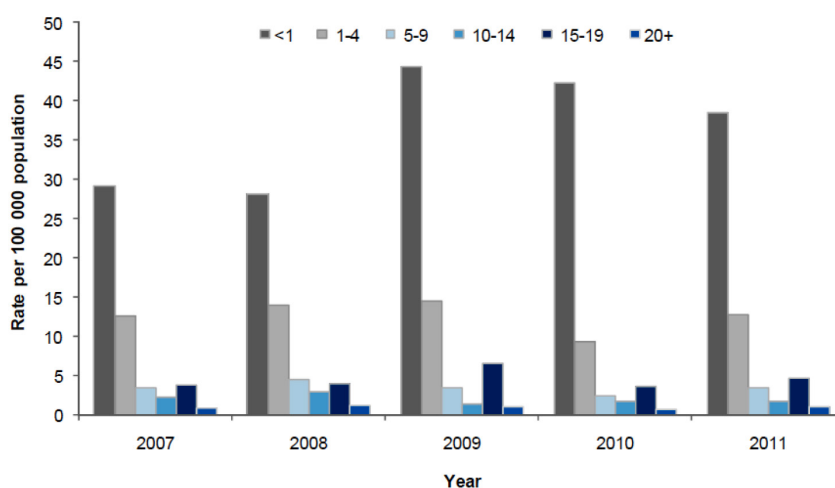


Figure 3. Meningococcal disease rates by age group, 2007-2011 (3)

3.1.2 Rates by ethnicity

Highest disease rates occurred in Pacific Peoples followed by Māori. The highest rate by age and ethnicity was in Pacific Peoples age less than one year (126.7 per 100,000). The rates by ethnicity are presented in Figure 4 and Figure 5 (3).

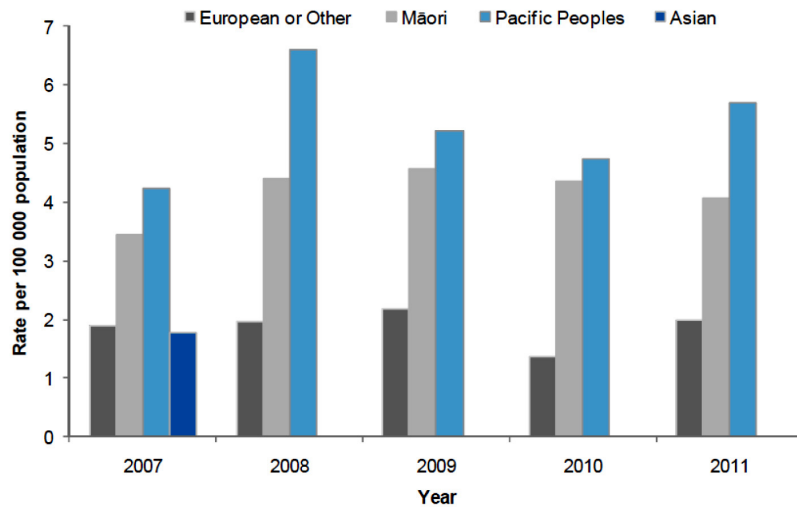


Figure 4. Age-standardised meningococcal disease rates by ethnic group, 2007-2011

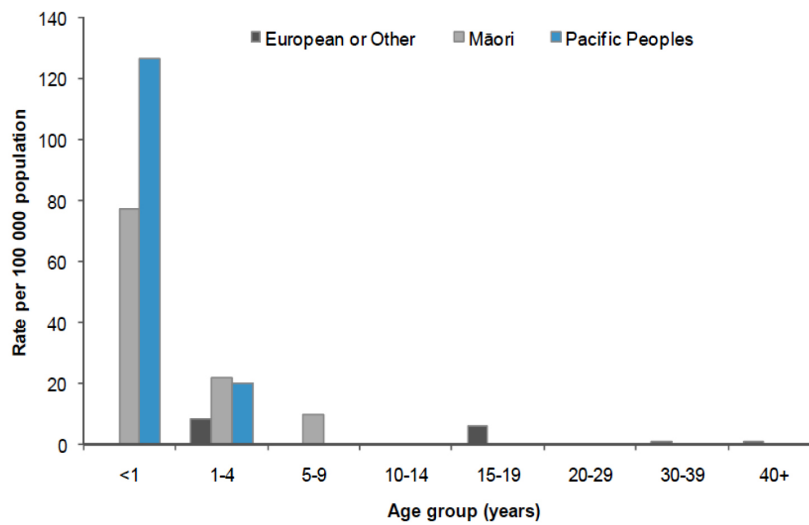


Figure 5. Meningococcal disease rates by age group and ethnic group, 2011

3.1.3 Incidence by deprivation index

There is a gradient in the disease rates of meningococcal disease and socioeconomic status. The incidence of disease rises with increasing deprivation and this pattern has remained constant over time. The rates by deprivation for cases under 20 years are presented in Figure 6.

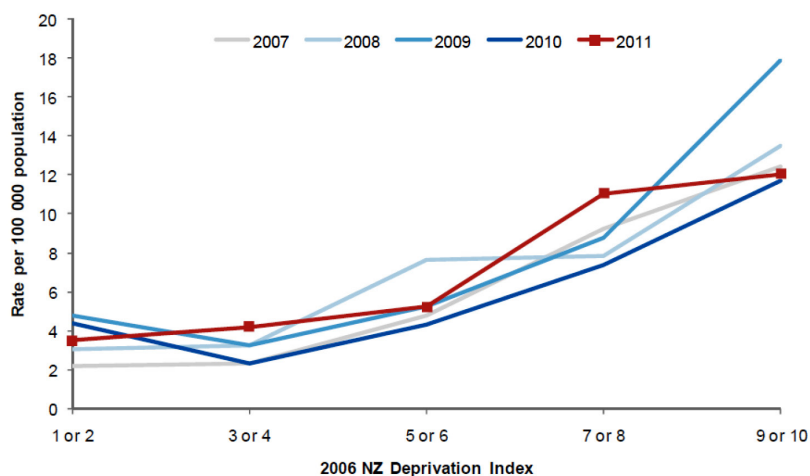


Figure 6. Meningococcal disease rates by quintiles of NZDep06 for cases aged less than 20 years, 2007–2011

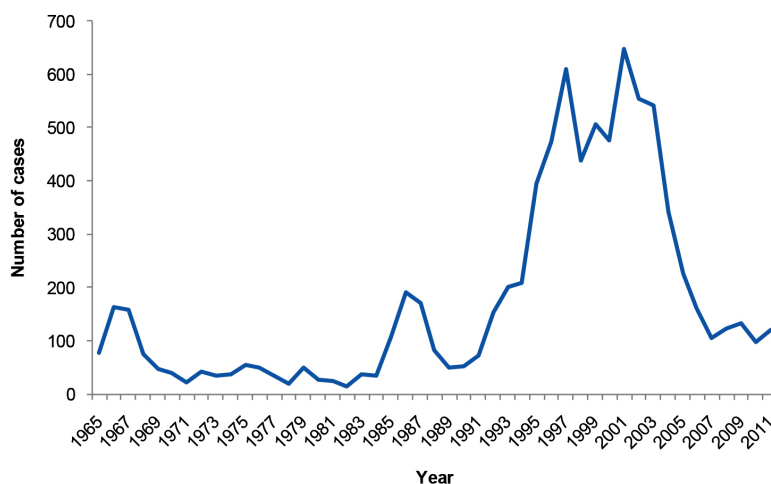


Figure 7. Total cases of notified meningococcal disease in NZ

3.1.4 Strain types among confirmed cases

Laboratory typing was performed on 100 out of the 108 confirmed cases, with group B isolates (62%) and group C isolates (32%) making up most of the cases. Sub-typing showed that the most common strain was B:P1.7-2,4, the NZ epidemic strain (37 isolates), followed by C:P1.5-1,10-8 (27 cases); see Table 3 and Figure 8. The number of cases of C:P1.5-1,10-8 has risen from five cases in 2007 to 27 in 2011 with the majority of the 2011 cases occurring in Northland District Health Board.

Table 3. Distribution of strain types among meningococcal disease cases in 2011

Strain group	Number of cases	Percentage (%) ¹
Group B	62	62.0
P1.7-2,4	37	37.0
Other group Bs	25	25.0
Group C	38	38.0
P1.5-1,10-8	27	27.0
Other group Cs	5	5.0
Other	6	6.0
Group Y	4	3.0
Group W135	2	2.0
Non-groupable	1	1.0
Total	100	100.0

¹% was calculated using the total number of laboratory-confirmed cases where strain group was determined.

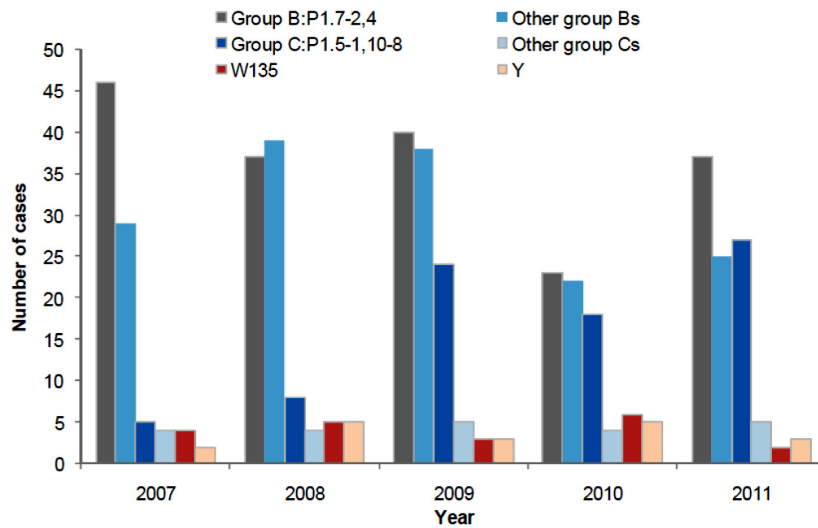


Figure 8. Groups and dominant subtypes among strain-typed meningococcal disease cases, 2007-2011

3.1.5 Geographical distribution

In 2011, the highest DHB rates were recorded in Northland and Lakes DHBs. The DHBs with the lowest rates of meningococcal disease were Auckland and Waitemata (see Figure 9).

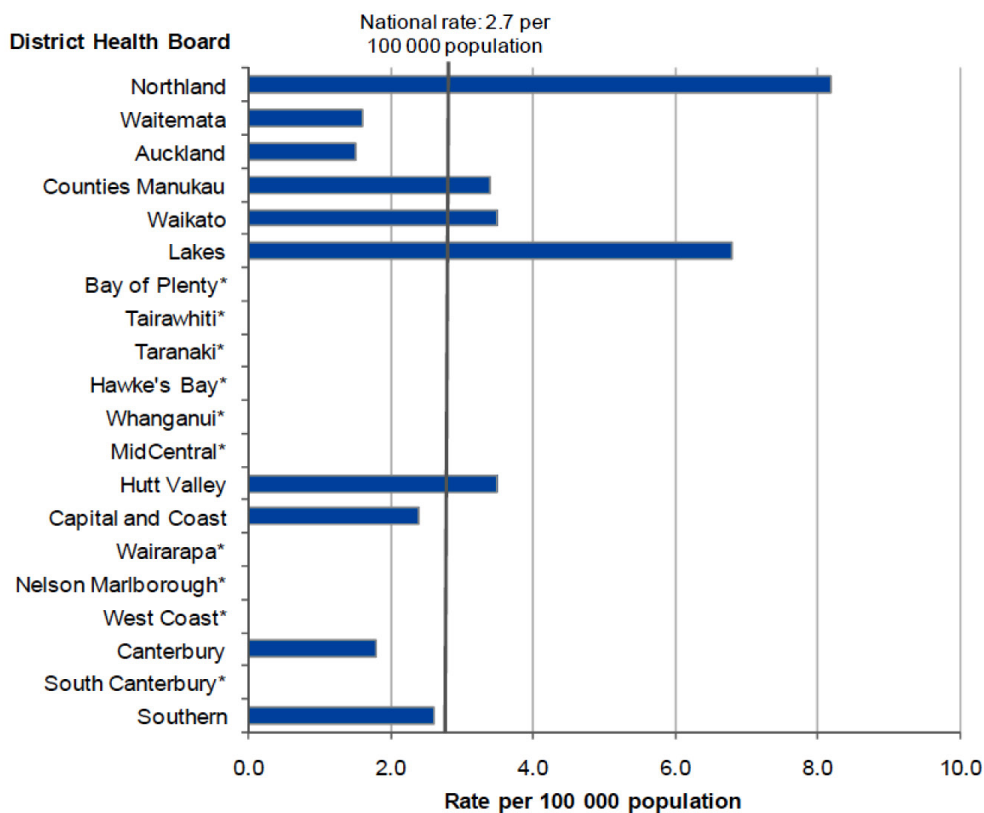


Figure 9. Meningococcal disease rates by District Health Board, 2011

3.1.6 Meningococcal disease cases and vaccination

Of the 37 cases caused by the epidemic strain in 2011, and therefore targeted by the MeNZB™ vaccine, five were reported to have been vaccinated (three or four doses) with MeNZB™ and one with a meningococcal vaccine, but no further details were given. None of the group C cases were reported as having been vaccinated with the group C conjugate vaccine.

Between 2007 and 2011, the number of cases due to strains targeted by MeNZB™ fell from 50 to 37, whereas the number of cases due to C conjugate vaccine-targeted strains quadrupled from nine to 32 cases. The increase in cases due to strains targeted by the quadrivalent vaccine is largely being driven by the increase in group C disease, with 5/37 quadrivalent vaccine-targeted strains in 2011 due to non-group C strains.

The number of meningococcal disease cases caused by vaccine-targeted strains by age group is presented in Table 4.

Table 4.
Number of meningococcal disease cases in 2011 caused by vaccine-targeted strains for each age group

Vaccine	Age group (years)						Total
	<1	1-4	5-9	10-14	15-19	20+	
MeNZB™ ¹	7	12	3	1	1	13	37
C conjugate ²	3	6	4	3	7	9	32
Quadrivalent ³	3	7	4	3	8	12	37

3.2 Summary of New Zealand epidemiology

The rate of meningococcal disease in NZ in 2011 was similar to the rates seen over the last four years and remained significantly higher than the pre-epidemic rate. The majority of cases occurred in the northern regions of the North Island, and those aged less than one year remain the most vulnerable age group. Māori and Pacific Peoples have higher rates compared with the European or Other ethnic group and this is most marked in the less than one year age group. A secondary peak of disease occurred in the 15–19 year old age group, which was particularly apparent in the European ethnic group. Meningococcal disease rates continued to be higher in the most socioeconomically deprived group, decile 9–10, compared with less socioeconomically deprived groups.

Group B strains continued to be the most prevalent, causing over 60% of the cases. The epidemic B:P1.7-2,4, was responsible for 37% of all meningococcal disease in 2011. The number of cases of meningococcal disease caused by group C strains has increased since 2007. This has been largely due to the increase in one particular strain, C:P1.5-1,10-8. The group C:P1.5-1,10-8 strain has been particularly prevalent in Northland in 2011, where one-third of all the cases caused by this strain occurred. Vaccination with the group C conjugate vaccine provides cover for this particular strain and is used to control community outbreaks of meningococcal disease.

4. Safety

4.1 Objective

The objective of this section is to review the most recent safety data for currently licensed meningococcal vaccines. The focus is on studies of the conjugate vaccines Meningitec® (group C conjugate vaccine using CRM₁₉₇ as the conjugate), NeisVac-C® (group C conjugate vaccine using TT as the conjugate), Menactra® (group ACW135Y conjugate vaccine using D as the conjugate), and the polysaccharide vaccines Mencevax® and Menomune®. Consideration is given to vaccines undergoing clinical trials and vaccines not currently licensed in NZ, but which have been approved in countries of similar stature. These include group C conjugate vaccines using alternative carrier proteins, quadrivalent conjugate vaccines using alternative protein carriers and group B vaccines.

Only Adverse Events Following Immunisation (AEFI) that have been considered subsequent to the pivotal clinical efficacy trials are reviewed here and any major clinical differences between vaccine types.

4.2 Outcomes

Outcomes are vaccine safety AEFI and serious adverse events (SAE). Excluded is reactogenicity (injection site reactions and minor systemic reactions) as these are thoroughly considered in the pivotal licensure studies, with the exception of new vaccines, where reactogenicity is presented.

4.3 Review

4.3.1 Safety of polysaccharide vaccines

The polysaccharide vaccines have been in use for several decades. There are few recent studies that specifically investigate the safety of these vaccines, in which they are usually reported as a control vaccine for the assessment of other investigational vaccines.

The polysaccharide vaccine Mencevax® is licensed for use in NZ from age two years and all safety concerns have been addressed during the licensure procedure. Mencevax® has been used as a control vaccine in recent safety studies of other experimental vaccines and safety in age groups two-10 years and 11-17 years has been evaluated. SAE identified in these studies were not considered to be vaccine related (4, 5).

The polysaccharide vaccine Menomune® is also licensed for use in NZ from age two years and there have been no safety concerns raised since the licensure procedure. Menomune® has been used as a control vaccine in recent safety studies of other experimental vaccines with no adverse events being considered as vaccine related (6).

Two studies specifically assessing the safety of polysaccharide vaccines were identified from the recent literature, one in children and young adults and one in pregnant women.

The first was described as a phase III study in Taiwanese children and adults aged two years to 30 years of age receiving quadrivalent MPV (Mencevax®). Of note, the reactogenicity data presented in this study is clearly defined according to the International Brighton Collaboration definitions for local injection site reactions. However, the study included only 105 participants and there was no control, which would seem to preclude it as an efficacy study. The percentage of subjects reporting any symptom (solicited/unsolicited or local/systemic) was 39%. The symptom most often reported was pain at the injection site (31.4%). Fever, with an axillary temperature $\geq 37.5^{\circ}\text{C}$, was reported by 3.8%. One subject in the two to five years age group experienced a rash that was considered to be related to vaccination by the investigator. There were no SAE were reported during this study (7).

4.3.1.1 Immune hyporesponsiveness and polysaccharide vaccines

A 2011 expert review has summarised the current understanding of the immune hyporesponsiveness associated with polysaccharide vaccines. Immune hyporesponsiveness to meningococcal group C has been demonstrated to occur across age groups following MPV. Using a MCV for the primary vaccination does not prevent the development of hyporesponsiveness on subsequent exposure to polysaccharide vaccine. This phenomenon has also been observed following the use of conjugate Group C after polysaccharide W135 in African infants (8). It is thought that the production of immune memory cells induced by exposure to MCV is impaired by exposure to MPV, either before or after MCV.

This issue has implications for scheduling of meningococcal vaccines, particularly in older populations. The hyporesponsiveness to MPV appears

dose related, with more marked effects when doses over 10µg are administered. The authors of this review concluded that introduction of polysaccharide vaccines, anywhere into the vaccination schedule, may result in reduced immune responses on subsequent exposure, even in previously conjugate-vaccinated individuals. The use of polysaccharide vaccines to demonstrate immune memory has previously been a basic requirement for licensure of new conjugate vaccines. World Health Organization (WHO) recommendations now discourage this practice (9, 10).

4.3.1.2 Safety in pregnant women

Vaccination of high risk pregnant women against pneumococcal disease is recommended in some countries. A systematic review evaluated the safety of MPV during pregnancy. There were three studies identified on MPV alone and a further three that used MPV concurrently with pneumococcal polysaccharide vaccine. Post marketing surveillance data from the Vaccine Adverse Event Reporting System (VAERS), the Vaccines and Medications in Pregnancy Surveillance System and the Merck pregnancy registries were accessed. The studies included a total of 335 women. Four of the studies were RCTs, one was a cohort and two were retrospective studies. There did not appear to be association with any teratogenic effects on the fetus, preterm labour or spontaneous abortion. The most common adverse events were injection site reactions. The post marketing surveillance data identified one report following MPV. Available data supports the safety of MPV in pregnant women, but the numbers are small and larger prospective studies are required in order to draw firm conclusions (11).

4.3.1.3 Concomitant use

The polysaccharide vaccines have been used in conjunction with all routine vaccinations. There have been no recent reports regarding adverse events following use with routine vaccines.

4.3.2 Safety of group C conjugate vaccines

The safety of meningococcal group C conjugate (C-MCV) vaccines was clearly established in early studies, prior to the first licensed vaccine being given in the United Kingdom (UK) in 1999. Generally, from both the pre-licensure trials in the UK and post-licensure surveillance, the most commonly reported adverse event is a transient headache of mild to moderate severity (12%) within the first three days of vaccination. This is more commonly reported by secondary students than primary school students.

Local reactions are less common than those associated with DT boosters in the same groups. There were five cases of Guillain-Barre Syndrome (GBS) reported in immunised individuals during a catch-up campaign in the UK; millions of doses were administered during this campaign. This number of cases was considered lower than the expected background rate (12).

Two vaccines are licensed for use in NZ (Meningitec®, a CRM₁₉₇ conjugate vaccine, C-MCV-CRM; NeisVac-C®, a TT conjugate vaccine C-MCV-TT) and all safety concerns have been addressed in the licensure procedure. No recent studies have identified concerns regarding safety in the administration of C-MCV vaccine to infants (13). NeisVac-C has been used as a control in studies of alternative MCV, and no AEFI or SAE associated with the vaccine use have been reported (14, 15). A third C-MCV vaccine conjugated to CRM₁₉₇ Menjugate™, has also been developed, but is not licensed for use in NZ. No recent studies regarding the safety of this vaccine were identified in the literature search. However, a 2009 Cochrane Review was available. A 2011 revision of this review was withdrawn due to the unavailability of the authors.

4.3.2.1 2009 Cochrane Review

A 2009 Cochrane Review assessed the safety of MCV against group C disease (16). The specific safety hypothesis tested was that there is no difference in the number or severity of adverse effects (both systemic and localised) between C-MCV and placebo/control groups. After evaluation of the eligible 39 studies, 22 studies were included in the review corresponding to 28 publications. Fourteen were RCT, four were RCT during the first phase with a second phase consisting of a non-randomised age strata-matched control group, four observational studies were included (in the absence of efficacy studies), 11 studies evaluated monovalent C-MCV, five studies evaluated AC-MCV and one study evaluated the 4-MCV.

The C-MCV vaccine was shown to have an excellent safety profile in infants. The adverse events most frequently reported in infants were: fever (1 to 5%), irritability (38 to 67%), crying more than expected (1 to 13%), redness at the site of vaccination (6 to 97%), tenderness at the site of vaccination (11 to 13%) and swelling at the site of vaccination (6 to 42%). The adverse events were similar in groups vaccinated with MCV and with the control vaccine hepatitis B (HBV), but following booster doses, they were more frequent in the MCV group in one trial.

Table 5 (see pages 16-17) summarises some of the studies included in the Cochrane review with respect to reactogenicity, where sufficient information was available. Heterogeneity between studies prevented combining them. Heterogeneity was due to vaccine formulation (concentration of oligosaccharide and protein carrier) and different assays to measure immunogenicity.

4.3.3 Safety of a combined Hib-MenC conjugate vaccine

Hib-MenC (Menatorix[®]) vaccine is well tolerated in premature infants (17). Concomitant administration with MMR and pneumococcal conjugate vaccine (PCV-7) did not result in any more adverse events compared with separate administration. Coadministration with these vaccines results in overall slightly lower proportions with post vaccination fever (18).

4.3.4 Safety of quadrivalent conjugate vaccines

4.3.4.1 Safety of Menactra[®] (ACWY-D)

The quadrivalent conjugate vaccine Menactra[®] (ACWY conjugated to D, ACWY-D) is licensed for use in NZ for ages two-55 years and all safety concerns have been addressed in the licensure procedure. No additional concerns have been raised in studies using Menactra[®] as a control vaccine for developmental vaccines (19, 20). Menactra[®] is also available for use off-label in infants nine-23 months old.

4.3.4.1.1 Safety of Menactra[®] in infants from nine months

The safety of MenACWY-D (Menactra[®]) in infants vaccinated at nine months was determined in a US phase III clinical trial using a two dose schedule (9 months and 12 months)(21). The age of nine months corresponds with a well-baby check in the US, providing the opportunity to add a new vaccine without interfering with the established schedule. There were 4874 children of whom, 3491 received the 4-MCV either alone or with standard paediatric vaccines, and 1383 received combinations of MMRV, PCV7, Hib and HepA vaccines. The percentages of participants reporting solicited injection-site reactions after MenACWY-D were similar when MenACWY-D was administered alone at 9 months (46.8%) or at 12 months (43.2%). These rates were similar to those observed when MenACWY-D was administered with MMRV (46.8%) or with MMRV and Hib (44.4%) at 12 months and tended to be lower than when MenACWY-D was administered with PCV7 (54.6%)

or with PCV7 + MMRV + HepA (57.5%). There were no immediate unsolicited systemic events reported. Two immediate unsolicited systemic reactions were reported, a case of diarrhoea after a 9-month vaccination and a case of urticaria after a 12-month vaccination.

Solicited systemic reactions after MenACWY-D administration alone at 12 months (60.6%) was lower than after the 9-month MenACWY-D vaccination (68.2%) and lower than what was observed in the control groups at 12 months (76.6% of participants who received MMRV + PCV7, 75.2% of participants who received MMRV + PCV7 + HepA and 84.1% of participants who received MMRV + PCV7 + Hib). The percentage of participants with solicited systemic reactions after MenACWY-D administration alone at 12 months was also lower than that observed after MenACWY-D was given concomitantly with MMRV (71.1%), PCV7 (68.3%) or MMRV + PCV7 + HepA (73.2%). Grade 3 solicited systemic reactions were reported in $\leq 8.1\%$ of participants in each vaccination group. Fever was reported at similar (or lower) rates among participants who received MenACWY-D concomitantly with routine childhood vaccines (20.2–24.5%) compared with recipients of routine vaccines without MenACWY-D (21.8–31.7%); fever was reported less frequently when MenACWY-D was given alone at 9 months or 12 months (12.4% and 13.7%, respectively). Rates of grade 3 fever were also similar between recipients of MenACWY-D and concomitant vaccines (1.7–2.7%) and control vaccines alone (2.0–3.6%). Over all, injection-site and systemic events were similar to those of currently licensed, routinely administered paediatric vaccines (21).

4.3.4.2 Safety of Menveo[™] (ACWY-CRM)

The quadrivalent conjugate vaccine, Menveo[™], has been developed using CRM₁₉₇ as the conjugate protein (ACWY-CRM). The vaccine covers meningococcal groups A, C, W135 and Y, but is not currently licensed in NZ. Studies have evaluated the safety of the vaccine in infants (22), children (23), adolescents (24) and adults (25, 26). Reactogenicity and adverse events were similar across study and control groups, and none of the reported SAE was considered to be vaccine related in any of the studies referenced. One study looked at the safety of Menveo[™] in adults aged 56-65 years (26). AEFIs after immunisation were slightly higher in this group than the control (Menomune[®]

Continued pg.18

Table 5. Summary of selected trials of meningococcal conjugate vaccines containing group C in infants, children and adolescents that were included in the 2009 Cochrane Review of conjugate meningococcal vaccines (16).

Study	Vaccine	Population	Local reactions	Fever $\geq 38.3^{\circ}\text{C}$	Other systemic
Champagne 2000	C-MCV, 3 formulations each oligosaccharide A-C 1 μg , 4 μg or 16 μg and TT 5.8 μg , 32.2 μg or 160 μg (Aventis Pasteur); MPV A-C with 50 μg of each oligosaccharide; Hib conjugate vaccine	180 Nigerian infants receiving 1/3 formulations at 6, 10 and 14 weeks	tenderness and redness: 37% and 18.1% after C-MCV, 30.8% and 7.5% after MPV 19.6% and 11.2% in the Hib group	Not recorded	Systemic events: 4 μg up to 37%. 16 μg 38.9% to 57.1%
English 2000	Lederle, oligosaccharide C 10 μg and CRM197 25 μg and hepatitis B vaccine (SmithKline)	237 infants, 3 doses C-C-MCV at 2, 3 and 4 months.	any redness: 41% (C-MCV), 40% (HBV); any swelling: 6% (C-MCV), 8% (HBV); any tenderness: 13% (C-MCV) and 15% (HBV). None severe, differences NS	5% (C-MCV) and 1% (HBV);	crying more than expected: 13% (C-MCV), 8% (HBV); irritability: 67% (C-MCV) and 67% (HBV)
Halperin 2002	Menjugate: oligosaccharide C 10 μg and CRM197 25 μg (Chiron Corporation) and hepatitis B vaccine (SmithKline)	348 infants, 3 doses at 2, 4 and 6 months	any redness: 6% (C-MCV) and 6% (HBV); any swelling: 6% (C-MCV) and 8% (HBV); any tenderness: 11% (C-MCV) and 9% (HBV). Redness at 4 & 6 months: 15% and 14% in C-MCV group; 7% and 9% in HBV group Induration at 4 & 6 months: 14% and 14% C-MCV group, 3% and 8% HBV group	3% (C-MCV) and 3% (HBV)	crying more than expected: 1% (C-MCV) and 1% (HBV); irritability: 38% (C-MCV) and 45% (HBV); sleepiness: 41% (C-MCV) and 36% (HBV); analgesic/antipyretic use: 20% (C-MCV) and 27% (HBV). Only persistent crying was reported more frequently with booster dose of C-MCV (3%) than HBV (0%) (p = 0.02).
MacLennan 2000	C-MCV-1: oligosaccharide C 10 μg and CRM197 20 μg or C-MCV-2: oligosaccharide C 10 μg and CRM197 13 μg (Chiron Corporation) and HBV (SmithKline)		redness: 97% (C-MCV) and 95% (HBV) any induration: 42% (C-MCV) and 47% (HBV) any tenderness: 41% (C-MCV) and 40% (HBV).		
Tejedor	Meningitec® oligosaccharide C 10 μg and CRM197 15 μg (Wyeth Lederle)	452 infants, 3 doses at 2, 4 and 6 months of age coadministered with DTPa-HBV-IPV-Hib or alone at 3, 5 and 7 months	pain: 11.0% (coadmin) and 9.4% (alone); redness: 14.4% (coadmin) and 21.3% (alone); swelling: 9.5% (coadmin) and 12.8% (alone)	13.0% (coadmin) and 16.2% (alone)	Drowsiness: 27.3% (coadmin) and 24.1% (alone); irritability: 32.1% (coadmin) and 31.6% (alone); antipyretic use: 14.5% (coadmin) and 14.9% (alone). loss of appetite: 24.0% (coadmin) and 20.6% (alone). Co-administration of both vaccines did not result in increased reactivity.

Buttery	Pnc9-MenC, oligosaccharide 2µg of pneumococcal saccharide conjugates 1, 4, 5, 9v, 14,18C, 19F and 23F; 4µg of pneumococcal saccharide conjugate 6B; and 10µg of meningococcal group C oligosaccharide and 38.5µg of CRM197 (Wyeth Vaccines) and Meningitec® (Wyeth Lederle) oligosaccharide C 10µg and CRM197 15µg	240 infants, 3 doses at 2, 3 and 4 months Group 1 – pneumococcal vaccine Group 2 – meningococcal vaccine	Local reactions were uncommon in both groups	35.3% Group 1 26.7% Group 2 (p = 0.15).	Irritability occurred in 65.2% in Group 1 versus 48.7% in Group 2 (p = 0.02); decrease activity: 33.0% in Group 1 versus 20.2% in Group 2 (p = 0.03)
Lieberman 1996	C-MCV - oligosaccharide A/C 11µg of each and CRM197 48.7µg (Chiron Biocine) and Menomune® ACYW135 (Connaught)	86 children aged 18-24 months 2 doses of either C-MCV or MPV		Dose 1: 0% (C-MCV) and 11% (MPV); Dose 2: 3% (C-MCV) and 6% (MPV)	Dose 1 irritability: 35% (C-MCV) and 29% (MPV); change in eating habits: 14% (C-MCV) and 19% (MPV) Dose 2 irritability: 31% (C-MCV) and 29% (MPV); change in eating habits: 18% (C-MCV) and 13% (MPV).
Pichichero 2005	4-MCV (quadrivalent conjugate vaccine) with 4µg of A, C, Y, W135 polysaccharide conjugate to 48µg of diphtheria toxoid protein and MPV ACYW135 quadrivalent (Aventis Pasteur)	1375 children, 80% aged 2 - 5 years 1 dose of either 4-MCV or 4MPV	any local reaction: 58.8% (MCV) and 58.3% (MPV); redness: 29.5% (MCV) and 30.4% (MPV); swelling: 20.5% (MCV) and 16.6% (MPV); induration: 22.1% (MCV) and 15.6% (MPV); pain: 48.1% (MCV) and 46.9% (MPV).	Fever ≥38.3°C 11.4% (MCV) and 12% (MPV)	Any: 53.3% (MCV) and 52% (MPV); anorexia: 22.7% (MCV) and 20.3% (MPV); diarrhoea: 15.9% (MCV) and 15.7% (MPV); drowsiness: 26.6% (MCV) and 24.1% (MPV); fussiness: 35.2% (MCV) and 30.1% (MPV)
Choo 2000	Oligosaccharide C 10µg and CRM197 25µg (Chiron) and Meningivac AC (Pasteur Mérieux)	176 adolescents aged 11-17 years 1 dose of either MCV or MPV	Pain: 75% (C-MCV) and 72% (MPV); redness: 32% (C-MCV) and 28% (MPV); induration: 22% (C-MCV) and 12% (MPV)	Fever ≥38.3°C 3% (C-MCV) and 7% (MPV)	Headache: 49% (C-MCV) and 56% (MPV); myalgia: 56% (C-MCV) and 49% (MPV); malaise: 35% and 40% (MPV); analgesic use: 21% (C-MCV) and 17% (MPV). The incidence of adverse events was not significantly different in the two vaccine groups.

4.3.4.3 Investigational quadrivalent MCV

Two investigational quadrivalent conjugate vaccines are in development, one from GlaxoSmithKline (GSK) and one from sanofi-pasteur (SP), both using TT as the conjugate protein. The safety of the ACWY-TT (SP) has been assessed in 12-month old children using a single dose of vaccine (14). Five formulations were tested: two low-dose (4µg of each serogroup plus 22.1µg or 33.9µg of TT); one medium-dose (10µg serogroup A and W135, 4µg C and Y plus 36.6µg TT); and two high-dose 10µg of each serogroup plus either 54.8µg or 84.8µg TT). NeisVac-C® was used as the control. No difference in AEFI was seen between the ACWY-TT (SP) vaccine formulations and the control group. Seven SAE were reported, six of which were considered unrelated to vaccination. The seventh, monoarticular inflammatory arthritis, with onset one day after vaccination, was considered possibly related. There was no further data on the other vaccine.

4.3.5 Safety during concomitant use

4.3.5.1 Concomitant use of C-MCV

The C-MCV vaccines have been used in conjunction with routine national schedule vaccinations with no adverse effects. A UK study of 146 children receiving routine vaccinations (DTaP₅/IPV/Hib-TT, at two, three and four months old; PCV7 at two and four months) together with one dose of either NeisVac-C® or Menjugate at three months old raised, no concerns regarding concomitant administration of the C-MCV vaccines (13). A similar study looked at co-administration of the three C-MCV vaccines with PCV7 and DTaP₅/IPV/Hib-TT (27).

4.3.5.2 Concomitant use of 4-MCV

No concerns were raised for concomitant administration of the ACWY-CRM vaccine together with Tdap and HPV vaccines in adolescents (24, 28). Nor were safety concerns were seen in children two-10 years old receiving routine US vaccinations plus ACWY-CRM (29). A study investigating concomitant administration of the routine US vaccinations, DTaP/IPV/HPV and PCV7 vaccines then PCV7, HAV, MMRV vaccines at 12 month visit, together with ACWY-CRM showed no concerns after the fourth dose of ACWY-CRM at 12 months (30).

4.3.6 Safety in HIV infected individuals

4.3.6.1 Safety in HIV-infected children

HIV infection increases the risk of infections with encapsulated bacteria, even under Highly Active Antiretroviral Treatment. Also, the immune response to a number of vaccines can be impaired in patients with HIV infection. The safety (and immunogenicity) was assessed for a two-dose series of 4-MCV in 59 two to 10-year-old HIV-infected children with CD4+ of at least 25%. There were no adverse events reported in the 42 days following each vaccine dose, other than mild local pain, tenderness, and/or redness as reported by five participants, 4 (7%) after dose one and 2% after dose two. There were two neutropenia episodes and one fever which both occurred at least 24 weeks after a dose and were not considered related to vaccination (31).

4.3.6.2 Safety in HIV-infected youth

To compare the safety (and immunogenicity) of a single doses versus two doses of 4-MCV in HIV-infected youth, 324 subjects aged 11-24 years were randomised to receive one or two doses of 4-MCV. The second dose was administered 24 weeks after the first. Within 42 days of administration of the second dose, to those randomised to receive two doses, the single dose control group reported no adverse events (AE), while two subjects in the second dose group reported grade 3 or higher signs/symptoms (yielding AE rates of 6.5% for group 2 vs. 0 for group 1, Fisher exact test $p = 0.01$). One subject reported migraine and ocular pain (judged to be possibly vaccine-related) and one reported a lip lesion (judged to be not vaccine-related). Similar to the safety evaluation after the first dose (reported separately), there were no serious haematological AE. The most common post-vaccination site injection grade was "mild" (primarily, pain and tenderness), and was reported by fewer than 5% of vaccinees. There were no cases of invasive meningococcal infections or meningitis reported during the study period. Two subjects died while in the study; neither of the deaths was judged to be treatment-related (one due to methamphetamine overdose, one due to HIV-related complications) (32).

4.3.7 Safety in patients after allogeneic hematopoietic stem cell transplantation

Safety of the 4-MCV has not previously been evaluated in stem cell transplant patients. The safety (and immunogenicity) was evaluated in 46 patients who were assessed retrospectively. Despite the study title “Safety and Immunogenicity of the Tetravalent Protein-Conjugated Meningococcal Vaccine (4-MCV) in Recipients of Related and Unrelated Allogeneic Hematopoietic Stem Cell Transplantation” safety is not actually measured or reported on in the study (33).

4.3.8 Safety of group B vaccines

These fusion proteins plus NadA are used either together or combined with an OMV preparation containing a fourth protein porA. A third vaccine uses only one of the four proteins, fHbp, as the immunogen. This is a bivalent vaccine containing equal amounts of a variant from each of the two sub-families of fHbp previously identified.

The vaccines covered in this safety review include:

- OMV vaccines.
- Recombinant meningococcal vaccine (rMenB): contains 50 µg of each antigen (fHbp, NHBA and NadA) plus aluminium hydroxide
- 4CMenB: rMenB plus 25µg detoxified OMV from the NZ epidemic strain NZ98/254.
- Recombinant lipoprotein 2086 (rLP2086): equal amounts of lipidated recombinant lipoprotein 2086 subfamily A (A05 variant) and B (B01 variant).

4.3.8.1 Safety of Outer Membrane Vesicle (OMV) vaccines

A number of OMV vaccines have been developed mostly to control epidemics of group B disease caused by a single strain of the meningococcus. OMVs consist of lipid vesicles produced naturally by the meningococci or from detergent-treated meningococci. The OMVs contain outer membrane proteins, the main one being porA. In epidemic situations the epidemic strain is used to generate the OMV vaccine (e.g. MeNZB™ in NZ or MenBvac in Norway). Further development of OMV vaccines has included genetically engineering meningococci to include six or nine porA types (HexaMen, NonaMen) or to include group C polysaccharide (VA-MENINGOC-BC®).

A recent phase I trial evaluating *Neisseria lactamica* OMVs as a potential vaccine has been published. *N. lactamica* does not contain porA nor have a capsule and so cannot induce capsule or porA-specific responses. Adult males 18-55 years old received one, two or three doses of the vaccine on days 0, 42 and 84. No SAEs were reported and no cases of fever >38°C (34).

4.3.8.2 Safety of rMenB and rMenB+OMV vaccines

Phase I clinical trials of rMenB have been performed, and the results from the ‘first use of recombinant antigens in humans’ trial have been published. No SAEs were reported in thirty-four adults (age range 20-40 years) who received 3 or 4 doses of rMenB (month 0, 2 and 6 or 0, 1, 2 and 6), indicating that the recombinant proteins used in the vaccine were safe. In the same study, the combination of rMenB with OMVNW (the detoxified OMV from the Norwegian epidemic strain 44/76) showed that vaccination with a combination of recombinant antigens plus OMV was also safe. Again, no SAE were reported in thirty-six adults (age range 19-40 years) who received rMenB + OMVNW (schedule as for rMenB). For both the rMenB and rMenB+ OMVNW, reactogenicity was greater than in the control vaccines (Menomune® and Energix-B) (35).

A phase II trial in two month old infants was performed using rMenB. Vaccine was administered at 2, 4, 6 and 12 months old to 45 infants and safety assessed. Routine vaccinations were also received. One SAE, a transient episode of reactive arthritis, was classified as possibly related to the vaccine. All other SAE were considered not to be vaccine related (36). A phase II trial in infants, six-eight months old, was performed. Vaccine safety was assessed in 30 infants using a three dose schedule (month 0 and 2 then at 12 months old). Routine vaccinations were also administered with a Hib + group C MCV (Menitorix®) at 12 months old. Five SAE were recorded, but none were thought to be vaccine related (37).

4.3.8.3 Safety of 4CMenB

4.3.8.3.1 Safety of 4CMenB in adults

Phase I clinical trials of 4CMenB have been performed. Fourteen adults (age range 18-38 years) were administered three doses of 4CMenB (month 0, 1 and 2). One AEFI, pruritus, was seen following vaccination and none of the SAE were considered vaccine related (35).

Phase II trials were conducted in adults (age range 18-50 years) at risk from occupational exposure to meningococci. Three doses of 4CMenB were administered at month 0, 2 and 6. Fifty-three adults received a least one dose of 4CMenB and fifty received all three doses. AEFI included fever in three participants, however, no SAE were recorded (38).

4.3.8.3.2 Safety of 4CMenB in adolescents

A phase IIb/III trial using 4CMenB in adolescents has been published. In that study, 1631 Chilean adolescents aged 11-17 years old received at least one dose of 4CMenB. Participants received one, two, or three doses of 4CMenB at 1-month, 2-month, or 6-month intervals. Reactions were recorded seven days after each vaccination, and adverse events were monitored throughout the study. Participants were initially randomised to five groups (3:3:3:3:1) during the primary phase to receive either one dose, two doses 1 or 2 months apart, or three doses of 4CMenB, or three doses of placebo, with an additional three groups generated for a booster phase (39).

Most events were injection-site reactions. Rate of reactions were generally similar after each dose, including placebo injections. Overall, following 3330 doses of 4CMenB, the rates of solicited local and systemic reactions for any injection were higher than for the 2739 placebo injections; most reactions were described as mild to moderate in severity and resolved within a few days. The most common local reaction was pain, reported after 2863 (86%) of 3330 of 4CMenB injections versus 1648 (60%) of 2739 after placebo injections, with 563 (17%) of 3330 cases described as severe after 4CMenB injections versus 105 (4%) of 2739 after placebo injections ($p < 0.0001$). Severe pain occurred after 563 (17%) of 4CMenB injections compared with less than 4% of placebo injections.

The most common systemic events were malaise (1703, 51%) of 3330 4CMenB and 809 (30%) of 2739 placebo, $p < 0.0001$ and headache (1412, 42%) of 3330 4CMenB and 741 (27%) of 2739 placebo, $p < 0.0001$. Fever ($\geq 38^\circ\text{C}$) was reported after 123 (4%) of 3329 4CMenB doses and 44 (2%) of 2738 after placebo injections ($p < 0.0001$). Fever 39°C or above occurred in 20 (1%) of 2738 participants given 4CMenB and eight ($< 1\%$) of 2738 given placebo ($p = 0.0689$). Medical attention for fever was sought by four 1480 4CMenB and two of 1290 placebo recipients.

Unsolicited events were reported by 641 (43%) of 1503 recipients of 4CMenB and 57 (45%) of 128 recipients of placebo ($p = 0.679$). Events considered by

the investigator as possible and probably related to study injection were reported by 240 (16%) of 1503 recipients of 4CMenB and 15 (12%) of 128 recipients of placebo ($p = 0.204$). There were two cases of juvenile arthritis reported at 170 days and 198 days, which were assessed as possible and probably related to 4CMenB vaccination, one participant who reported juvenile arthritis 170 days after the third dose had symptoms of ankle pain and tendinitis before study entry. Other reported serious adverse events, which were all judged to be unrelated to the study vaccine by the investigator, included four cases of appendicitis, and individual cases of shigella infection, drug-related toxic effects, pneumococcal meningitis, urticaria, and asthmatic crisis. All of these events were reported 23–95 days after the latest study injection, and resolved within 3 days with the exception of the case of meningitis, which lasted 8 days (39).

A phase II trial was conducted in 11-18 year old adolescents in the US, but data have not been published from this trial, as of early 2013 (see [ClinicalTrials.gov NCT00297817](http://ClinicalTrials.gov/NCT00297817)).

4.3.8.3.3 Safety of 4CMenB in infants and children

Phase II studies

Two phase II infant trials have been published. The first assessed the safety for 4CMenB in 48 infants (two months old), which used a dose schedule at 2, 4, 6 and 12 months old administered with routine vaccines. AEFI included fever in a minority of participants, however, none of the SAE reported were thought to be associated with the vaccine (36). A second phase II trial was conducted in 30 older infants (six-eight months old), through a month 0, 2 and 6 schedule, with routine vaccinations (Hib + group C MCV [Menitorix®] at 12 months old). AEFI included fever in one child and the one SAE reported was not thought to be associated with the 4CMenB vaccine (37).

A phase IIb trial was conducted in which over 1600 infants aged 2 months received at least one dose of 4CMenB in one of three schedules (2, 4 and 6 months old concurrently with routine vaccines; 2, 4 and 6 months old with routine vaccines at 3, 5 and 7 months; 2, 3 and 4 months old with routine vaccines). Higher rates of fever were observed in the groups receiving 4CMenB than in the control group (routine vaccines alone). One hundred and sixty-six SAEs were reported, of which, 20 were thought to be related to 4CMenB or routine vaccinations. Higher rates of fever were seen in those infants receiving the 4CMenB than in the control group. One child had febrile convulsions two days following 4CMenB administration (40).

Phase III studies

The first large-scale phase III trials of primary doses of 4CMenB in infants and a booster dose in children aged 12 months were reported in January 2013 as summarised below. These studies were multicentre phase III studies, conducted between March 2008 and August 2010 at over 70 sites in Finland, the Czech Republic, Germany, Austria and Italy. There were 2627 infants enrolled in an open-label phase, 1003 in an observer-blind phase and 1555 children in a booster study (41).

Reactogenicity profiles in both infant cohorts (the open label and observer blind) were similar and did not change with subsequent doses; therefore, the safety and report data for all doses was combined. Injection-site reactions peaked on day 1, with a steep decrease in occurrence noted on day 2. The most frequent reaction was tenderness, reported in 87% of 4CMenB recipients; 29% of cases were described as severe, defined as crying when the limb was moved.

When administered concomitantly with various combinations of routine scheduled vaccines, 4CMenB and PCV7, DTaP-HBV-IPV/Hib vaccine elicited similar occurrence of local tenderness—any (80%) and severe

(24%) as when PCV7 and DTaP-HPB-IPV/Hib was given without the 4CMenB. Without 4CMenB, the occurrence of any tenderness was lower: 59% with PCV7 only, and 68% with both PCV7 and MenC. Although erythema and induration, and to a lesser extent swelling, were reported frequently, less than 1% of these reactions were reported as severe.

Booster doses of 4CMenB in children aged 12 months elicited lower occurrence of all injection-site reactions, including any (71% with and without MMRV) and severe tenderness (15% with MMRV, 14% without MMRV).

There were no major differences in safety reporting study groups except for the proportions of participants with medically attended fever. In the open-label sub study, medical attention for fever after any vaccination was sought for 1.4% (28 of 1966) of infants in the 4CMenB plus routine vaccines group and 1.8% (12 of 659) of infants in the routine vaccines only group. In the observer-blind sub study these proportions were 5.3% (26 of 493) for the 4CMenB group and 2.8% (13 of 470) for the routine vaccines plus MenC group. Local reactogenicity is summarised in Table 6 from the manuscript and systemic reactions in Table 7 (41).

Table 6. Participants with any local reactions within seven days of any dose of vaccine (41)

	Primary series									Booster	
	4CMenB plus routine vaccines			Routine vaccines only		Routine vaccines plus MenC			4CMenB (N=765)	4CMenB plus MMRV† (N=789)	
	4CMenB (N=2477)	DTaP (N=2478)	PCV7 (N=2478)	DTaP (N=659)	PCV7 (N=659)	DTaP (N=490)	PCV7 (N=490)	MenC (N=490)			
Tenderness	2147 (87%)	1986 (80%)	1961 (79%)	388 (59%)	352 (53%)	331 (68%)	303 (62%)	266 (54%)	546 (71%)	563 (71%)	
Severe*	723 (29%)	607 (24%)	596 (24)	51 (8%)	38 (6%)	47 (10%)	40 (8%)	23 (5%)	104 (14%)	115 (15%)	
Erythema	2049 (83%)	1900 (77%)	1724 (70%)	469 (71%)	408 (62%)	363 (74%)	307 (63%)	261 (53%)	504 (66%)	539 (68%)	
Induration	1908 (77%)	1674 (68%)	1360 (55%)	424 (64%)	321 (49%)	368 (75%)	271 (55%)	227 (46%)	388 (51%)	424 (54%)	
Swelling	1174 (47%)	919 (37%)	794 (32%)	222 (34%)	176 (27%)	146 (30%)	99 (20%)	84 (17%)	284 (37%)	287 (36%)	

Data are n (%). DTaP=diphtheria-tetanus-acellular pertussis, inactivated poliovirus, hepatitis B plus *Haemophilus influenzae* type b vaccine. PCV7=seven-valent pneumococcal vaccine. MenC=meningococcal serogroup C conjugate vaccine. MMRV=measles, mumps, rubella, varicella. *Cried when limb moved. †Reactions at 4CMenB site only because MMRV administered subcutaneously.

In the open-label sub study, medical attention for fever after any vaccination was sought for 1.4% (28 of 1966) of infants in the 4CMenB plus routine vaccines group and 1.8% (12 of 659) of infants in the routine vaccines only group. In the observer-blind substudy, these proportions were 5.3% (26 of 493) for the 4CMenB group and 2.8% (13 of 470) for the routine vaccines plus MenC group. Fever of 40.0°C or more was reported in 1.2% (29 of 2468), 0%, and 0.2% (one of 489) of these groups, respectively. Antipyretic use was frequent in all groups; rates of medical attention for fever were 2–3% of doses.

There were two cases of febrile seizures in infants temporally associated with and assessed as probably related to vaccination with 4CMenB. They occurred within 24 h of the second vaccinations with 4CMenB and routine vaccines. One of these cases was a complex febrile seizure in a child with underlying neurological and renal pathologies and developmental delay, with no previous history of seizures. After withdrawal from the study, this child had another apparent febrile seizure five months later. Two additional seizures—one case reported as leg convulsions and another of jerking movements of the right arm—occurred on the same day as the first vaccinations with 4CMenB and routine vaccines. These events occurred in the presence of fever, were deemed mild or moderate in severity, possibly related to 4CMenB, and resolved spontaneously (41).

In total, 13 phase II and phase III trials using 4CMenB have been conducted (42). Over 7800 participants have received at least one dose of 4CMenB, including 5850 infants (two months to two years old), 250 children (two–10 years old) and 1712 adolescents and adults, according to a Novartis presentation.

4.3.8.4 Safety of rLP2086

A phase I trial of an investigational bivalent vaccine in children aged 18–36 months was reported. Sixty-seven participants received at least one dose of the vaccine containing 20µg, 60µg or 200µg rLP2086 per dose. Four cases of fever (>40°C) were reported in participants receiving the vaccine. Two SAE were recorded that were deemed vaccine related (urticaria and accidental overdose in which one participant was given 200µg instead of 20 µg) (43).

A phase II trial of the rLP2086 vaccine in adolescents was performed. In total 415 participants received at least one dose of vaccine containing 60µg, 120µg or 200µg rLP2086. No cases of fever >40°C were reported. Two SAEs were considered vaccine related. One SAE, a potential case of anaphylaxis, resulted in a pause in the study. The event occurred after administration of the third dose of 200µg rLP2086. A review by an independent safety committee concluded that the safety profile of the vaccine was unchanged. The second SAE was a case of photophobia (44).

Table 7. Participants with any systemic reactions within seven days of any dose of vaccine (41)

	Primary series			Booster	
	4CMenB plus routine vaccines (N=2478)	Routine vaccines only (N=659)	Routine vaccines plus MenC (N=490)	4CMenB (N=765)	4CMenB plus MMRV* (N=789)
Change in eating habits	1787 (72%)	329 (50%)	257 (52%)	312 (41%)	318 (40%)
Sleepiness	2159 (87%)	476 (72%)	353 (72%)	362 (47%)	355 (45%)
Vomiting	662 (27%)	104 (16%)	116 (24%)	54 (7%)	36 (5%)
Diarrhoea	1086 (44%)	218 (33%)	164 (33%)	188 (25%)	160 (20%)
Irritability	2296 (93%)	544 (83%)	370 (76%)	560 (73%)	540 (68%)
Unusual crying	2109 (85%)	424 (64%)	352 (72%)	327 (43%)	294 (37%)
Rash	318 (13%)	77 (12%)	43 (9%)	57 (7%)	56 (7%)
Medically attended fever	57 (2%)	12 (2%)	16 (3%)	8 (1%)	13 (2%)
Antipyretic use	2302 (93%)	471 (71%)	325 (66%)	436 (57%)	406 (51%)

Data are n (%). MenC=meningococcal serogroup C conjugate vaccine. MMRV=measles, mumps, rubella, varicella vaccine.

4.3.8.5 Concomitant use with OMV vaccines

OMV vaccines have all been shown to be safely administered with routine childhood vaccination schedules in a number of countries, including NZ. The rMenB vaccine has been co-administered with the routine UK vaccines at 12 months of age (C-MCV plus Hib, Mentorix®). No safety issues were raised, but there was no investigation of the antibody responses to the C-MCV or Hib following vaccine administration (37). Similarly, a study investigating the administration of rMenB or rMenB+OMV at two, four and six months of age with the routine UK vaccination schedule did not raise any safety concerns, but no data on the antibody responses were provided (36). In a study of 4CMenB co-administered with the routine UK childhood vaccines (Infanrix-hexa® and PCV7), measurement of the response to the routine vaccine antigens showed non-inferiority except for pertactin and serotype 6B of the PCV7 (40). The clinical significance of this is unknown. No data is available on the use of rLP2086 with routine vaccines.

4.3.9 Safety of VA-MENGOC-BC®

Cuba developed a vaccine over 20 years ago in response to epidemic meningococcal disease with predominant serogroups C and B. The vaccine contains purified group C polysaccharide adsorbed to aluminium hydroxide and OMVs from serogroup B:4:P1.19,15:L3,7,9 strain. The vaccine acts as a protein-based vaccine. Phase III trials included 105,251 adolescents for which detailed safety data was collected. Local reactions occurred in 56% and systemic 44%. The most common systemic events were headache, general discomfort, nausea and fever. Post licensure, several phase IV studies were conducted both in Cuba and in other countries. A retrospective study, conducted in 1998 using clinical records of 12,822 children aged three to five months of age, found that adverse events were consistent with those found in the clinical trials and all settled within 72 hours. Based on data from Brazil for 9 million people, the vaccine was considered of “slight reactogenicity” and well tolerated. There were similar conclusions from Argentina for adults and Uruguay in children and adolescents. As of 2007, there had been over 55 million doses administered with rare, serious events (i.e. anaphylaxis) occurring after fewer than 1 per million doses (45). There were no recent trials for this vaccine identified for the past four years. The clinical studies were published in the early 1990’s, not all in English.

4.3.10 Safety of all meningococcal vaccines in older adults

A recent study providing information on vaccine safety in the older age group (56-65 years old), was the only publication identified in the literature search relating to this age group. This was a randomised study in 2831 adults aged 19-55 years receiving either C-MCV (conjugated with D or CRM₁₉₇) or 4-MCV and 326 adults aged 56-65 years of age randomised to either 4-MCV or MPV. Solicited events were collected for seven days post vaccination. Frequencies of subjects reporting any local reaction were similar across age groups and vaccine used. Local reactions described as severe ranged between 1.8-5.6% and were largely related to pain. Participants experiencing any unsolicited AE were similar between vaccine groups. In the 56–65 years age group, the percentage of subjects experiencing any unsolicited AE was slightly higher for 4-MCV-CRM recipients than MPV recipients (25% vs 15%). The percentage of subjects experiencing possibly or probably related AE was similar between the vaccine and age groups (9%), except for 4-MCV-CRM at 15%, in the 56–65 years age group. The authors concluded the vaccines were well tolerated in these adult age groups (26).

4.4 Summary vaccine safety

Polysaccharide vaccines have been in use for many decades, and generally, little has been updated to their already established safety profile, recently. However, one important issue has emerged over the past few years. As with pneumococcal polysaccharide vaccines, MPV have been demonstrated to induce immune hyporesponsiveness, which is not reversible with the use of conjugate vaccines either as primary or subsequent doses. This has clinical implications, particularly, when considering schedules that may need to repeatedly use meningococcal vaccine doses.

The safety of the group C vaccines in all age groups has been well established with no additional concerns being raised for either the quadrivalent or monovalent form. Use of these vaccines in control cohorts, during the development of new vaccines, did not highlight any safety concerns. The quadrivalent vaccines have been assessed for concomitant use with a range of other vaccines with no issues identified. Safety of use of the group C containing vaccines has been assessed in patients with HIV and found to be acceptable, including when given as a two dose schedule. A widely

used Cuban BC vaccine appears to have an acceptable safety profile in all age groups. Closer examination of the reactogenicity profile would provide more detail about the frequency of local and systemic reaction and their relative severity.

Until recently, group B vaccines have been restricted to serospecific OMV vaccines. Licensure has been granted in Europe for a new vaccine, which has large scale clinical trial data to support its use. Safety data for the 4CMenB vaccine (Bexsero®) suggests that, compared with some other childhood other vaccines, it is relatively locally reactogenic and possibly more pyrogenic. However, no serious concerns have been raised. Febrile seizures have occurred in temporal association with this vaccine. While these simple febrile seizures usually resolve without complications, this may be an area that will need to be monitored should this vaccine be considered for use in NZ and consideration given to additional communication with Health professionals and parents.

5. Immunogenicity, efficacy, effectiveness and vaccine impact

5.1 Objective

The objective of this section is to review the most recent performance data for currently licensed meningococcal B and C vaccines and those undergoing clinical trials. Consideration is given to relevant immunogenicity data, efficacy and effectiveness studies that contribute to the current understanding of the effectiveness of meningococcal vaccines and evidence of their impact in populations

5.2 Outcomes

The outcomes considered for this review are:

- The outcomes considered for this review are:
- Meningococcal meningitis
- Immunogenicity
- Nasopharyngeal carriage
- Indirect effect/herd immunity
- Duration of protection

5.3 Review

The capsule of the meningococcus is the major virulence factor and is important for survival in the blood. Other virulence factors include the outer membrane proteins and lipo-oligosaccharides, which reside in the outer membrane of the pathogen. The impact of vaccines on disease will be influenced by their effect on carriage of invasive strains.

5.3.1 Carriage

Meningococci form part of the normal commensal population of the nasopharynx in a healthy person. Understanding carriage and the effects of vaccines on carriage and disease is important. Eliminating one particular strain or groups of strains in the carriage population may simply provide a convenient niche for a second strain to enter and cause disease. Continued surveillance of strains causing disease is critical for identifying possible changes in bacterial populations, which can lead to increased rates of disease.

The 2009 Cochrane review included a cross sectional study from the UK, which compared the carriage of meningococci in isolates from 14,064 students aged 15 to 17 years during the immunisation campaign in 1999 with those of 16,583 students in the same age group, surveyed one year later. The proportion of individuals carrying meningococci fell by an average of 66% (from 0.45% to 0.15%). The proportion of meningococci expressing serogroup C polysaccharide fell by 69% ($p = 0.001$). Analysis by self-reported vaccination status showed a C carriage rate of 0.127% in vaccinated individuals compared with 0.342% in unvaccinated individuals; a protective effectiveness against carriage of 63% (95% CI 50 to 80) (16).

The rate of carriage varies significantly depending on age and environment, ranging from 10-35% in young adults (46, 47). Carriage rates are low in the first year of life rising sharply in teenage years and peaking in 20-24 year olds. Factors influencing carriage rates include close contact communities, such as military camps or university students. Analysis of carriage populations shows that they are genetically very diverse compared to isolates from patients with meningococcal disease. The majority of invasive isolates belong to a limited number of genotypes, so called 'hyperinvasive lineages' (48, 49). Lineages are not group specific and group B and group C meningococci can belong to the same hyperinvasive lineage. This arises due to capsular switching and such organisms can escape vaccine protection. As most cases of meningococcal disease have not been in contact with other cases, it is assumed that carriers are the source of the virulent strains.

Due to low incidence of meningococcal disease in Finland, vaccination is only recommended for high risk groups including military recruits who received a 4MPV on entry to service. Recent carriage studies among 892 military recruits in Finland showed that carriage was significantly higher at the end of two years military service than on arrival (18.5% vs 2.2%); that 66% of carriage isolates were nongroupable (no capsule); and that most carriage isolates belonged to carriage-associated ST-60 (50). Recruits received an ACWY polysaccharide vaccine on entry. Group B accounted for 74% of the carriage isolates and 24% to group Y. No group C isolates were identified. No cases of meningococcal disease were reported. The carriage rates in this study were lower than those in

similar populations, which ranged from >16% to 70%, although, the latter studies were carried out in largely unvaccinated populations (51-54). This finding does not support a role for polysaccharide vaccines in affecting carriage.

To ascertain the carrier rate and the types of *Neisseria meningitidis* circulating in students, a sample of 583 medical students in Italy provided a nasopharyngeal swab. The carriage rate was 2% with nine of the 12 isolates being nongroupable. No group C isolates were identified. Italy has recommended C-MCV for infants and pre-adolescents aged 11-12 years since 2005 and the authors concluded the lack of Group C carriage was likely to be as a result of their immunisation policy (55). This supports the impact of the vaccination programme on an overall reduction in carriage.

The effect of vaccination on carriage has been particularly well documented after the introduction of the group C conjugate vaccine in the UK (47). Carriage rates of group C meningococci in adolescents fell and the fall has been sustained. No recent updates on the effect of the quadrivalent conjugate vaccines or polysaccharide vaccines on carriage were identified in the literature search.

5.3.2 Immunogenicity

The major antigens associated with meningococcal vaccines are the capsular polysaccharide and surface associated proteins. The antibodies elicited bind to the meningococcus and activate the complement system, which then lyses the bacteria or provokes phagocytosis. The role of these antibodies in protecting against infection was demonstrated in the 1960s and it is accepted that a serum bactericidal antibody (SBA) titre of <1:4 or greater using a human complement source, or <1:8 using rabbit complement, is a correlate of the protection provided by a meningococcal vaccine. In studies where the participants have a baseline titre of <1:4, a four-fold rise in titre is taken as protective. One of the limitations in assessing bactericidal antibody responses against a wide panel of strains in clinical trials is the limited volume of serum available from vaccinees and a shortage of suitable human complement. It is also thought that previously established correlates of protection may not be applicable to all bacterial antigens, of particular relevance to the newer vaccines. These challenges along with the low incidence of disease pose significant barriers to evaluating potential efficacy in prelicensure trials (1).

5.3.2.1 Polysaccharide vaccines

There is an age-related response to polysaccharide vaccines as detailed by Granoff et al. (12). Bactericidal antibodies are lower in infants under five than older children and adults when immunised with polysaccharide vaccine. Antibody levels decline over two years in adults, but remain above pre-immunisation levels for up to 10 years. Antibody levels decline more rapidly in children under five, returning to baseline within a year. Hyporesponsiveness is also seen in all age groups with repeat vaccinations. The use of polysaccharide vaccines as controls for developmental vaccines has been reported with no concerns were raised relating to the immunogenicity (5, 56, 57). A randomised study assessed immunogenicity in 2505 adults aged 19-55 years who received either 4-MCV-CRM (conjugated with CRM₁₉₇) or 4-MCV-D, and 326 adults aged 56-65 years of age randomised to either 4-MCV-CRM or MPV. The study found that 4-MCV-CRM was non-inferior to 4-MCV-D, with consistently higher geometric mean titres (GMT) for all four serogroups. In the 56-65 years age group, post-vaccination GMTs were 1.2- to 5.4-fold higher for the 4-MCV-CRM than for MPV for all four serogroups (26).

5.3.2.2 Group C conjugate vaccine

The immunogenicity of C-MCV vaccines has been demonstrated in many pre-licensure studies in infants and children. The three conjugate vaccines (Meningitec[®], Menjugate and NeisVac-C[®]) all show adequate increases in antibody titres following either two (3 and 4 months old) or three dose (2, 3, 4 months old) primary schedules in infants.

A 2009 Cochrane review concluded that C-MCV vaccine was highly immunogenic in infants after two and three doses, in toddlers after one and two doses and in older age groups after one dose (16). In general, higher titres were generated after C-MCV than after MPV. Immunological hypo-responsiveness seen after repeated doses of MPV may be overcome with C-MCV; however, this has since been questioned (8, 9).

Recent studies have questioned the persistence of antibodies in recipients of C-MCV conjugated to CRM₁₉₇ (58). A study in Spain measured the GMT of group C bactericidal antibodies in infants who had received a primary dose and a booster dose 12 months later of C-MCV-TT or C-MCV-CRM. Twelve months after the booster dose the seroprotective GMTs (<1:8) were significantly higher in children who received the C-MCV-TT vaccine in their primary and booster

dose than those who received C-MCV-CRM (92.8% vs 61.5%, respectively). The same study showed that regardless of the booster dose, priming with C-MCV-TT gave significantly higher GMTs. A similar finding was found by Khatami et al. who found that two years after boosting with C-MCV-CRM₁₉₇ the proportion of children with protective SBA levels was the same as a control group who had not received a booster (59).

A UK study in infants also raised concerns about the ability of the C-MCV-CRM to prime adequate increases in SBA following a booster using C-MCV-TT (Hib/C-MCV-TT vaccine, Menitorix®) (57). The GMTs measured prior to the booster, following two primary doses of the C-MCV, showed the proportion of infants with SBA titres <1:8 were significantly less in those vaccinated with C-MCV-CRM (21% Menjugate and 17% Meningitec®) than C-MCV-TT (48% NeisVac-C®). SBA titres were then measured one month and two months following a booster dose of Hib-MenC vaccine (Menitorix®). Infants whose primary vaccinations used C-MCV-CRM gave significantly lower GMTs than those vaccinated with C-MCV-TT vaccine, and the decline in SBA by the second month after the booster was significantly greater in the C-MCV-CRM cohort. The significant difference in SBA GMTs continued in the 24 month samples. In addition, the proportion of children with titres of <1:8 after one year (85% NeisVac-C®, 38% Menjugate and 33% Meningitec®) and two years (43% NeisVac-C®, 22% Menjugate and 23% Meningitec®) following the booster was higher in the C-MCV-TT cohort. Possible reasons given were the use of the same conjugate in the primary and booster vaccines, the superiority of TT as a conjugate or the different acetylated form of the polysaccharide use in the TT vaccine. Interestingly, the rate of antibody decline (as measured by serogroup C IgG levels) was similar to the Hib antibody decline, which indicates that the magnitude of the booster response determines antibody persistence. Southern et al. measured the GMTs one month after one dose of C-MCV at two months of age and showed the C-MCV-TT GMTs were higher than the C-MCV-CRM (60).

A study looking at the SBA titres in children who received a single dose of C-MCV (the majority were vaccinated with C-MCV-CRM, Meningitec®) (UK national campaign in 1999 to 2000, ages 1 to 4 years) had serum samples taken at intervals up to ten years later, to 2010. This study showed that by 2010 only 15% of children had protective levels of antibody which is only slightly higher than the prevaccination era. The decline in the proportion of children with protective antibody titres was independent of the age at which

the vaccine was administered. Decrease in SBA titres over time have been demonstrated in other age groups (see above) with more marked waning in infants immunised at younger ages. This study indicates that waning continues into adolescence with no boosting from natural exposure (61).

In a phase IV clinical trial, the persistence of SBA titres were measured six years following primary immunisation with three (at < 6 months of age), two (age 5-11 months) or one (age 1-7 years) dose of C-MCV. Overall, only 25% of all participants had protective levels of SBA six years after immunisation. When stratified by age at immunisation, only 12% of infants immunised at age < 6 months had protective SBA titres, while 48% of children immunised at age 5-6 years had protective SBAs. Persistence after a single dose of C-MCV in infants immunised at age one to four years was not age dependent and waning continued in agreement with previous studies (62).

Two five-year follow-up studies have recently been reported. A study measuring the GMT in infants, after either a Hib-C-MCV-TT or C-MCV-CRM primary dose and a Hib-C-MCV-TT booster at 12-15 months old, showed that at follow-up at five years old the titres were still highest in children whose primary vaccination used C-MCV-TT. The proportion of five year olds with protective SBA titres was 59.3% in C-MCV-TT cohort and 44.8% in the MenC-CRM cohort (63). A second study looked at GMTs in infants vaccinated with C-MCV-TT, for both primary and booster dose at 13-14 months old, compared to a control group receiving C-MCV-CRM for both primary and booster doses. The SBA titres, five years after the booster for children primed with C-MCV-TT, were significantly higher than those primed with C-MCV-CRM. The percentage of children with protective SBA titres was after five years was 82.6% (C-MCV-TT) and 60.9% (C-MCV-CRM). These figures are higher than those of other studies, the differences being ascribed to differences in methodology (15).

A seroprevalence study, looking at SBA titres across a range of age groups ten years after the introduction of the group C vaccination campaign in the UK, showed that the protective antibody levels in all immunised cohorts had declined, but the levels in those eligible for the catch-up vaccination (approximately all those aged five years and over) had proportionately more seroprotective antibody than those immunise at an earlier age (64). Similar results were seen in the Dutch population following introduction of a single dose of C-MCV at 14 months of age with a catch-up campaign for those age 14 months to 18 years (65).

5.3.2.3 Quadrivalent Conjugate Vaccines

The immunogenicity of ACWY-D (Menactra®) has been established in prelicensure studies. Several large studies have recently been published comparing the immunogenicity of ACWY-D and ACWY-CRM (Menveo®). A multicentre phase III randomised study of 2180 adolescents 11-18 years receiving a single dose of either ACWY-D or ACWY-CRM showed that ACWY-CRM induced a higher GMT for all four serogroups and was non-inferior for the proportion of subjects achieving protective titres of SBA for group C (19). ACWY-CRM also demonstrated significantly greater immunogenicity for group C when compared with a polysaccharide vaccine (Menomune®) in a phase II study in 524 adolescents, and was comparable 12 months post-vaccination (6). Results in adults were generally similar with ACWY-CRM showing non-inferiority to study comparing ACWY-D and ACWY-CRM the strict non-inferiority criteria for group C seroprotection was not met although non-inferiority was met for GMTs (26). In older adults aged 56-65 years, ACWY-CRM was as immunogenic as a polysaccharide vaccine (Menomune®) and gave rise to higher GMTs against all serogroups (26).

The immunogenicity of a quadrivalent conjugate vaccine using TT as the conjugate ACWY-TT has also been determined. Non-inferiority of the ACWY-TT (GSK) vaccine compared to C-MCV-CRM (Meningitec®) in children aged 12-23 months was shown in a phase III trial (66). This study also showed that the children immunised with ACWY-TT had significantly higher serogroup C GMTs. In a phase III trial, conducted in the Philippines, India, Saudi Arabia and Lebanon, 1501 children aged two-10 years were vaccinated with one dose of ACWY-TT (GSK) or a polysaccharide vaccine (Mencevax®) (4). Non-inferiority of the ACWY-TT vaccine was shown and the GMTs were significantly higher for all serogroups.

One study examined four formulations of ACWY-TT (GSK) using different amounts of the four polysaccharides and spacer technology. The responses were compared in two age groups, 12-14 months (using C-MCV-CRM as a control) and three-five years old using a polysaccharide vaccine (Mencevax®) as a control. All four formulations were immunogenic. Two formulations, which used spacer technology to link groups A and C polysaccharide to the conjugate, gave significantly higher serogroup C SBA GMTs one month after vaccination, when compared to the C-MCV-CRM control group. For the three - five year olds, all four serogroup GMTs were statistically higher than the control group (57). A phase II trial compared one dose of ACWY-TT (GSK) or ACWY-D in 11-25 year

old subjects. The study showed that, while the SBA GMTs for all serogroups were higher in the ACWY-TT group, the proportion of subjects achieving protective SBA titres (<1:4) for serogroup C was similar for both vaccines (20).

An assessment of the immunogenicity of ACWY-TT (SP) in infants given one dose of vaccine at 12 months old was reported. Five formulations were tested (see section 4.3.4.3). C-MCV-TT was more immunogenic than any of the formulations of ACWY-TT (SP) for serogroup C. Recipients of the higher doses of TT gave the highest titres against serogroup C, regardless of the serogroup C polysaccharide content in the formulation (14).

5.3.2.4 Group B vaccines

Clinical trials of the group B vaccines need to determine the level of bactericidal antibodies induced, as this is used as a surrogate marker for protection, as for other meningococcal vaccines. The surface proteins (fHbp, NadA, NHBA and porA) used in the group B vaccines are all variable in sequence. To understand the role of each vaccine antigen in protecting against infection, it is important that the bactericidal antibodies being measured are specific to each of the different antigens in the vaccine. The variants of the surface proteins used in the rMenB and 4CMenB vaccines are fHbp variant 1.1, NadA variant 3 NHBA variant 1.2 and porA 1.4 (67). For the fHbp-based bivalent rLP2086 vaccine the antigens are derived from the two major fHbp sub-families, variants 2 and 3 (subfamily A) and variant 1 (subfamily B) (68, 69). In an SBA assay the bacteria are killed by a combination of the antibodies produced by the vaccine. For the rMenB, rMenB+OMV and 4CMenB vaccines it is necessary to determine the immunogenicity against the three or four components of the vaccine. To this end, four reference strains matched to the individual components have been selected. These are strain 44/76-SL (fHbp, variant 1.1), 5/99 (NadA, variant 2.2), M4407 (NHBA variant 1.2) and NZ98/254 (porA variant 1.4) (47). These strains have been widely used to assess the immunogenicity of group B vaccines. Protective immunity is provided at SBA titres of <1:4 using human complement or a fourfold rise in titre. One of the most important aspects of group B vaccines is how effective they are against strains of meningococci carrying variants of the vaccine antigens and also the effect that differing levels of expression make to the ability of the antibodies to kill the organism. The use of SBA GMTs and proportion of subjects with titres <1:4 (or four fold rise in titre) to evaluate how well the vaccine will perform is based,

primarily, on efficacy data from OMV vaccines directed against *porA*, such as the Cuban OMV vaccine (VA-MENINGOC-BC), Norwegian OMV vaccine (MenBvac) and MeNZB™ vaccine (1). Surveillance studies following licensing of the 4CMenB in the UK early in 2013 should provide important data about the efficacy of the vaccine against heterologous strains.

Early studies with rMenB showed that the three recombinant proteins in the vaccine, fHbp, NadA and NHBA elicited protective GMTs (titres >1:4 using human complement or four fold rise in titre) in adults. For the reference strains (44/76-SL, 5/99 and NZ98/254), 86% of subjects achieved protective levels of antibody. Among the 12 heterologous strains also tested, protective levels varied between 14-100% of subjects (70). In the same study, rMenB+ OMVNW was also found to induce protective levels of SBA. In a similar phase I study in adults using 4CMenB, again multiple heterologous strains were killed in the SBA indicating that the multi-antigen vaccine may provide protection against a variety of different strains (35). The data from these studies indicated that a vaccine based on these three or four antigens warranted further investigation.

A phase II trial in adults at occupational risk of meningococcal disease assessed the immunogenicity of 4CMenB against three reference strains (44/76-SL, 5/99 and NZ98/254). Three doses of vaccine were given at 0, 2 and 6 months and titres determined one month after each vaccination. For the three strains tested, 64-100% of participants had a protective titre after the third dose. Waning of the titre was evident four months after the second dose (38). A phase II trial in healthy two month old infants evaluated 4CMenB and rMenB vaccines given at 2, 4, 6 and 12 months of age or a single dose at 12 months of age. Immunogenicity was determined from serum samples taken before and one month after all vaccinations and also before vaccination at 12 months of age. Seven group B strains were used to assess immunogenicity (44/76-SL, 5/99 and NZ98/254 plus four genetically diverse strains). After three doses, both vaccines were immunogenic against strains expressing homologous or related antigens. The 4CMenB was more immunogenic than rMenB inducing higher GMTs against all the strains tested. Six months after the third dose, titres had fallen, but were still greater than in unvaccinated individuals. After the fourth dose of 4CMenB, large increases in SBA GMTs were seen against homologous antigen-containing strains. The GMTs following the dose at 12 months of age were greater in those subjects immunised in a primary schedule than those only immunised at 12 months of age indicating an anamnestic response (36).

A randomised single blind study of 60 healthy infants aged six to eight months vaccinated with 4CMenB or rMenB at 0, 2 months and at 12 months of age, showed that three doses of 4CMenB induced protective levels of SBAs in 90% of the participants against five of the six meningococcal strains (44/76-SL, 5/99 and NZ98/254 plus three heterologous strains) (37). There was limited immunogenicity against fHbp variants, 1.15 and 1.4 and 1.14 (NZ98/254), indicating that the fHbp 1.1 variant in the vaccine does not provide cross protection against other fHbp 1 subvariants. Further work is also required to determine the contribution of NHBA in protection. Minimal SBAs titres were observed in subjects immunised with rMenB and tested against NZ98/254 despite having the same NHBA variant. Interestingly, while the OMV might not be expected induced protective antibodies against heterologous *porA* types, the 4CMenB showed increased immunogenicity compared to rMenB suggesting that antigens other than *porA* associated with the OMV might induce bactericidal antibodies.

In a phase IIb multicentre, open-label, parallel group, randomised control trial, 1885 two month old infants were immunised with 4CMenB at 2, 3, 4 months old or 2, 4, 6 months old plus routine vaccines; at 2, 4, 6 months old with routine vaccines at 3, 5, 7 months old; or routine vaccines. Immunogenicity was tested using the three test strains described above and a titre of <1:5 or greater, one month after vaccination, was taken as protective. Protective titres against two of the three test strains were seen in >99% of participants, and in 79% for NZ98/254 (when given at 2, 4, 6 months old with routine vaccines) or 81.7% (when given at 2, 4, 6 months old with routine vaccines at 3, 5, 7 months old), which met the predefined criteria of a sufficient immune response. The study showed that the 4CMenB vaccine was immunogenic and able to induce protective levels of antibody in infants (40). A phase IIb/III 4CMenB trial was carried out in adolescents aged 11-17 years who received one dose, two doses one month or two months apart or three doses one month apart, with all receiving one dose six months after the first dose. Sera were collected one month after each vaccination. The SBA GMTs were determined using the three test strains with a titre of <1:4 as indicative of protection. Over 90% of participants developed protective levels of SBAs to the three tests after one dose of vaccine and 99-100% after two doses, irrespective of the time interval between doses. A third dose did not provide any further benefit. This suggests that two doses of the vaccine given at least one month apart induces protective levels of SBAs against the test strains. The effectiveness of the vaccine in different geographical

regions will depend on the distribution of strain types in the region and the cross protection provided by the antigens in the vaccine (39).

The bivalent fHbp vaccine rLP2086 has been tested in a phase I trial involving 99 children (18-36 months old) immunised with three 20µg, 60µg or 200µg doses of rLP2086 or control vaccine (HAV) at 0, 1 and 6 months. Immunogenicity was evaluated on sera taken one month after vaccination, using five diverse meningococcal strains. Seroconversion post-dose three was evident in 61.1% - 83.3% of participants (depending on dose) using a subfamily A homologous meningococcal strain or 77.8% - 88.9% using a subfamily B homologous strain. Seroconversion post 200µg-dose three, using heterologous strains, ranged from 11.1% - 44.4%. An additional four heterologous strains were tested in SBA assays and showed 100% (subfamily A) and 81.8% - 94.4% (subfamily B) in the post 200µg dose-three sera. GMTs tended to increase following each dose for all three dose groups (43). In a phase II trial, 511 adolescents aged 11-18 years received three 60µg, 120µg or 200µg doses of rLP2086 or placebo at zero, two and six months. Eight meningococcal strains were used in the SBA assay, two of which were reference strains homologous or closely related to the fHbp in the vaccine. Between 67.7% - 100% of participants were considered responders after the third dose of the 120µg and 200µg dose and for the two reference strains 84.8% - 94% seroconverted (44). From both these studies, it is evident that bactericidal antibodies are elicited by the vaccine and that they act against a range of meningococci, but not all invasive meningococci are susceptible.

An OMV vaccine derived from *N. lactamica* was tested for immunogenicity in a phase I trial. The vaccine was immunogenic, eliciting rise in IgG titre against the OMV as measured by ELISA. A modest increase in SBA against group B strains of meningococci was seen (34).

The recent development of the group B vaccine has potential to reduce the burden of disease caused by this serogroup. Further studies are required to determine the ability of the vaccines to cover a significant range of heterologous strains within any geographical region, which would make the introduction of the vaccine cost-effective. It is also important to note that the expression of some antigens on the surface of the meningococci are variable and may not allow sufficient complement activation to kill the bacteria. The introduction of a group B vaccine may select for strains of meningococci with either reduced expression of surface proteins or variants that are not susceptible to the SBAs induced by the vaccine.

5.3.3 Efficacy and Effectiveness

The effectiveness of the polysaccharide vaccines containing group C has been established and will not be elaborated on. No recent reports of the efficacy or effectiveness of the group C polysaccharide vaccines were identified in the literature search.

As meningococcal disease is rare, and there are reasonable immune correlates of protection available, efficacy studies are not required for the licensure of meningococcal vaccines. Immunological data is usually used to bridge the lack of efficacy data. Effectiveness of the vaccines is assessed after introduction into the target populations.

5.3.3.1 2009 Cochrane review

A 2009 Cochrane Review assessed the effectiveness of C-MCV against group C disease (16). The specific hypotheses were:

- There is no difference in the number or severity of meningococcal cases.
- There is no difference in nasopharyngeal carriage of meningococci.

After evaluation of the eligible 39 studies, there were 22 studies included in the review that corresponded to 28 publications. Fourteen were RCTs, four were RCTs in the first phase, but in the second phase, a non-randomised age strata-matched control group was added. Four observational studies were included, in the absence of efficacy studies, 11 studies evaluated monovalent C-MCV, five studies evaluated AC-MCV and one study evaluated the 4-MCV.

The authors concluded that observational studies have documented a significant decline in meningococcal C disease in countries where C-MCV vaccines have been widely used. The timing of the vaccination schedules, the specific conjugate used and the vaccines given concomitantly or combined, may be important, but no specific recommendations were provided (16).

5.3.3.2 Group C vaccines

The effectiveness of group C conjugate vaccines has been well established in studies in the UK. By 2002, the overall direct vaccine effectiveness was estimated to be well over 90% (57). In 2004, estimates of vaccine effectiveness were >83% in all children between the ages of five months and 18 years (71). In infants however, effectiveness falls significantly one year after the last scheduled dose (72). A recent estimate of effectiveness in infants, one year after routine vaccination, was as low as 7%,

although the confidence interval was large (73). An update indicated that within twelve months of routine vaccination, vaccine effectiveness was 97% falling to 68% twelve months or more post-vaccination (74). Estimates of effectiveness in all other age groups ranged from 83% - 97%. In children, one to two years old vaccinated with a single dose, effectiveness was estimated to be 89% falling to 71% twelve months or more post-vaccination. A seven year follow-up of a group C vaccination campaign in Canada estimated the overall effectiveness of the conjugate vaccine as 87.4% and suggested higher short-term protection with increasing age of vaccination and higher waning in children immunised at a young age compared with those vaccinated at an older age (75). In cases of vaccine failure, it has been shown that immunologic memory was present and disease was due to the rapidity of the infection (68).

There were no studies that have commented on any overall clinical differences between the conjugate vaccines in terms of effectiveness.

An early estimate of the effectiveness of the quadrivalent conjugate vaccine, among adolescents in the US, was recently determined as 80% - 85%, which is similar to that reported for the polysaccharide vaccines (76). No published data for evidence of the effectiveness in older adults were identified in the literature search.

5.3.3.3 Efficacy and Effectiveness of VA-MENGOC-BC®

A phase III efficacy trial for the Chilean VA-MENGOC-BC® vaccine was carried out in 1987. It was a randomised controlled double-blind study in 106,251 boarding school students, aged 10-16 years of age, receiving two doses with a 6-8 week interval. The estimated efficacy after 16 months was 83%. There was an associated decrease in incidence of disease in the vaccinated provinces among children under six years of age indicating herd immunity. A summary of the efficacy trials of this vaccine are summarised in Table 8 (45).

Table 8. Results Obtained from a VA-MENGOC-BC® Phase III Clinical Trial Conducted in Seven Cuban Provinces

Group	Number contracting disease	Participants aged 10-16 years	Attack Rate per 100,000 pop.
Vaccine	4	52,966	7.6
Placebo	21	53,285	39.4

Since a mass vaccination campaign and introduction of this vaccine to the National Immunisation Schedule in Cuba, excellent disease reduction of meningococcal disease caused by group C and their epidemic group B strain has been shown. The incidence of meningococcal disease in Cuba, since implementation of the VA-MEN-BC vaccine, is presented in Figure 10. In 2006, the rate was 0.2 per 100,000 (45)..

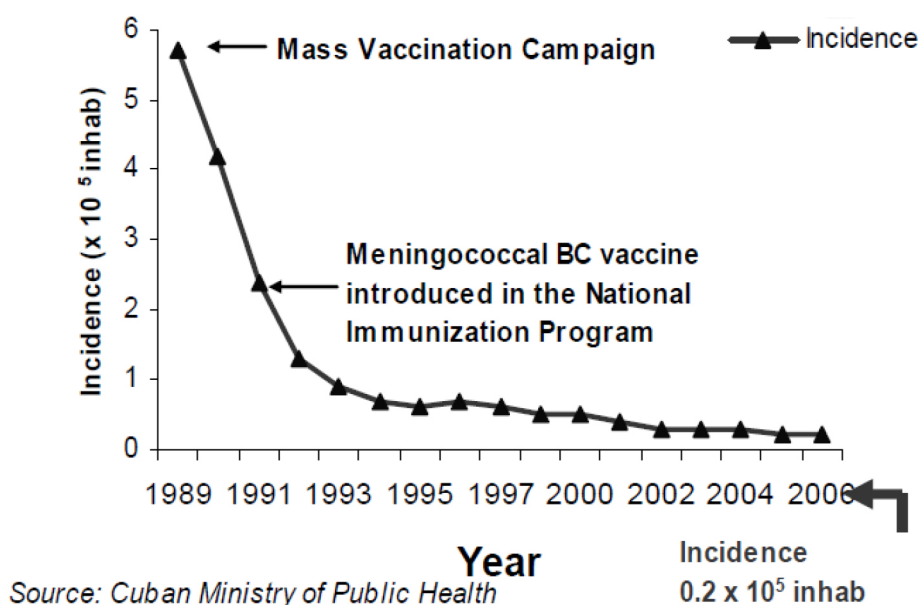


Figure 10. General Incidence of Meningococcal Disease in Cuba after Vaccination: 1989-2006 (45)

5.3.3.4 Group B vaccines

5.3.3.4.1 OMV vaccines

Estimates of the efficacy of OMV vaccines have come primarily from control studies in Brazil, Chile, Cuba and Norway. The Cuban OMV vaccine VA-MENINGOC-BC was estimated to have an efficacy of 83% among adolescents (47). For the Norwegian OMV vaccine, MenBvac, efficacy in 13-14 year olds was estimated to be 57% after 29 months (77). This was re-evaluated as 87% after 10 months (47). The efficacy of the MeNZB™ vaccine could not be determined as no control studies were completed. Estimates of the effectiveness of the vaccine have been 80% for >5 year olds, and 73% for all ages. A recent evaluation of the NZ data estimated effectiveness at 77% (78).

5.3.3.4.2 rMenB, 4CMenB and rLP2086 vaccines

As of early 2013, there is no data on the efficacy or effectiveness of these vaccines in any age group.

5.3.4 Herd Immunity

The ability of a vaccine to provide protection through the reduction in carriage and transmission of a pathogen is known as herd immunity. This has been identified as an important consequence of introducing group C conjugate vaccine (73, 74). The incidence of disease in the UK fell from 1.85 to 0.02 per 100,000 population. In the under-20 year olds, it fell by 99.1%, and in infants under one year of age, it fell by 99%. A reduction in disease was also seen in age groups not offered the vaccine (over 25 year olds and under three months of age) consistent with herd immunity (74). The duration of herd immunity is not known nor the protection against carriage of group C meningococci. Although, the levels of group C SBA fall in infants in the twelve months following routine immunisation, there is clear evidence of protection from disease due to herd immunity.

For the group B OMV-based vaccines, no recent updates on the effect of vaccines on carriage and the effect on herd immunity have been published.

5.3.5 Duration of Protection

Protection from group B and C meningococcal disease is based on a combination of herd immunity and levels of SBA. Measuring the GMTs and using a titre of <1:4 or a four-fold rise in titre as a correlate of protection has allowed vaccine development without the need for Phase III efficacy trials. The measurement of GMTs has also been used to determine the duration of protection that a vaccine can induce.

5.3.5.1 Group C conjugate vaccines

The SBA GMTs measured twelve months or more after administration of Group C conjugate vaccine show a decline in both infants and children whether they have had a routine schedule followed by a booster or a single vaccination. The percentage of children showing protective levels of SBAs two years after vaccination range from 22% - 45% depending on the vaccine (see section 5.3.2 Immunogenicity) (57, 62). Other studies have shown protective SBA titres in 97% of children up to five years after a booster at that age (15).

In general, levels of SBA have been shown to fall following immunisation and the earlier immunisation occurs the faster the decline in SBA, particularly in young infants (62). The decline continues throughout childhood, which has increased calls for a booster dose as children enter adolescence (61). Much better persistence of protective levels of SBA is seen in those immunised at a later age (79). Despite the fall in SBA among the younger age groups the incidence of disease in the UK remains very low suggesting that the reduction in carriage of group C meningococci is the major determinant of vaccine effectiveness.

5.3.5.2 Group B vaccines

For OMV vaccines, a rapid decline in SBAs has been reported after primary immunisation (47, 80). For NZ, this rapid decline resulted in only 48% of infants having protective SBAs post third dose of MeNZB™ and the introduction of a fourth dose at 10 months of age (80). No data are available on the long term persistence of SBA in the recent trials of rMenB, 4CMenB or rLP2086. Measurement of SBA titres, six months after administration of two or three doses of 4CMenB, showed 91% - 100% of participants had titres of <1:4 to the three reference strains used in the study, but only 73% - 76% in those who had received one dose (39). The effect of the new group B vaccines on carriage has not been determined and no information on herd immunity is available.

5.4 Summary of effectiveness

There are no recent publications specifically looking at effectiveness of polysaccharide vaccines, although, irreversible hyporesponsiveness has been documented resulting in the cessation of its use as booster vaccine in clinical trials assessing anamnestic immune responses.

In adults aged 56-65 years, there was superior immunogenicity induced by a conjugate vaccines compared with a polysaccharide vaccine. All three conjugate vaccines demonstrate adequate immunogenicity in infants, as either two dose or three dose schedules. The persistence of antibodies, following TT conjugated vaccine use in infancy, is longer and higher than those observed following D and CRM₁₉₇ conjugates. In adolescents, the CRM₁₉₇ conjugate produces higher antibody levels than the D conjugate. There is a decline in the proportion of children with protective antibodies, over time, and this is independent on the age at which the vaccine was received in children from over a year of age; there is a marked waning in infants immunised a younger age. Generally, there is a higher response to group C when given as a monovalent vaccine as opposed to a quadrivalent vaccine. There are no data to determine whether the immunogenicity differences for different conjugates translate to differences in effectiveness of the vaccines or to waning immunity.

C-MCV demonstrated a significant effect on carriage, which has been shown consistently in populations who have used these vaccines. The group C conjugates have effectively controlled group C disease in many countries. In cases of vaccine failure, it is assumed to be due to the rapidity of disease progression due to low serum antibody rather than a lack of immunological memory, indicating that booster doses are required to maintain protection. There is no evidence available for efficacy in older adults.

There is clear evidence that conjugate vaccines provide excellent herd immunity. Despite falls in serum antibodies, the impact of conjugate vaccines on incidence of disease suggests that the reduction in carriage is a major determinant of the overall vaccine effectiveness.

The Cuban BC vaccine has been widely used internationally since the 1980s and its implementation has resulted in excellent control of meningococcal disease. Herd immunity has also been demonstrated associated with its use.

Late-phase trials have demonstrated good immunogenicity for the group B 4CMenB vaccine, Bexsero[®]. There is not yet any effectiveness data for this vaccine. The duration of protection provided to the population receiving these vaccines is based on a combination of herd immunity and individual levels of SBA.

6. Age-specific issues

6.1 Objective

This section considers the differences that need to be considered for various age groups. Literature for age-related morbidity and mortality is included. Issues around the use of available vaccines in age groups other than infants and young children are also considered.

6.2 Review

6.2.1 Burden of disease by age

Meningococcal infections are most common in children under one year of age (Figure 11). In NZ, the rate for this age group in 2011 was 38.5 per 100,000. In the US, the rate for this age group in 2010 was 2.23 per 100,000 (81). The rate for England & Wales in 2010/2011 was 30.5 per 100,000, where currently there is a very high incidence of group B disease (82). For the one-four year olds, the rate in NZ was 12.7 per 100,000 and in England & Wales 11.6 per 100,000. There is a slight increase seen in 15-19 year olds, with 4.7 per 100,000 in NZ and 2.8 per 100,000 in England & Wales. Meningococcal disease in the over 65 year olds is uncommon (0.7 per 100,000 in England &

Wales) (82). In NZ, the rate for those over 40 years of age is 1 per 100,000. Twelve cases of meningococcal disease were confirmed in the over 55 years of age group in NZ in 2011 with two fatalities.

Within the under-one age group, there is a significant disparity with regard to ethnicity. The highest disease rate by age group was found in the under-one year olds in the Pacific Peoples ethnic group (126.7 per 100,000) followed by Māori (77 per 100,000). Three cases of meningococcal disease were reported in the under-one year old European or Other ethnic group.

The NZ case fatality rate (CFR) was 10.9% in 2011, compared with an average of 5.3% for 2006-2011 in England & Wales (82). The NZ CFR for the under-one year olds for 2007-2011 was 9.6%, the highest of any age group. The majority of cases (62%) in NZ were caused by group B meningococci and over half of these were due to the NZ epidemic strain (37%). Group C meningococci caused 32% of disease with most of these (27%) being one particular strain (C:P1.5-1,10-8). The group C meningococci had the highest CFR in NZ, as seen in England & Wales (82).

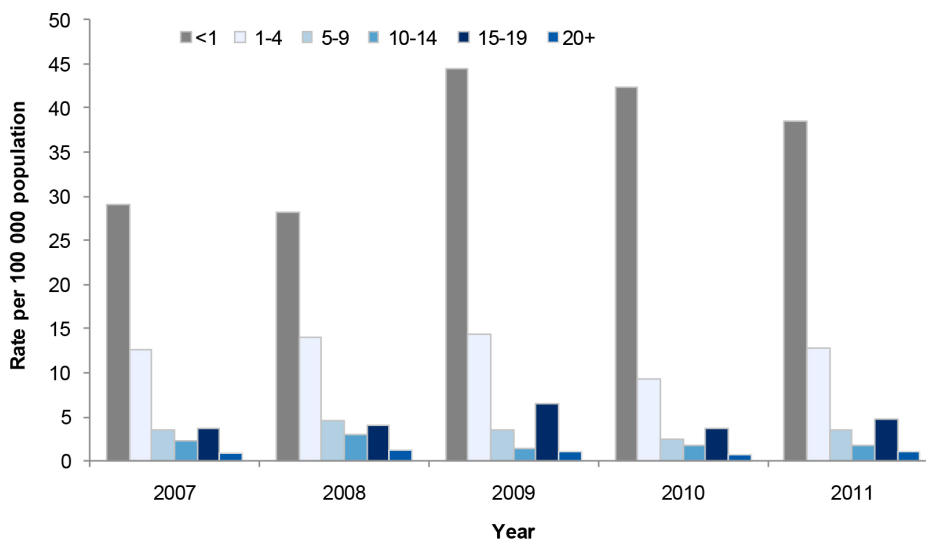


Figure 11. Rates of meningococcal infections in NZ by age group

6.2.2 Vaccine issues for different age groups

The data around meningococcal vaccines have been determined in a range of age groups. Most consider the infant and young adult age groups as they are the most vulnerable.

6.2.2.1 Infants

The use of polysaccharide vaccines against group C meningococci is not recommended in the infant age group, and only conjugate vaccines induce an appropriate immune response. No polysaccharide vaccines against group B meningococci are available. Schedule options for the administration of these vaccines are given in section 8.

The SBA titre has been shown to decline more rapidly in this age group prompting the need for booster vaccinations at a later age.

6.2.2.2 Adolescents and young adults

The increase in disease rates among the 15-19 year olds, and the measured decline in SBA titres up to five years after the last meningococcal vaccination, resulted in recommendations in the US for a booster dose of the quadrivalent conjugate vaccine at age 16 years following routine vaccination at age 11-12 years (83). In the UK, meningococcal vaccination in this age group was part of a catch-up campaign against group C meningococci. There is some debate about the necessity of a booster for young adults, who only received the primary schedule of doses, given the rapid decline in SBA titres and potential loss of herd immunity leading to a possible increase in infections in this age group (62, 64). Both polysaccharide and conjugate vaccines are effective against disease in this age group. However, given the issues with hyporesponsiveness, it may be prudent to avoid polysaccharide vaccines, even as boosters.

This age group is most likely to be carriers of disease. Vaccination strategies that include a focus on herd immunity need to focus on this group, not just for individual protection, but also to reduce community spread.

Multiple studies have identified the risk of meningococcal disease in college and university students, especially among those in halls of residence or dormitories. The US, Advisory Committee on Immunisation Practices (ACIP) recommends that all college freshmen are vaccinated against meningococcal disease (22, 83).

6.2.2.3 Adults

The polysaccharide vaccines are effective in adults, although hyporesponsiveness is a concern for repeated vaccinations. The provision of a better immune response in adults by conjugate vaccines over polysaccharide vaccines suggests that they are likely to offer better protection against disease. There is no recent data on the use of conjugate vaccines in the over 55 year olds, apart from a study on the use of ACWY-CRM, which showed the conjugate vaccine gave higher GMTs than a polysaccharide vaccine (26). No studies were identified in the literature search looking specifically at the over 65 age group.

6.3 Summary of age-specific issues

The burden of meningococcal disease in NZ is caused by group B and group C organisms. The under-one year olds are disproportionately affected by the disease due, primarily, to a lack of SBAs against meningococci. The 15-19 year olds also experience an increased risk of disease and are the age group most likely to be carrying the disease. A successful campaign against group C meningococcal disease in the UK was run based on infant vaccination and a catch-up campaign in the under-25 year olds.

Only conjugate vaccines should be used in the infant age group. Polysaccharide vaccines may still be effective in the adult population for short term protection, although hyporesponsiveness is an issue. Conjugate vaccines should be considered in preference to polysaccharide vaccines for these adult groups, as overall, they elicit a better antibody response without hyporesponsiveness. No data on the efficacy of the conjugate vaccines in the over 65 year olds have been reported.

The 4CMenB vaccine has been evaluated in infants, children, adolescents and young adults and is immunogenic against the NZ epidemic strain of group B.

7. Vaccine options

7.1 Objective

The objectives of this review are to consider the vaccine options available to NZ against group C and group B meningococci in terms of available vaccines and schedules. Consideration is given to the effect of these vaccines the meningococcal populations in NZ, their pathogenicity and the implications for herd immunity.

7.2 Review

7.2.1 Prevention of meningococcal group C

There are a number of different options group C vaccines.

7.2.1.1 Polysaccharide vaccine

The group C polysaccharide vaccines can either be bivalent (A and C polysaccharide, Mengivac) or quadrivalent (A, C, W135 and Y polysaccharide, Menomune[®] and Mencevax[®]). The bivalent vaccine is not licensed for use in NZ, but is available and has been shown to be effective in the prevention of group C meningococcal disease (75). There are two available quadrivalent polysaccharide vaccines, Menomune[®] and Mencevax[®]. Both are licensed for use in NZ. The number of cases of meningococcal disease due to non-group C or B meningococci in NZ is very small (in 2011, there were no cases of group A, three group Y and two group W135 cases of meningococcal disease notified). The ready availability of the quadrivalent vaccine and the effective immune response to group C meningococci in all age groups, except the under-two year olds, indicates an effective vaccine for the control of group C meningococcal disease.

The limitations of polysaccharide vaccines, outlined in the preceding sections, do not make these vaccines good candidates for use on the immunisation schedule, including for high risk groups.

7.2.1.2 OMV vaccine incorporating group C polysaccharide

The Cuban vaccine VA-MENINGOC-BC incorporates group C polysaccharide into OMV derived from the Cuban group B epidemic strain. This vaccine has been effective in the control of group C disease in Cuba, and other countries, and is part of the Cuban immunisation schedule. The vaccine is not currently licensed for use

in NZ, but may be considered for control of group C meningococcal disease based on a cost-benefit analysis.

7.2.2.1 Monovalent conjugate vaccine

There are three monovalent group C conjugate vaccines; NeisVac-C[®] (conjugated to TT) Meningitec[®] (conjugated to CRM₁₉₇) and Menjugate (conjugated to CRM₁₉₇). NeisVac-C[®] and Meningitec[®] are licensed for use in NZ. All are effective in controlling group C meningococcal disease.

7.2.1.4 Quadrivalent conjugate vaccine

One quadrivalent conjugate vaccine is licensed for use in NZ (Menactra[®], ACWY-D), two other are available, namely, Menveo[®] (ACWY-CRM) and a developmental vaccine, ACWY-TT. All three vaccines have been shown to be effective in inducing protective levels of antibody against group C meningococci. Given that there is an absence of Group A diseases in NZ, and very little Group W135 or Y disease, there may be little gain in using these vaccines on the schedule, particularly for infants. Given the limitations of the quadrivalent polysaccharide vaccine, the 4-MCV could be considered for travellers and high risk groups in preference.

All applications of group C vaccines have resulted in the effective control of group C disease. The UK implementation suggested herd immunity is important for successful reduction in disease rates.

7.2.2 Group B vaccines

7.2.2.1 OMV vaccines

There are a number of OMV vaccines that have been used for the control of epidemic and outbreaks of group B disease. The most notable from a NZ perspective is MeNZB[™], an OMV vaccine specific for the epidemic group B strain (P1.7,2-4). The vaccine has been withdrawn and is no longer available. Other OMV vaccines include the Cuban vaccine VA-MENINGOC-BC (P1.19,15), which has been used both in Cuba, as part of the routine immunisation schedule, and in Brazil to control group B outbreaks. A Norwegian OMV vaccine MenBvac (P1.7,16) has been used effectively to control epidemic and outbreaks of group B disease (68). All OMV vaccines are effective in controlling group B meningococci which have

homologous porA proteins. The possible impact of the Cuban vaccine on group B disease in NZ is not known, but is unlikely to be significant.

7.2.2.2 rMenB, 4CMenB and rLP2086

These are vaccines currently being developed for the control of group B disease. They are effective in eliciting bactericidal antibodies to a range of reference strains of meningococci. Their efficacy and effectiveness for the control of group B disease resulting from a range of different strains is as yet unknown, but immunogenicity data are now available to inform licensure. The 4CMenB vaccine (Bexsero®) has recently been licensed by the European Medicines Agency and US FDA licensure is anticipated.

The 4CMenB vaccine has been assessed for its potential to prevent circulating strains in the UK and Australia. It is estimated that this vaccine would be immunogenic against 70% - 80% of group B in those countries. This assessment has not yet been made for NZ. Given that more than half of the group B cases in NZ over the past five years have been caused by P1.7-2,4 and the 4CMenB is highly immunogenic against the strain, due to the inclusion of the NZ OMV in the formulation, NZ could stand to benefit more than other countries should the remaining group B strains prove to be similar to the panels in UK and Australia. A rough estimate is presented in Table 9.

Table 9. Group B meningococcal disease cases in NZ 2007-2011 with number and proportion caused by P1.7-2,4 and 'other' group B strains and potential coverage by 4CMenB

Group B P1.7-2,4 Number of cases 2007-2011	183 (54% of group B)
Group B other Number of cases 2007-2011	153 (46% of group B)
Potential number and proportion of cases preventable by 4CMenB over five year period 2007-2011	297 (88%)
Assuming the Group B 'other' is similar to those in the UK and Australia, and assuming 75% coverage of circulating strains.	

7.3 Summary for vaccine options

Group C conjugate vaccines are available for use for the effective control of group C meningococcal disease. There is also a Cuban BC vaccine that includes an OMV protein as opposed to a protein conjugate. This vaccine appears to be an immunogenic protein-based vaccine and induces herd immunity. It has successfully controlled group C disease as well as group B caused by the vaccine OMV. There may be little gain in using a quadrivalent over a monovalent conjugate vaccine in terms of number of cases of meningococcal disease prevented. A general group B vaccine 4CMenB (Bexsero®) is now available and has the capacity to target a significant proportion of group B disease in NZ. Evaluations of just how much will need to be undertaken, however, the inclusion of the NZ OMV in the formulation, and its relative immunogenicity, indicate that it will be protective against our epidemic strain and likely much more.

8. Options for scheduling

8.1 Objective

This section reviews the evidence for different options for placement of the group B and group C vaccines on the childhood immunisation schedule.

8.2 Review

The impact of a vaccine is its ability to reduce the burden of disease within a population in a cost effective manner. The major age groups affected by meningococcal disease are the under-five year olds and mid to late adolescents. All meningococcal vaccine campaigns have been aimed at reducing the incidence of disease in these age groups.

There are a number of different implementation schedules around the world for group C vaccines. In general, wherever a mass vaccination campaign has been introduced, there has been a significant reduction in cases of group C meningococci. Four vaccination schedules have been identified in Europe (84). These range from two or three doses of MCV in the first year plus a dose in the second year with a catch-up campaign to a single dose in the second year with a catch-up campaign. In the US, the ACIP recommends routine vaccination of 11-12 year olds with a quadrivalent conjugate vaccine and a booster dose at 16 years. Australia has a routine vaccination with C-MCV at 12 months old with a catch-up campaign for those who were 1-19 years old between 2003 and 2006. The catch-up campaign in the UK was considered the major determinant of the programs outcome and cost-effectiveness as it established herd immunity reducing transmission to the vulnerable populations (69).

8.2.1 Group C vaccines

NZ does not have group C vaccine as part of its immunisation schedule. The scheduling of group C vaccines is different in a number of countries (85). Where a country does have group C vaccination as part of its immunisation schedule, the majority use C-MCV vaccines. The options currently employed are as detailed below.

8.2.1.1 Routine infant immunisation plus catch-up

This is used in UK, Spain, Greece, Ireland, Iceland and Portugal targeting the most vulnerable age group. Infants receive two doses of vaccine (ages vary between countries, but generally at 2 and 4 months) plus a booster at 12-15 months (except Iceland). All countries except Iceland and Portugal have implemented a catch-up campaign.

Countries where the incidence of group C meningococcal disease is high have adopted this strategy.

8.2.1.2 Routine child immunisation strategy plus catch-up

This is used in a large number of countries (Australia, Belgium, Brazil, Canada, Netherlands, Germany, Switzerland and France). Children aged 12-15 months receive a single dose of vaccine. A booster dose at 12-15 years is given in Canada and Switzerland. A catch-up campaign was implemented in all countries except Germany and Switzerland. This strategy is based on effectiveness of the vaccine and cost-benefit analysis.

8.2.1.3 Adolescent only immunisation strategy

This is used in the US targeting the peak of cases among adolescents and young adults. Routine vaccination (using a quadrivalent conjugate vaccine) is recommended at 12 years old with a booster at 16 years old.

In all countries where routine immunisation and catch-up has been implemented there has been a significant fall in the number of cases of group C meningococcal disease. The rapid fall seen in SBA titres associated with a decline in vaccine effectiveness in infants vaccinated against group C disease indicates that protection against the disease in this age group is temporary. Herd immunity plays a large part in the protection of infants and in older adults who have not been included in the vaccination strategy.

8.2.1.4 Booster doses

Booster doses have been implemented in three different strategies, a booster dose at 12-15 months of age following primary doses at 3 and 4 months (UK), 2 and 6 months (Spain), 4 and 6 months (Ireland), a booster dose in early adolescence (11-15 years old) (Canada, Switzerland) or no booster (Australia, Belgium, Netherlands, Iceland, Germany) (85). The need for a booster dose at 12 months was based on the rapid waning of SBA titres following primary vaccination (84). While this schedule has been effective in reducing the incidence of group C disease concerns have been raised about the future protection of young adults in the UK who only received the infant doses and booster dose at 12 months of age and the impact on herd immunity (57, 62, 64). A study by Snape et al. showed 88% of adolescents boosted at age 10-15 years had protective levels of antibody at age 14-20 years suggesting an additional booster at this age would be beneficial (22). The introduction of a booster at 12 years of age may allow for the cost-effective removal of some of the infant doses (62).

In adolescents, aged 13-15 years old, a booster dose of group C polysaccharide vaccine following primary vaccination with a C-MCV vaccine has been found to be as effective in eliciting SBAs as a booster with the conjugate vaccine. Measurement of GMTs one year following the booster showed no difference between either vaccine (79).

8.2.1.5 Special groups

Recent US studies on the use of the quadrivalent conjugate vaccine in HIV-infected adolescents and young adults (11-24 years old) showed that a single dose of the vaccine was safe and immunogenic (86). Lower antibody response levels to serogroup C meningococci were associated with high viral load and low CD4 count. A two-dose schedule in children (2-10 years old) was also shown to be safe and elicit a protective antibody response against all four serogroups, but waned significantly for serogroups A and C one year after the final dose (31). A comparison of a one or two dose schedule in 11-24 year olds showed that in those with a CD4% >15 a protective level of antibody was maintained against all but serogroup C through to week 72 whether they received one or two doses. The antibody titres in those who

received a second dose were significantly higher which may afford longer term protection although such studies have yet to be conducted. The value of vaccinating those with a CD4% <15 was questioned given the low response in this group (32).

The literature search did not identify any recent studies looking at group C conjugate vaccines in pregnancy. The safety and immunogenicity of C-MCV in pre-term infants was investigated in two recent studies (17, 87). Both studies showed that pre-term infants were able to mount a protective response to C-MCV, although the response rates were lower than those seen in full-term infants.

The combination vaccine used in the UK Hib-MenC can be used for both primary and booster vaccination and can be coadministered with both Prevenar® and MMR (18). This could enable the placement of a dose of Meningococcal C vaccine on the schedule at 15 months without the need for a further separate injection.

8.2.2 Group B vaccines

At present Cuba is the only country to have a vaccine that targets group B vaccine on the routine immunisation schedule. Infants receive two doses of VA-MENINGOC-BC at three and five months old. The vaccine has been effective in controlling the group B epidemic. Other countries including NZ have implemented vaccination campaigns against epidemic group B infection using OMV vaccines but these have been withdrawn following the decline in the rates of group B disease. Schedules using the OMV group B vaccines have adopted a three or four dose regime with a catch-up campaign in older age groups. Where implemented the vaccination campaigns have been effective in reducing the incidence of disease. The recent trials of a group B vaccine 4CMenB have used a three dose primary regime with two timings (2, 3, 4 months old and 2, 4, 6 months old) (40), both inducing protective levels of SBAs. Further work is required to determine the optimal schedule for this vaccine.

8.3 Summary of options for routine scheduling of group B and C vaccines

Three general alternatives are available for group C vaccine scheduling, an infant primary series with or without booster plus a catch-up campaign, a single dose at one year old with or without booster plus a catch-up campaign or an adolescent dose plus booster at 16 years. The option taken is dependent on the local epidemiology of group C disease and a cost-benefit analysis. There are several factors that may support not using a group C vaccine in the early infant schedule:

- NZ does not currently have a major epidemic of group C disease
- There is better immunogenicity of conjugate vaccines observed in older infants and children associated with a reduced number of doses required
- NZ is now able to achieve higher rates of immunisation coverage than it did several years ago making herd immunity a realistic goal.

Given these issues it may be pragmatic to use one or two doses of meningococcal C vaccine later in the first year of life or during the second year of life with a booster dose in early adolescence and a catch-up campaign with the view to achieving and maintain population herd immunity.

With respect to group B disease, the larger burden of disease caused by group B and the rates in the under one year olds supports that initially the best placement of a group B vaccine would be on the infant schedule, at least until herd immunity is observed when moving it to an older age with fewer doses may be pragmatic and cost effective. The 4CMenB vaccine has been assessed for concomitant use with the other infant vaccines including pneumococcal vaccine. Some options for schedule placement of meningococcal vaccines are presented in Table 10, based on current international practice and immunogenicity data for the vaccines.

Table 10. Options for placement of meningococcal B and C vaccines on the NZ immunisation schedule

	6 weeks	3 months	5 months	12 months	15 months	4 years	11/12 years	Booster / catch-up 16-20 years
MCV 2+1		*	*		* booster with hib/menC*		*	*
MCV 1 dose infant + booster					* (or 12 months)		*	*
MCV 1 dose adolescent							*	*
4CMenB 3 doses infant	*	*	*					
4CMenB 3 doses infant		*	*	*				
4CMenB 2 dose infant/ child			*	*				
4CMenB 1-2 doses adolescent							* (1 or 2 doses)	

*The UK use a Hib/MenC combination vaccine

9. Implementation issues

9.1 Objective

The objective of this section is to review the most recent data for the currently licensed vaccines with respect to potential implementation issues in the NZ context. This includes the effect of vaccines on capsular switching, types and timing of schedules, outbreak control, co-administration, and specific vulnerable population groups.

The current schedule does not provide for routine meningococcal vaccination. Group C vaccines are only provided in the event of a community outbreak and the tetravalent vaccines (conjugate or polysaccharide) to pre and post splenectomy patients or children with functional asplenia.

9.2 Review

9.2.1 At risk populations

At-risk populations include infants, patients with complement deficiencies, microbiologists working routinely with *N. meningitidis*, asplenic patients, new college/university students, patients infected with HIV. In NZ, in addition to the above, other at-risk populations identified include young people living in lower decile housing, Māori and Pacific Island children. The current US recommendations for **conjugate meningococcal vaccination** of at-risk groups are given in Table 11. The only at-risk group currently funded for meningococcal vaccination with the **quadrivalent polysaccharide vaccine** in NZ are asplenic children and adults. Vaccination is recommended for other at-risk groups but not funded.

If NZ were to change from a polysaccharide vaccine to a conjugate vaccine, for persons aged two to 55 years with high risk conditions, there may be further challenges with providers over the differences between polysaccharide and conjugate vaccines. While both types of vaccines are available on the market, there is likely to be an increase in administration errors, as occurs currently with administration of polysaccharide vaccines instead of conjugate vaccines in NZ, as reported by the NZ 0800 Immunisation Advisory Service.

Table 11. Summary of meningococcal conjugate vaccine recommendations, by risk group — Advisory Committee on Immunization Practices (ACIP), 2010 (83)

Risk group	Primary series	Booster dose
Persons aged 11 to 18 years	1 dose, preferably at age 11 or 12 years	At age 16 years if primary dose at age 11 or 12 years
		At age 16 to 18 years, if primary dose at age 13 to 15 years
		No booster needed if primary dose on or after age 16 years
HIV-infected persons in this age group	2 doses, 2 months apart	At age 16 years if primary dose at age 11 or 12 years
		At age 16 to 18 years if primary dose at age 13 to 15 years
		No booster needed if primary dose on or after age 16 years
Persons aged 2 to 55 years with persistent complement component deficiency* or functional or anatomical asplenia	2 doses, 2 months apart	Every 5 years
		At the earliest opportunity if a 1-dose primary series administered, then every 5 years
Persons aged 2 to 55 years with prolonged increased risk for exposure	1 dose	Persons aged 2 to 6 years: after 3 years
		Persons aged 7 years or older: after 5 years

9.2.2 Implementation issues around introduction of Group C vaccine

The significant number of group C cases in the UK during the 1990s warranted implementation of the vaccination schedule which has been successful in reducing the incidence of disease. As yet, no capsular switching has been reported among the current cases of invasive meningococcal disease in the UK. Such replacement has been seen previously (46, 88, 89).

Which schedule is adopted depends on the local epidemiology and a cost-benefit analysis. The susceptibility of infants to disease would suggest targeting this age group would be beneficial, but the rapidly waning antibody levels after vaccination indicate this would give only short term protection, and may not be the only or a sufficient strategy. Herd immunity is important for the reduction of this disease and from the UK experience targeting teenagers is crucial to decreasing carriage and transmission. The optimal implementation strategy will depend on the number of doses chosen, the timing of the doses and the cost. No issues have been identified with respect to co-administration of the MCV with routine vaccinations.

The evidence for administering the group C vaccine as a universal programme was clearly shown in the UK where the number of cases of group C meningococcal disease fell from 955 in 1998/1999 to 24 in 2010/2011 (82). The implementation of a universal programme is dependent on the incidence of group C disease in the country at the time. Where the rates are high, a universal programme will prove cost-effective as seen in Europe. Where the rates are low, a directed programme, such as that seen in the US, may be more cost-effective. In NZ, the rate of group C meningococcal disease is 0.7 per 100,000 compared with a rate in the UK of 5.3 per 100,000 in 1998/1999 prior to the introduction of the group C vaccine campaign (57).

Implementation of a group C vaccine into the infant schedule at six weeks will add a third injection to the primary series. If a group B vaccine were also being considered for introduction at this time, the administration of four injections at a single visit may pose challenges for vaccinators, and it is likely that education would be required on both techniques for administering multiple injections and managing parents and caregivers during the session.

Should the Cuban VA-MENGOC-BC® vaccine be considered for use on the NZ schedule for the prevention of Group C disease, attention will need

to be given to the acceptability to the public on the presence of thiomersal in the formulation. The vaccine also contains a relatively high amount of aluminium adjuvant (the amount of elemental aluminium needs to be confirmed). Globally, there has been a move to remove thiomersal from vaccines and the vaccines on the NZ childhood schedule have been thiomersal-free since around 2000. Although there is no evidence that thiomersal in vaccines poses any risks to health, the introduction of a vaccine with a formulation high in aluminium adjuvant and the presence of thiomersal could create concerns, affecting uptake of all scheduled vaccines.

9.2.3 Implementation issues around introduction of 4CMenB

One of the issues highlighted as vital as part of any implementation of meningococcal vaccines is the post-implementation of vaccine safety and effectiveness. Post implementation surveillance can identify not only the potential herd immunity impact, but also the need for boosters and any interactions with other routine vaccinations. This is particularly so for post implementation surveillance of group B vaccines where the range of strain coverage, validation of surrogates used to estimate this, effects on carriage, herd effects, safety and acceptance by both the public and health professionals should be addressed. These issues have been considered in a 2012 Lancet article and are summarised below (90).

1. **Pre-implementation data:** accurate epidemiology of disease and the potential for herd immunity including associated microbiology and immunology. Infrastructure must guarantee accurate information on the timing and distribution of vaccines, disease monitoring and associated morbidity and mortality, collection and analysis of infection-related isolates and a system for recording AEFI. This infrastructure well established in NZ.
2. **Post-implementation surveillance to monitor vaccine effectiveness:** the novel, multivalent, nature of meningococcal B vaccines presents difficulties in determining the proportion of group B disease likely to be covered by immunisation. These challenges are exacerbated by the considerable variability of target antigens between and within strains, and the potential for changes in these antigens over time and between geographical regions. This uncertainty makes the surveillance following the introduction group B vaccines of even greater importance than has been the case for more traditional vaccines. As

in the case of 4CMenB, evidence of protection against a few target strains does not provide sufficient information about the protection against all circulating disease-causing strains.

3. **Monitoring vaccine uptake and direct vaccine protection:** in order to determine vaccine effectiveness, accurate information on vaccine uptake and robust disease notification are required. In NZ, the National Immunisation Register and established database systems, for collecting and monitoring the microbiology of notifications of disease, can be used to estimate vaccine effectiveness using a variety of epidemiological methods.
4. **Monitoring the indirect effects:** if immunisation with a group B vaccine reduced carriage of *Neisseria* species and the age of peak nasopharyngeal carriage, and if the vaccine was employed in a way that facilitated this impact (e.g. through a mass immunisation campaign of adolescents and young adults), then reduced circulation of strains bearing one or more of the vaccine target antigens may well be observed. This may be detected either in nasopharyngeal carriage studies or in reduced rates of disease due to 'susceptible' Neisserial organisms in unimmunised cohorts. Alternatively, effects on Neisserial carriage could apply selective pressure and increase the carriage of pathogenic strains that do not bear the vaccine antigens.
5. **Monitoring of AEFI:** the pre-licensure trials of 4CMenB showed that 61% of two month old infants became febrile following concomitant administrations with a licenced hexavalent vaccine and PCV-7 with 11% having axillary temperatures >39°C. Such events cause anxiety to parents and often result in contact with health services (as observed in NZ associated with administration of Fluvax® in 2010). Febrile seizures have also been documented to occur with 4CMenB. Close monitoring for these events will be important as will careful communication about an increased risk for fever associated with this vaccine. NZ has demonstrated its ability to rapidly and accurately assess the rate of vaccine associated fever during the H1N1 influenza pandemic, therefore, determining the risk for febrile events following administration of any vaccine in the NZ population would be straight forward (91).

6. **Communication and public acceptance:** there are at least two issues around the communication about the implementation and surveillance of 4CMenB, (or any other group B vaccine); how to coordinate and deliver the relevant information about the vaccine to the community as a whole, including the public, health professionals, media and government and non-government funding organisations; and how to furnish new information regarding attitudes about the vaccine and its overall impact on public health. Social marketing may be a means to shape beliefs, although care must be taken. Many factors are involved, such as how debilitating the disease is perceived to be (likely to be high in NZ), the extent to which "another jab" within the routine immunisation schedule of infants is acceptable to parents and vaccinators, and the importance of safety to consider concerns about common adverse events such as fever. Educating parents and healthcare professionals regarding potential vaccine reactions will be an important element of any campaign introducing 4CMenB into routine use. It may be advisable to carry out attitudinal research in order to hone communication strategies.

NZ has learnt many lessons about introducing a vaccine against meningococcal group B disease, which are likely to be of particular relevance to any implementation of 4CMenB vaccine.

9.2.4 Outbreak control

The incidence of meningococcal disease can fluctuate over time which can be seen as sporadic cases, outbreaks or epidemics. Epidemics can be group A (meningitis belt in Africa), group B (NZ, Norway, Cuba and Brazil) or group C (Brazil, Vietnam, Burkina Faso) according to the World Health Organization (92). Although a large increase in cases of group C disease was seen in the UK, Canada and some parts of Europe they have not been described as epidemic. The group B epidemics tend to be caused by the spread of a single strain in the population while the group C tend to be of a certain sequence type, such as ST8 or ST11 (22). The control of epidemics is governed by the availability of an appropriate vaccine. For group B epidemics, this requires a strain-specific OMV-based vaccine, while the recent increases in group C require a vaccine specific for the group C polysaccharide. Control of group B epidemics has been effective in countries that have introduced a strain-specific vaccine and universal vaccination, such as Cuba and NZ. Control of group C disease has also been effective in countries that have introduced universal vaccination using group C vaccines, specifically, UK and Canada.

Local outbreaks of meningococcal disease can be due to group B or C meningococci. A local outbreak of group B disease (P1.7,16) in a region of France was effectively controlled by the introduction of the Norwegian OMV vaccine, MenBvac™, with the same porA type (68). The incidence of disease due to this strain was significantly reduced after the primary vaccination period. This strategy would only be effective if the porA type in the local outbreak was the same as an available OMV vaccine. Local outbreaks of group B and C disease, such as those occurring in university or college halls of residence, may be controlled by the administration of prophylactic antibiotics. The rapidity of disease onset for meningitis would preclude an effective immune response to the infection and antibiotics may be appropriate. Vaccination in this situation would reduce carriage of the invasive organism, and hence, stop further spread. Community outbreaks of group C disease would also benefit from vaccination since the elimination of carriage of the organism would prevent future cases of the disease within the same community.

9.2.4.1 Recent NZ experience

In NZ, group C tends to occur sporadically. In 2011, there was a community outbreak of group C disease in Northland. The public health response to this outbreak included a mass immunisation campaign for children and youth aged one year to 20 years of age with meningococcal C conjugate vaccine. Significant challenges in implementing the programme were identified, including insecurity of vaccine supply, lack of central government funding support, inadequate numbers of authorised vaccinators, traditionally very low immunisation coverage rates in the region and associated socioeconomic and health inequities.

Despite these challenges, there were factors that facilitated the overall success of the programme. These included:

- Excellent collaboration across the health sector and with education partners.
- A multi-pronged public communications strategy including: traditional media (Māori and mainstream), Facebook and Internet, local “champions” and regular communications through a wide range of networks, from early childhood centres to St Johns and other community organisations, *rūnanga* (a traditional Māori assembly or tribal gathering), community meetings and *hui*.

To address the social and ethnic inequities and access barriers, “walk in” community and mobile clinics staffed by public health nurses, *kaimahi* and health promoters were implemented. These were being utilised in greater numbers by Māori *whānau*, and youth (93).

The lessons learnt in Northland will be valuable considerations for future meningococcal C outbreak control in NZ.

9.3 Summary for implementation issues

Currently, NZ uses MPV in patients considered at high risk for meningococcal disease. If there is a move towards using MCV instead, consideration should be given to the communication required to providers for whom some there is still significant confusion about the different types of vaccine. Should a group C vaccine be considered for the infant schedule, the number of separate injections may require consideration in terms of vaccinator education.

The post implementation monitoring of both vaccine effectiveness and safety has been highlighted as vital part of the post implementation component of a vaccination programme against meningococcal disease, and more so, should a group B vaccine be introduced. NZ already has in place excellent systems and infrastructure for monitoring the epidemiology of disease including infection-related isolates. Establishing vaccine effectiveness will be an important component of a group B programme. And NZ has the databases required to evaluate both effectiveness and safety.

The NZ epidemiology of meningococcal C is relatively sporadic, and in the absence of a universal programme, outbreak control may be required periodically. Northland recently implemented a mass immunisation programme to control a community outbreak of group C and there are lessons on the factors that both enable and posed challenges for this campaign.

Finally, communication is a vital issue and likely to be of particular relevance to outbreak control and any use of a group B vaccine. The 4CMenB vaccine appears to be more reactogenic than the current routine childhood vaccines and co-administration has the potential to affect perception of all childhood vaccines should significant febrile events occur frequently. Managing parental expectations around vaccine reactions will need to be addressed carefully.

10. International policy and practice

10.1 Objective

The objective of this section is to summarise some of the different policies and practices of meningococcal immunisation internationally.

10.2 Review

10.2.1 United States

In January 2005, a tetravalent meningococcal polysaccharide-protein conjugate vaccine Menactra™ was licensed for use among persons aged 11-55 years. Advisory Committee on Immunisation Practices (ACIP) recommended routine vaccination of young adolescents with 4-MCV at the preadolescent healthcare visit at age 11-12 years. For those persons who had not previously received 4-MCV, ACIP recommended vaccination before high-school entry, at approximately age 15 years, as an effective strategy to reduce meningococcal disease incidence among adolescents and young adults. Routine vaccination with meningococcal vaccine was also recommended for college freshmen living in dormitories and for other populations at increased risk, such as military recruits, travellers to areas in which meningococcal disease is hyperendemic or epidemic, microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*, patients with anatomic or functional asplenia, and patients with terminal complement deficiency. Other adolescents, college students and individuals infected with human immunodeficiency virus who wish to decrease their risk for meningococcal disease may elect to receive vaccine (94).

In October 2010, the ACIP approved updated recommendations for the use of quadrivalent MCV (serogroups A, C, Y, and W-135; Menveo®, Novartis; and Menactra®, Sanofi Pasteur) in adolescents and persons at high risk for meningococcal disease. These recommendations supplemented the previous ACIP recommendations for meningococcal vaccination with two new recommendations: 1) routine vaccination of adolescents, preferably at age 11 or 12 years, with a booster dose at age 16 years and 2) a 2-dose primary series administered 2 months apart for persons aged 2 through 54 years with persistent complement component deficiency (e.g., C5-C9, properdin, factor H, or factor D) and functional or anatomic asplenia, and for adolescents with human immunodeficiency virus (HIV) infection (83).

10.2.2 United Kingdom

The impact of group C vaccines has been clearly demonstrated in the UK, where the number of cases of invasive disease due to group C meningococci has fallen in England & Wales from 955 in 1998/99 to 29 in 2011/12 following the introduction of the conjugate vaccine (95). A concerted effort was made to immunise the relevant age groups first, the 15-17 year olds and routine immunisation in infants, with three doses initially, followed by a roll-out to all children under two, then 11-14 year olds and eventually to all under the age of 25. This effective campaign reduced the incidence of group C disease (73). The schedule for immunisation in the UK was altered based on measurement of GMTs and routine immunisation was changed to two doses at three and five months old.

The UK was the first country in the world to introduce meningococcal serogroup C conjugate (MenC) vaccination. Incidence of meningococcal disease is highest in the under ones, followed by one to five year-olds with a second peak of risk occurring in 15 to 19 year-olds, particularly in those living in crowded or closed communities, such as military barracks and student halls. Immunisation with MenC vaccine started in November 1999, for everybody up to the age of 18 years, and to all first year university students over a two-year period. In January 2002, the campaign was extended to include all adults less than 25 years of age. This has since been extended to include everybody under 25 years of age as well as anyone at increased risk of infection.

Table 12. UK Meningococcal immunisation schedule as of early 2013 (96)

Vaccine	Risk Group	Dose
MenC vaccine	Infants under one year of age	First dose of MenC vaccine.
		Second dose, one month after the first dose
		A third dose of MenC-containing vaccine should be given at the recommended interval
Children over one year of age, adults under 25 years and individuals outside this age range who may be at increased risk from meningococcal C disease should have a single dose of MenC-containing vaccine		
Combined Hib/MenC	Children over one and under two years of age	One dose
Quadrivalent (ACWY) conjugate vaccine	Children over two months of age and under one year	First dose
		Second dose at least one month after the first dose
A reinforcing dose of 0.5ml should be given 12 months after the primary course if the child continues to be at risk		
MenC vaccine or Combined Hib/MenC	Children aged over one year of age and adults	Single dose
Quadrivalent (ACWY) polysaccharide vaccine	Children over five years of age and adults	Single dose
Reinforcing doses should be given at recommended intervals		

10.3.2 Australia

In January 2003, the Australian Government commenced the National Meningococcal C Vaccination Program, which provided free C-MCV to all children between the ages of one to 19 years during 2003. C-MCV was also added to the National Immunisation Program (NIP) schedule at 12 months of age at that time. Children turning 12 months receive this vaccine with their other routine immunisations due at that age. Vaccine is recommended but not funded for (97):

- Transplant recipients or people with a damaged or no spleen.
- Everyone less than 25 years of age.
- 4vMenCV as a 2-dose schedule is recommended as a primary course of vaccination for those (≥ 9 months of age) with complement component deficiencies (e.g. C5-C9, properdin, Factor D, Factor H), functional hyposplenism or anatomical asplenia.

10.2.4 Canada

In 2001, the Canadian National Advisory Committee on Immunization (NACI) recommended group C MCV for infants, children up to four years old and adolescents and young adults. In 2010, NACI recommend the use of quadrivalent conjugate vaccine in place of the monovalent group C conjugate vaccine in early adolescence and for two to 55 year olds who are high risk (98).

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