Antigen Literature Review for the New Zealand National Immunisation Schedule, 2018:
Meningococcal

Prepared as part of a Ministry of Health contract for services by Dr Mary Nowlan of the Immunisation Advisory Centre at the University of Auckland

This review is part of a series of antigen literature reviews commissioned by the Ministry of Health to help inform the National Immunisation Programme.

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Executive summary

Meningococcal disease is caused by the gram-negative, endotoxin-producing bacterium, Neisseria meningitidis. Distinct groups of these bacteria are distinguished by their capsular polysaccharides. Of the more than 12 serologically distinct groups, capsular groups A, B, C, W, Y and X are responsible for almost all of the disease cases worldwide. Generally, across all age groups, invasive meningococcal disease (IMD) occurs at a rate of two cases per 100,000 population in countries with adequate and consistent surveillance. Outbreaks and epidemics are known to occur associated with virulent encapsulated strains of N. meningitidis, which are identified further based on gene sequencing of the outer membrane protein. The human nasopharynx is the reservoir of meningococci with highest rates of carriage in adolescents and young adults.

In New Zealand, meningococcal disease is caused predominantly by capsular groups B, C, W and Y. Over the last five years, the average annual incidence of meningococcal disease in New Zealand has been 1.6 per 100,000 population, overall. The highest rate of 18.6/100,000 occurs in infants younger than 1 year and another peak in incidence is seen in adolescents aged 15-19 years (3.3/100,000). Older adults and individuals with compromised immune systems are also at increased risk of IMD.

Currently in New Zealand, immunisation for meningococcal disease is only provided as part of the National Immunisation Schedule for certain individuals at high risk of invasive meningococcal disease (IMD) and close contacts of cases against MenA, C, W and Y. Immunisation is recommended, but not funded, for other groups at increased risk of exposure to meningococci, such as laboratory workers, travellers to high-risk countries and young adults living in communal living environments. Localised vaccination programmes are implemented in the case of an outbreak.

This is a review of scientific literature, published from January 2014 to March 2018, considering licensed meningococcal vaccines and their role in prevention of IMD. The aim is to inform policy decisions around the routine use of these meningococcal vaccines in New Zealand. It is not a systematic review and does not consider cost related analyses.

Meningococcal conjugate vaccines

Vaccines containing capsular polysaccharides have been used for several decades against meningococcal disease. However, there are several limitations to the type of immune response induced by polysaccharide vaccines. Following the introduction of technology to conjugate polysaccharides with immunogenic proteins, targeted and routine usage of meningococcal conjugate vaccines in some countries have resulted in substantial declines in groups A and C disease.

Meningococcal group B (MenB) is an unsuitable target for conjugate vaccines due to poor immunogenicity and human protein cross-reactivity of the group B capsular polysaccharides, as well as antigenic variability. The group B vaccine options are discussed separately.

Meningococcal group C conjugate vaccines (MenCCV) have been widely used in many countries routinely, including the United Kingdom (UK), Europe, Australia and Canada, targeting young infants, toddlers and adolescents. Due to the increasing incidence of groups W and Y disease, immunisation programmes have been replaced or augmented with quadrivalent conjugate vaccines against meningococcal groups A, C, W and Y (MenACWY). As MenCCV vaccines have been used routinely for nearly two decades and their safety and immunogenicity are well characterised, this review will focus predominantly on the more
recently introduced quadrivalent vaccines, ACWY-CRM (Menveo®), ACWY-D (Menactra®) and ACWY-TT (Nimenrix®).

**Safety**

This review did not identify any serious safety concerns associated with meningococcal conjugate vaccines. These vaccines are contraindicated for use in individuals with a known hypersensitivity to the vaccine components, including the conjugate proteins. Most commonly reported adverse events are solicited and associated with previously described vaccine reactogenicity, such as injection site pain and swelling, and systemic reactogenicity, such as headaches and mild fever. These do not increase when these vaccines are given concomitantly with other vaccines.

Except for the rare, but known, possibility of anaphylaxis, no other severe adverse events have been identified as being causally associated with these vaccines in children or adults. As with all vaccines, meningococcal conjugate vaccines are contraindicated for individuals with a history of hypersensitivity to any vaccine component, including the conjugate protein (i.e. tetanus or diphtheria proteins).

A temporal increase in incidence of Bell’s palsy in adolescents aged 11-21 years was observed during one study following concurrent administration of ACWY-CRM (Menveo®) with tetanus-diphtheria-acellular pertussis vaccine (Tdap), human papillomavirus (HPV) vaccine and/or influenza vaccine, but not when given separately. Further investigation is required to determine whether the apparent increase can be attributed to the vaccines or whether other vaccine-independent factors were associated with these isolated cases.

**Immunogenicity**

IMD occurs too infrequently to measure vaccine efficacy by comparing the rates of disease in vaccinated versus unvaccinated control groups in clinical trials. Therefore, immunogenicity has been used to infer vaccine efficacy. Protective immunity is quantified by measuring the serum antibody titres required to kill *N. meningitidis* isolates. No correlate of protection has been defined for protection against IMD.

The quadrivalent meningococcal conjugate vaccines are immunogenic from 2 - 12 months of age (age depending on vaccine). Seroprotection is observed in 79-99% of vaccine recipients aged from 2 years of age at one month post vaccination with a single dose of a MenACWY conjugate vaccine. Antibody titre proportions varied between capsular groups – generally the highest were seen against group C and lowest group A. This variability between groups is not consistent across studies and is potentially an artefact of whether human or rabbit complement was used in the serum bactericidal activity (SBA) assay.

**Variation in immunogenicity by conjugate**

The vaccine formulation, specifically the protein used to conjugate the meningococcal capsular polysaccharides, can influence the immunogenicity of meningococcal conjugate vaccines. Three different MenACWY vaccines have been licensed with tetanus toxoid (TT; Nimenrix®), diphtheria toxoid (D; Menactra®) or a non-toxic diphtheria toxin derived protein (CRM; Menveo®) conjugate proteins. However, any measurable differences between the antibody responses have not been shown to give clinically important outcomes. Head to head studies are rarely conducted. One phase II clinical study showed comparable immunogenicity profiles for ACWY-CRM and ACWY-TT in toddlers.

**Duration of antibody protection**

Immune memory was demonstrated by revaccination with booster doses. Booster doses with meningococcal conjugate vaccines given four or five years after priming to infants or
toddlers induce good antibody responses against all meningococcal vaccine serotypes. Bactericidal antibodies are also understood to play a part in reducing carriage and transmission of disease-causing meningococci, although recent studies are limited. The longevity of seroprotective antibodies and the optimum time interval between booster doses remains undetermined, particularly through to adolescence.

There are limited recent studies that assess the immunogenicity of MenACWY vaccines in adolescents and young adults. A single dose of ACWY-TT induces a robust immune response in healthy adults and adolescents and is likely to provide antibody protection for at least five years.

**Concurrent vaccine delivery**

When given concurrently with other vaccines, no impact on overall effectiveness against meningococcal disease or the other vaccines’ antigens has been observed in relation to these different conjugates. Any possible blunting effect of the immune response on clinical protection has not been verified.

ACWY-CRM does not appear to significantly interfere with routine primary immunisations in infants. ACWY-D is not recommended for children aged under 2 years due to potential interference with antibody titres against three of the PCV-7 serotypes (4, 6B, 18C). Little interference with the antibody response against pneumococcal vaccine serotypes has been seen when ACWY-TT is co-administered with PCV-10, apart from potential interference with TT conjugated serotype 18C.

Some immune modulation has been observed when MenACWY vaccines are co-administered with other vaccines in adults and adolescents. Concomitant diphtheria-containing booster vaccines (Td or Tdap), but not HPV vaccine, can influence immunogenicity of ACWY-CRM in adolescents. However, seroprotective antibody titre thresholds were achieved against all four meningococcal capsular groups.

Previous vaccination with meningococcal polysaccharide vaccines has been associated with hyporesponsiveness to MenCCV antigens in adults aged over 55 years. The vaccine response rate to ACWY-TT was also significantly lower in older adults with pre-existing seroprotective antibodies who had received polysaccharide MenACWY vaccine.

**High-risk groups**

Recent immunogenicity data is limited for high-risk groups. Immunomodulatory biological therapies can accelerate the waning of seroprotective anti-meningococcal antibodies, leaving some individuals unprotected. Frequent vaccine booster doses are required to overcome waning protection. Although the optimum frequency has not been defined, five-yearly boosters are generally recommended. Where possible, it is recommended to vaccinate prior to transplantation or commencement of immunosuppressive therapy to ensure an adequate immune response to the vaccine.

**Vaccine effectiveness and duration of protection**

Effectiveness of conjugate meningococcal vaccination against laboratory-confirmed disease is difficult to assess due to the low incidence of cases, even during localised epidemics.

A targeted immunisation campaign demonstrated that MenCCV vaccination was 98% effective against MenC disease in young children, adolescents and young adults during a MenC epidemic in Salvador, Brazil.

The duration of protection of MenCCV depends on the age at which primary vaccination takes place. When vaccinated by one dose at 12-19 years of age, VE has been shown in one
study to remain virtually unchanged (0.1% decrease) for at least 10 years, whereas in those vaccinated as infants with two or three doses, VE declines by 50% over 10 years.

A single dose of ACWY-D at age 11-12 years maintains 69% VE for up to eight years post vaccination. The US Advisory Committee on Immunization Practices recommended that a second dose be given at age 16 years to extend protection into the high-risk period of early adulthood, but the impact gained by booster doses on the number of cases is likely to be limited. The duration of protection of other MenACWY vaccines was not investigated in the literature and these findings cannot be extrapolated to the other vaccines.

**Herd immunity: Impact on disease control**

The impact that conjugate vaccines, MenC and MenACWY, have on carriage of vaccine-group meningococci plays an important role in disease control through herd immunity.

Herd immunity can be achieved by targeting the particular age group where carriage rates are highest (such as older teenagers). Significantly reducing the amount of disease-causing *N. meningitidis* in circulation through herd immunity is the most effective strategy to prevent disease and is more effective than an individual protection strategy alone.

Meningococcal immunisation programmes using conjugate vaccines have made significant impacts on the epidemiology of meningococcal C disease (and MenA in Africa, data not presented here) in countries that have implemented these programmes. This has been achieved by targeting both infants and young children (under 4 years of age) to prevent disease and by targeting adolescents or young adults to provide both individual protection and herd immunity.

Countries that included catch-up vaccinations for older children and adolescents, including the UK and Australia, have observed the greatest effect from meningococcal immunisation campaigns through herd immunity and a reduction in transmission across all age groups.

In recent years, hypervirulent group W strains (strain type 11, clonal complex 11) have emerged in several countries, as well as an increase in group Y disease. Internationally, meningococcal immunisation programmes are now targeting adolescents with the quadrivalent MenACWY conjugate vaccines. However, the ability of MenACWY to reduce carriage of hypervirulent MenW strains is unclear and the role of MenACWY vaccines in herd immunity against MenW strains is not yet determined. Therefore, targeting of adolescents with this vaccine provides direct protection, but is potentially less effective in preventing group W transmission than MenCCVs have been against group C disease.

The timing of vaccination for adolescents is likely to an important factor in disease control. Vaccination prior to late adolescence could provide better protection by helping to prevent acquisition of the infection before the ages in which transmission and disease risk is highest.

**Recombinant Meningococcal B vaccines**

Since meningococcal group B (MenB) polysaccharides are unsuitable for conjugate vaccines, developing vaccines to target MenB disease has proved difficult. Recent technologies, using reverse vaccinology and recombinant proteins, have been used to generate multicomponent recombinant MenB vaccines. Currently, two vaccines have been granted regulatory approval – the four-component 4CMenB (Bexsero®) and the two-component MenB-fHbp (Trumenba®).

The UK is the first country to have included 4CMenB in the routine immunisation schedule for infants. Two doses are administered concurrently with other routine vaccines at 8 and 16 weeks of age, and booster dose is given at 12 months of age – this is one priming dose less than used in licensure RCT. Prior to this, usage of 4CMenB had predominantly been in
adolescents and young adults. A large clinical trial is underway in South Australian schools to investigate the affect 4CMenB may have in preventing MenB carriage and transmission in adolescents aged 15-18 years. During the time since this literature review was prepared 4CMenB was approved in New Zealand from 2 months of age.

**Safety**

Both of the meningococcal B recombinant vaccines are moderately reactogenic and associated with mild to moderate injection site and systemic reactions. Due to the high rate of fevers (up to 90%) in young children, MenB-fHBP vaccine was only approved in the US and Europe for use in children aged over 10 years. In adults and adolescents, mild to moderate pain and inflammation at the injection site and systemic responses, including headaches, fever and nausea, have been reported in around one quarter of recipients.

The use of 4CMenB vaccine routinely in infants from 2 months of age in the UK will provide further information about the reactogenicity and long-term safety of this vaccine. Currently, prophylactic paracetamol is recommended prior to receipt of this vaccine to help reduce the risk of febrile seizures and medically-attended fevers in young infants. The incidence of injection site pain and swelling was higher in toddlers aged 12 months to 2 years receiving catch-up or booster doses than reported in infants, although systemic reactogenicity such as fever was lower, particularly in the 2-year-olds. In adults, this vaccine is commonly associated with injection site pain, and with headaches, muscle ache and nausea in up to 40% of recipients. Prophylactic paracetamol to reduce injection site pain is likely to be beneficial in adults.

Vaccinated infants who have presented with fever to emergency departments have undergone potentially unnecessary invasive investigations and hospital admissions due to a lack of awareness of the expected adverse events following immunisation with 4CMenB.

This literature review did not identify any long-term safety data or new serious adverse events not previously reported during licensure clinical trials.

**Immunogenicity**

To measure the bactericidal activity of antibodies induced by these vaccines, sera from vaccinated individuals are tested against a panel of MenB strains with known antigenic types. One limitation of extrapolating immunogenicity data to clinical effectiveness for MenB is the selection of these test strains. Much of the clinical trial data, on which licensure of these vaccines were based, used the same set of test strains. It is less well studied how well these vaccines provide immunity against a wider range of circulating or emergent MenB strain variants.

These recombinant vaccines induce strong bactericidal antibody responses against the reference strains in infants (4CMenB only), adolescents and adults.

Questions remain around the longevity of the antibody. Booster doses appear to be required to maintain antibody titres following a two- or three-dose primary series with 4CMenB, at least in young children. To date data suggest that these responses are short-lived from six months after vaccination, but for children under the age of 4 years, this is likely to provide sufficient protection during this time of highest risk.

**Vaccine effectiveness and duration of protection**

Due to the relatively short time that these recombinant vaccines have been available and the rarity of meningococcal disease, there is limited data around the effectiveness of MenB vaccines in immunisation programmes.
In the UK, the risk of MenB disease has been halved in vaccine-eligible infants following the introduction of 4CMenB to the immunisation schedule compared with the pre-vaccination period, irrespective of vaccination status. Over the first 10 months of the programme, vaccine effectiveness following two primary doses was shown to be more than 82% against all MenB disease.

Reduction in carriage rates and herd immunity has not yet been observed with the recombinant MenB vaccines. It is too early to know the longer-term impact on group B disease and herd immunity, which would require high immunisation coverage in large populations.

For adults and adolescents, these vaccines are immunogenic and are likely to provide at least short-term protection against group B meningococcal disease. This may be sufficient to overcome high-risk periods of life, such as overseas travel and communal living. No literature was identified around the use of these vaccines in individuals with high medical or occupational risk of meningococcal disease.

**Impact on disease control**

Meningococcal B vaccines have been more recently introduced than conjugate vaccines and data on their impact is limited. In many countries these vaccines have been used to specifically target adolescent and young adult populations during localised epidemics with good effect, although when used during outbreaks in the US, these vaccines have had little effect on herd immunity. Starting in late 2015, the UK was the first country to administer 4CMenB to infants as part of its routine schedule. No literature has been published as yet reporting on the impact of this programme on meningococcal disease control.

**International policy and practice**

The use and recommended ages of administration of MenACWY conjugate and MenB recombinant vaccines vary between countries, depending on disease prevalence in the different age groups and how long meningococcal vaccination has been included in their national immunisation schedules.

In Canada, a universal MenCCV programme offers vaccination to infants up to 12 months of age and adolescents are recommended one dose of MenCCV or MenACWY at 12 years, depending on local epidemiology. For protection against group B IMD, 4CMenB is recommended according to individual risk from 2 months of age, as determined by relevant clinicians, and for immunisation of close case contacts and outbreak control of group B disease.

In Australia, a routine dose of Hib-MenC is funded for all infants at 12 months of age and is recommended in a targeted programme for refugees under the age of 20 years. ACWY-TT is recommended for all adolescents aged 15-19 years and is funded in certain states. The 4CMenB vaccine is recommended for all children younger than 2 years, but it is not funded. A school-based clinical study is providing 4CMenB to adolescents aged 15-19 years across South Australia during 2017 and 2018.

The UK immunisation schedule includes meningococcal vaccination against groups C, ACWY and B for infants, toddlers and adolescents. In infants, two doses of 4CMenB are given at 8 and 16 weeks. A combined Hib-MenC vaccine is provided at 1 year together with 4CMenB, PCV-13 and MMR. MenACWY-TT or –CRM are given at 14 years of age with Td-IPV.

In general, those deemed at high risk from IMD are similar between countries. These high-risk groups include individuals with splenic dysfunction, congenital or acquired complement deficiencies or HIV infection, bone marrow transplant recipients, laboratory workers and travellers to regions with high rates of meningococcal disease and transmission.
Meningococcal vaccines are also widely recommended for adolescents and young adults living in communal residences, including military barracks, university residences, correctional facilities and dormitories. During community disease outbreaks, close contacts and infants are also recommended strain appropriate vaccines.

**Options for New Zealand**

The age and number of priming doses of meningococcal conjugate vaccines necessary to control meningococcal disease depends on the age at which IMD is most prevalent and whether NZ chooses to adopt a catch-up programme at the start of a routine meningococcal immunisation programme.

While disease circulation is high for any particular group, priming of infants would likely to be required, with one or two doses of a conjugate vaccine (ACWY or C depending on group) followed by a booster dose in the second year of life. Offering simultaneous immunisation of adolescents is likely to achieve herd immunity, thereby reducing carriage rates of disease-causing strains. To gain herd immunity quickly, the most effective strategy would be a mass catch-up campaign for all children and adolescents, given alongside the routine doses. Herd immunity may also protect older adults in whom group W and Y is increasingly being notified.

Group B disease prevalence is greatest in children aged less than 1 year in New Zealand. Since the role of recombinant MenB vaccines in herd immunity is currently unknown, a routine immunisation programme, such as offered in the UK, which includes two or three primary doses of 4CMenB vaccine would be expected to provide direct protection against IMD caused by a range of group B strains during infancy.

If carriage and transmission of MenB strains is shown to be reduced by the use of 4CMenB in adolescents, then an adolescent dose could provide both direct protection to this targeted age group and herd immunity to younger children to overcome any waning of protection that may occur between infancy and early adolescence. The appropriate age for this dose cannot be determined from the current literature, as yet. It is expected that the four-component MenB recombinant vaccines will provide the broadest coverage against a range of circulating strains with potential for cross-protection against non-group B disease.

With this in mind, the broadest coverage against meningococcal disease in young children is likely to be best achieved with both 4CMenB and MenACWY on the childhood schedule in the second year of life. Routine vaccination with MenCCV in infants alone is unlikely to provide broad or long lasting benefit against IMD and, currently, little advantage would be gained by the additional coverage provided by routine infant doses of a MenACWY vaccine.

For high risk groups, MenACWY is likely to provide direct protection against these groups. There is insufficient data to comment on a role for 4CMenB in such groups. ACWY-CRM (currently unlicensed in NZ) would be suitable for high risk infants if groups W and Y became more prevalent in infants younger than 12 months.

As data becomes available, further information is required to better understand the role of MenACWY and recombinant MenB vaccines in controlling meningococcal disease and the herd immunity, cross-protection and duration of protection provided.
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<th>Description</th>
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<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
</tr>
<tr>
<td>ACWY-CRM</td>
<td>Meningococcal A, C, W and Y vaccine conjugated with diphtheria-derived cross-reactive material CRM197</td>
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<tr>
<td>ACWY-D</td>
<td>Diphtheria toxoid</td>
</tr>
<tr>
<td>ACWY-TT</td>
<td>Tetanus toxoid</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse events</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse Events Following Immunisation</td>
</tr>
<tr>
<td>4CMenB</td>
<td>Four-component meningococcal group B vaccine</td>
</tr>
<tr>
<td>C-CRM</td>
<td>Meningococcal C vaccine conjugated with diphtheria-derived cross-reactive material CRM197</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DTaP</td>
<td>Combined diphtheria, tetanus and acellular pertussis vaccine</td>
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<tr>
<td>EOI</td>
<td>Events of interest</td>
</tr>
<tr>
<td>ESR</td>
<td>Institute for Environmental and Scientific Research</td>
</tr>
<tr>
<td>fHbp</td>
<td>Factor H binding protein</td>
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<tr>
<td>GSK</td>
<td>GlaxoSmithKline Ltd</td>
</tr>
<tr>
<td>HepA or HepB</td>
<td>Hepatitis A or B</td>
</tr>
<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type b</td>
</tr>
<tr>
<td>Hib-MenC-TT</td>
<td>Combined <em>Haemophilus influenzae</em> type b and meningococcal C, tetanus toxoid conjugated vaccine</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
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<tr>
<td>HSCT</td>
<td>Haematopoietic stem cell transplant</td>
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<tr>
<td>IMD</td>
<td>Invasive meningococcal disease</td>
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<tr>
<td>IRR</td>
<td>Incidence risk ratio</td>
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<tr>
<td>KPSC</td>
<td>Kaiser Permanente South California</td>
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<tr>
<td>MATS</td>
<td>Meningococcal antigen typing system</td>
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<tr>
<td>MCV (MCV4)</td>
<td>Meningococcal conjugate vaccine (quadrivalent)</td>
</tr>
<tr>
<td>MenACWY</td>
<td>Meningococcal groups A, C, W and Y</td>
</tr>
<tr>
<td>MenB</td>
<td>Meningococcal group B</td>
</tr>
<tr>
<td>MenC</td>
<td>Meningococcal group C</td>
</tr>
<tr>
<td>MenCCV</td>
<td>Meningococcal C conjugate vaccine</td>
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<tr>
<td>MeNZB</td>
<td>New Zealand epidemic specific meningococcal group B vaccine</td>
</tr>
<tr>
<td>MMR</td>
<td>Combined measles, mumps, rubella vaccine</td>
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<tr>
<td>MMRV</td>
<td>Combined measles, mumps, rubella and varicella vaccine</td>
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<tr>
<td>NadA</td>
<td><em>Neisseria</em> adhesion antigen</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
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<tr>
<td>NHba</td>
<td><em>Neisseria</em> heparin binding protein</td>
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<tr>
<td>N. meningitidis</td>
<td><em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>PCV (-7, -10, -13)</td>
<td>Pneumococcal conjugate vaccine (7, 10 or 13 valent)</td>
</tr>
<tr>
<td>OMV</td>
<td>Outer membrane vesicles of <em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse events</td>
</tr>
<tr>
<td>SBA (rSBA or hSBA)</td>
<td>Serum bactericidal activity assay, with rabbit or human complement</td>
</tr>
<tr>
<td>Tdap</td>
<td>Combined tetanus, reduced antigen diphtheria and acellular pertussis vaccine</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
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<tr>
<td>VAERS</td>
<td>Vaccine Adverse Event Reporting System</td>
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<tr>
<td>VE</td>
<td>Vaccine effectiveness</td>
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<td>WHO</td>
<td>World Health Organization</td>
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# 1 Introduction

## 1.1 Meningococcal disease and immunisation

Meningococcal disease is caused by the gram-negative, endotoxin- (lipopolysaccharide) producing bacteria, *Neisseria meningitidis*, which is commensal in the human nasopharynx. Invasive meningococcal disease (IMD) often progresses very rapidly with a case-fatality rate of 10-15%, even with access to medical care. The initial signs of disease are non-specific and commonly diagnosed as a benign viral infection, but the illness can deteriorate rapidly into high fever, meningitis and haemorrhagic rash, and leads to sepsis in around 10-20% of cases. The rapid doubling time and release of endotoxin-rich outer membrane vesicles (blebbing) triggers proinflammatory cytokine production, leading to haemorrhage, intravascular coagulation and shock.

Rapid access to antibiotics and supportive medical care reduces mortality and long-term damage. Permanent sequelae occur in around 10-20% of survivors of meningococcal disease; these include vision and hearing loss, amputation of extremities, skin grafts due to skin necrosis, and cognitive deficits. Neurological sequelae are more frequent in adults than children, as shown in Table 1.

*Table 1: Neurological sequelae of bacterial meningitis in high-resource countries (reproduced with permission from Elsevier, Lucas, 2016)*

<table>
<thead>
<tr>
<th>Sequeleae</th>
<th>Pneumococcal meningitis</th>
<th>Meningococcal meningitis</th>
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<tbody>
<tr>
<td><strong>Focal deficits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>3-14%</td>
<td>3%</td>
</tr>
<tr>
<td>Adults</td>
<td>11-36%</td>
<td>2-9%</td>
</tr>
<tr>
<td><strong>Hearing loss</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>14-32%</td>
<td>4%</td>
</tr>
<tr>
<td>Adults</td>
<td>22-69%</td>
<td>3-40%</td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>15-48%</td>
<td>2%</td>
</tr>
<tr>
<td>Adults</td>
<td>31%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Hydrocephalus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>4-21%</td>
<td>-</td>
</tr>
<tr>
<td>Adults</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Cognitive impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>-</td>
<td>12-19%</td>
</tr>
<tr>
<td>Adults</td>
<td>32%</td>
<td>32%</td>
</tr>
</tbody>
</table>

Of the more than 12 serologically distinct meningococcal capsular groups, which have been defined by their capsular polysaccharides, groups A, B, C, W, X and Y are responsible for almost all disease cases worldwide. These groups have been further classified based on PorB and PorA outer membrane proteins into serotypes and sub-serotypes, respectively. Further variant classifications are based on gene sequencing.

Note that since molecular typing, rather than serology, is now used to differentiate the capsular polysaccharides of meningococcal strains, it is no longer appropriate to use the term ‘serogroup’. In this review, to match this convention, capsular group or just group will be used.
Only certain meningococci are predisposed to be invasive and cause IMD. Except in rare cases, IMD is caused by encapsulated strains and many colonising strains do not express capsules. This demonstrates the important role that the meningococcal capsule plays as a virulence factor. Global surveillance for polymorphisms in housekeeping genes, using multi-locus sequence typing, provides epidemiology information about meningococcal disease. Capsular switching, as a result of horizontal DNA transfer, may produce new disease variants.

Carriage rates of *N. meningitidis* vary with age, geography and time. The infection establishes a carrier state in the nasopharyngeal mucosal cells. The highest rates of carriage are usually in adolescents and young adults. In this age group, life-style associated behaviours (such as alcohol binge drinking, smoking, and kissing multiple partners, as well as respiratory viral infections and communal living) appear to increase the risk of developing meningococcal disease. In other age groups, comorbidities contribute to risk, including preterm birth and immune deficiency. Meningococcal infection rates are highest during the winter months in temperate climates, which is likely to be associated with increased proximity with others, lack of ventilation and upper respiratory infections that increase the chance of transmission and invasion of meningococci.

Meningococcal carriage is observed in around 10% of the population of industrialised countries, overall. However, most carried strains are non-encapsulated and not associated with invasive disease. It has been estimated that *N. meningitidis* carriage prevalence increases throughout childhood from 4.5% in infants and peaking at 23.7% in 19-year-olds, then decreases in adulthood to 7.8% by the age of 50 years.

The presence of functional serum antibodies helps to prevent invasive disease through complement activation, opsonisation and bacteriolysis. Once the infection has entered the bloodstream, the spleen is important for clearance of the meningococci. Individuals with complement deficiencies and dysfunctional spleen or asplenia are at highest risk from acquiring IMD.

**1.2 Objectives of this review**

This is a review of evidence-based literature published from January 2013–February 2018 concerning the use of meningococcal vaccines. The aim is to help to inform policy decisions for the New Zealand National Immunisation Schedule. It is not a systematic review and does not include cost-effectiveness or cost-benefit analyses.
2 Meningococcal disease epidemiology

2.1 Global epidemiology

Laboratory surveillance for meningococcal disease is essential to detect and confirm outbreaks, to monitor the incidence trends and to observe the evolution of capsular groups. It provides an estimate of the disease burden and can monitor the circulation of specific strains or antibiotic resistance. Surveillance can also be used to evaluate the impact of control strategies, including immunisation programmes.

The global distribution of meningococcal groups and disease outbreaks are reported by the World Health Organization (WHO) as shown in Figure 1.(6)

In Europe in 2012, 17% of cases of IMD were caused by group C and 68% caused by group B meningococci, and there has been an increase in group C, W and X epidemics in that region.(7) Some countries have experienced an increase in group Y and W strains.(1) In the United States (US), approximately 65% of IMD cases in infants are caused by group B. Groups C, Y and W were associated with 75% of disease in adolescents prior to routine vaccination recommendations for ages 11-18 years. However, meningococcal disease can occur in all age groups.(4)

Burden and transmission of meningococcal disease differs from other encapsulated bacterial infections. As illustrated in Figure 2, other vaccine-preventable invasive bacteria are predominantly transmitted from toddlers to infants and the elderly, including Streptococcus pneumoniae and Haemophilus influenzae type b (Hib).(8) Immunisation programmes target these young age groups as part of the childhood immunisation schedule, to reduce disease incidence and transmission. The burden of disease for these invasive infections is in the youngest and oldest members of the population with the least ability to resist opportunistic infections. However, the transmission of meningococci occurs from adolescents to more vulnerable age groups and secondary peak in disease incidence is also observed in this age group.
Capsular Group A disease

As mentioned, the prevalence of meningococcal groups varies geographically. The highest burden of meningococcal disease occurs predominantly in sub-Saharan Africa, through what is known as the African Meningitis Belt, from Senegal to Ethiopia. Prior to a targeted vaccination campaign that began in 2010, disease in that region was predominantly caused by group A. The vaccination campaign, which vaccinated 280 million individuals across 21 countries, dramatically reduced the proportion of group A disease; although around 30,000 cases of IMD are still reported annually. Epidemics of disease during the dry season are associated with dust winds, cold nights and upper respiratory tract infections that damage nasopharyngeal mucosa, and overcrowded housing facilitating transmission.(7)

Capsular Group B disease

In countries that have seen a dramatic decline in group C disease due to MenC vaccination programmes, group B disease has become the predominant capsular group. As of 2013, group B accounted for 90% of sporadic meningococcal disease cases in Europe and around a third of cases in the US. Meningococcal B disease is a predominant cause of IMD in infants in all developed countries. Group B epidemics have been associated with the emergence of hypervirulent strains. Since the 1970s, prolonged epidemics of single strains have been detected in Norway, Spain, Cuba and New Zealand. In New Zealand, an epidemic, caused by the strain identified as being B:4:P1.7-2,4, ST-41/44 complex, began in 1991 and lasted for nearly 16 years.(1)

The global incidence of group B invasive meningococcal disease was systematically reviewed by Sridhar et al (2015). The overall global burden of group B is low, with few countries have an annual incidence rate of more than two cases per 100,000 population. Wide variation exists between regions: group B disease is most frequently seen in Europe, the Americas and Australia, infrequently in China and India, and is almost absent in sub-Saharan Africa (except South Africa). A general decreasing trend in IMD incidence has been observed (in countries with consistently collected data available), although the proportion of cases caused by group B has increased. Case-fatality rates of group B IMD are consistently between 3% and 10%.(9)
**Capsular Group C disease**

The burden of IMD was dramatically decreased by the introduction of MenC vaccination in many countries, including Canada, Australia, the UK, the Netherlands and other European countries. Outbreaks of group C disease have been observed in men who have sex with men in the US and Europe. Sporadic cases of group C IMD are reported in Europe.(1)

**Capsular Group Y disease**

Some parts of the world, namely, the US, Colombia, parts of Canada, South Africa and some European countries, particularly in Scandinavia, have reported an increase in group Y disease. In other parts of the world, disease caused by group Y is rare despite evidence of colonization with group Y strains. Patients with group Y strain disease are more likely to develop pneumonia than patients with other strains, and are likely to be elderly.(1, 4)

**Capsular Group W disease**

Prior to 2000, group W (formerly designated W135) strains were not known to cause outbreaks and were relatively uncommon causes of IMD. During 2000-2001, outbreaks of group W disease occurred among Hajj pilgrims in Mecca, Saudi Arabia, where millions of pilgrims from around the world gather each year in overcrowded conditions. Capsular switching of a ST-11 complex group C polysaccharide occurred to form ST-11 complex group W bacteria. Group W ST-11 clonal complex strains, unrelated to the Hajj outbreak, are increasingly associated with disease globally, including in Africa, South America, the UK and Australia.(1) In the UK from 2010, there was a sharp rise in group W cases and group W accounted for a quarter of IMD cases during 2014-2015, resulting in the introduction of the MenACWY vaccination programmes in August 2015.(8)

Clinical presentation of group W disease is atypical, including gastrointestinal symptoms, conjunctivitis, pneumonia, epiglottitis, myocarditis and septic arthritis, which can delay diagnosis resulting in poorer outcomes.(10, 11)

In Chile, group W has been the predominant cause of invasive disease and is associated with elevated mortality since 2011. Routinely collected isolates were analysed from 119 patients with IMD (across all age groups) and from 184 healthy adolescent carriers aged 9-19 years between April–June 2013 from regions with the highest concentration of IMD cases. Group W clonal complex ST-11/ET37 was found in 66% of the total IMD isolates in one year, whereas carriage of the same clonal complex was 5%, lower than expected; in comparison, group C was detected in 18% of carrier isolates and less than 2% of IMD isolates. The elevated number of group W IMD cases could not be explained by a rise in carriage of pathogenic isolates and suggested that some strains have enhanced virulence to invade susceptible individuals. Higher rates of carriage of this strain were noted to be found within age groups where group W IMD is more prevalent (infants and the elderly).(12)
2.2 New Zealand epidemiology

In 2017, the rate of meningococcal disease notifications in New Zealand was 2.3 cases per 100,000 (112 cases). There was a significant increase in the number of cases compared with 2016 when there were 75 cases notified (1.6/100,000).\(^{(13)}\) Data for 2017 presented below was provided by ESR in a personal communication (as of 26 March 2018).

2.2.1 Age groups

As presented in Table 2, the highest average annual rates of meningococcal disease over the last five years were in infants aged less than one year and toddlers and, as observed internationally, a spike in incidence is also seen in adolescents aged 15-19 years.

Table 2: Meningococcal disease cases and rate per 100,000 population by age group, 2012 - 2017 (ESR)

| Age group (years) | Year | Total | Average annual rate
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
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<td>12</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>2013</td>
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<tr>
<td></td>
<td>2014</td>
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<tr>
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<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2017</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>1 to 4</td>
<td>2012</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>2017</td>
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<tr>
<td>5 to 9</td>
<td>2012</td>
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</tr>
<tr>
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<td>5</td>
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</tr>
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<td>10 to 14</td>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>2017</td>
<td>16</td>
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</tr>
<tr>
<td>15 to 19</td>
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<td>15</td>
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<td></td>
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<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2017</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>20 to 29</td>
<td>2012</td>
<td>12</td>
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<tr>
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<tr>
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<td>8</td>
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<tr>
<td></td>
<td>2016</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2017</td>
<td>13</td>
<td></td>
</tr>
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<td>30 to 39</td>
<td>2012</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
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<td>3</td>
<td>1.4</td>
</tr>
<tr>
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<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>0</td>
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</tr>
<tr>
<td></td>
<td>2017</td>
<td>0</td>
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</tr>
<tr>
<td>40+</td>
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<td>15</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2017</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>85</td>
<td>449</td>
</tr>
</tbody>
</table>

2.2.2 Ethnic group

The highest incidence of meningococcal disease is seen in Māori and Pacific peoples, followed by Middle Eastern / Latin American / African (MELAA) ethnicities as given in Table 3.

Table 3: Meningococcal disease cases and rate per 100,000 population by ethnic group, 2012 - 2017 (ESR)

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Year</th>
<th>Total</th>
<th>Average annual rate†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2012</td>
<td>2013</td>
<td>2014</td>
</tr>
<tr>
<td>Māori</td>
<td>29</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Pacific peoples</td>
<td>10</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>MELAA</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>European or Other</td>
<td>42</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td>Unknown</td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>68</td>
<td>45</td>
</tr>
</tbody>
</table>

† Average annual rate not calculated for fewer than 5 cases

Table 2: Meningococcal disease cases and rate per 100,000 population by age group, 2012 - 2017 (ESR)
2.2.3 Case fatality rate

The case fatality rate of meningococcal disease over the last five years has been highest for group W disease (14.3%) and then group C (9.4%), as presented in Table 4. The highest rates of deaths are seen for adults over the age of 40 years and those with MELAA ethnicity, although for this group, the numbers of cases and the size of the population are small, making it unstable to quantify.

**Table 4: Case fatality rate of meningococcal disease, 2012-2017 (ESR)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>Total fatality</th>
<th>Total cases</th>
<th>Case fatality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strain type</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B (P1.7-2,4)</td>
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<td>2</td>
<td>3</td>
<td>6</td>
<td>99</td>
<td>6.1</td>
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</tr>
<tr>
<td>All other Bs</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>158</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group C (P1.5-1,10-8)</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>53</td>
<td>9.4</td>
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<tr>
<td>All other Cs</td>
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<td>1</td>
<td>2</td>
<td>18</td>
<td>11.1</td>
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<td></td>
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<td>Group W</td>
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<td>3</td>
<td>4</td>
<td>28</td>
<td>14.3</td>
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<td></td>
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<tr>
<td>Group Y</td>
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<td>1</td>
<td>2</td>
<td>33</td>
<td>6.1</td>
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<td>36</td>
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<td>5 to 9</td>
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<td>15 to 19</td>
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<td>1</td>
<td>3</td>
<td>63</td>
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<td>13</td>
<td>110</td>
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<td>2</td>
<td>6</td>
<td>139</td>
<td>4.3</td>
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<td>1</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European or Other</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>20</td>
<td>229</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>9</td>
<td>28</td>
<td>449</td>
<td>6.2</td>
</tr>
</tbody>
</table>
2.2.4 Meningococcal disease groups

Meningococcal group B causes the greatest proportion of IMD in New Zealand and the numbers of cases have been increasing annually in the last five years. As shown in Figure 3, an increase in the incidence of group W and Y disease has also been observed in recent years, particularly in adults aged over 40 years. Group C disease is currently relatively stable.

During 2017, 109 cases out of 112 notifications were laboratory-confirmed and the strain type was identified for 105 cases: 70 cases of group B (including 27 cases of the formerly epidemic NZ B:P1.7-2,4 strain), 12 cases of group W, 11 group Y cases and five group C cases.

Figure 3: Meningococcal disease strain type distributions by year, 2012 – 2017 (ESR)

2.2.4.1 Meningococcal group B

During 1991-2007, NZ experienced an epidemic of a particular group B meningococcus strain (B:4:P1.7-2,4, ST-41/44 complex), and a specifically designed strain-specific vaccine (known as MeNZB) was used during 2004-2008 to control the epidemic.

As mentioned, most cases of IMD in NZ are caused by group B meningococci. More than a third of group B cases in 2017 were caused by the former epidemic strain. As presented in Figure 4 and Table 5, the highest rate of group B IMD is seen in infants aged less than 1 year (rate 13.9/100,000) and in Pacific peoples and Māori (rate 2.2/100,000 each). For some age groups there were fewer than five cases, although average annual rate is presented.
<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th><strong>Total</strong></th>
<th>Average annual rate †</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>8</td>
<td>9</td>
<td>4</td>
<td>11</td>
<td>6</td>
<td>12</td>
<td>50</td>
<td>13.9</td>
</tr>
<tr>
<td>1 to 4</td>
<td>11</td>
<td>9</td>
<td>11</td>
<td>12</td>
<td>11</td>
<td>17</td>
<td>71</td>
<td>4.8</td>
</tr>
<tr>
<td>5 to 9</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>10 to 14</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>0.3</td>
</tr>
<tr>
<td>15 to 19</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>10</td>
<td>24</td>
<td>1.3</td>
</tr>
<tr>
<td>20 to 29</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>9</td>
<td>7</td>
<td>28</td>
<td>0.7</td>
</tr>
<tr>
<td>30 to 39</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>0.4</td>
</tr>
<tr>
<td>40+</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>19</td>
<td>53</td>
<td>0.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th><strong>Total</strong></th>
<th>Average annual rate †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Māori</td>
<td>19</td>
<td>13</td>
<td>10</td>
<td>13</td>
<td>9</td>
<td>26</td>
<td>90</td>
<td>2.2</td>
</tr>
<tr>
<td>Pacific peoples</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td>38</td>
<td>2.2</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>10</td>
<td>0.3</td>
</tr>
<tr>
<td>MELAA</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>European or Other</td>
<td>15</td>
<td>12</td>
<td>13</td>
<td>17</td>
<td>26</td>
<td>31</td>
<td>114</td>
<td>0.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>43</td>
<td>30</td>
<td>26</td>
<td>41</td>
<td>47</td>
<td>70</td>
<td>257</td>
<td>0.9</td>
</tr>
</tbody>
</table>

† Average annual rate not calculated for fewer than 5 cases

Table 5: Meningococcal disease group B notifications by age group and ethnicity by year, 2012 - Nov 2017 (ESR)

Figure 4: Meningococcal disease group B rate by age groups, 2012 - 2017 (ESR)
2.2.4.2 Meningococcal group C

The number of cases of group C disease has been relatively stable over the last five years, although there was a higher rate in 2016 (Table 6). In 2017, there was a total of 11 group C IMD cases, four of which were aged 15-19 years.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Year</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>Total</th>
<th>Average annual rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>1.7</td>
</tr>
<tr>
<td>1 to 4</td>
<td></td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>0.7</td>
</tr>
<tr>
<td>5 to 9</td>
<td></td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>10 to 14</td>
<td></td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>15 to 19</td>
<td></td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>19</td>
<td>1.0</td>
</tr>
<tr>
<td>20 to 29</td>
<td></td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
<td>0.3</td>
</tr>
<tr>
<td>30 to 39</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>40+</td>
<td></td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>15</td>
<td>0.1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>23</td>
<td>17</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>11</td>
<td>71</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table 6: Meningococcal group C notifications by age group, 2012-2017 (ESR)

2.2.4.3 Meningococcal group W and Y

There has been a small increase in the number of cases of meningococcal group W and Y disease during 2017, particularly in older adults (aged >40 years) as presented in Table 7. As described above, Group W is associated with a higher case-fatality rate (14.8%) than other groups.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Year</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>Total</th>
<th>Group Y Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td></td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>1 to 4</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5 to 9</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10 to 14</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>15 to 19</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>20 to 29</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>30 to 39</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40+</td>
<td></td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>12</td>
<td>28</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 7: Meningococcal groups W and Y notifications, by age group 2012-2017 (ESR)
3 Meningococcal group A, C, W and Y vaccines

3.1 Background

Meningococcal vaccines utilizing high molecular weight meningococcal polysaccharides were first developed in the 1960s. The immune response to these polysaccharide vaccines is T cell independent, hence, poorly immunogenic in children aged less than 2 years, and does not provide long-lasting memory. However, they induce bactericidal-specific antibodies that protect against invasive disease and rapidly neutralize infections. A quadrivalent group ACWY polysaccharide vaccine (Menomun® ACYW-135) was previously registered in New Zealand but is no longer available.

Protein conjugation of polysaccharides, first developed for Haemophilus influenzae type B (Hib) vaccines, was applied to meningococcal C conjugate vaccines (MenCCV) to induce high antibody titres and boostable immune responses. These MenC vaccines were first introduced in the UK in 1999 and have been used as part of routine immunization schedules in Europe, Brazil, Canada and Australia.

Quadrivalent meningococcal conjugate vaccines, designated MCV4 or MenACWY, have since been developed to expand protection against group A, C, W (formerly W-135) and Y meningococci strains. MenACWY vaccines have been added to immunisation schedules in some countries, due to an increase in group W and Y cases.

Three different proteins are used as carrier proteins to conjugate these vaccines:

- tetanus toxoid (TT)
- diphtheria toxoid (D or DT)
- non-toxic mutant protein of diphtheria toxin, Cross Reactive Material-197 (CRM197)

3.1.1 Licensed meningococcal vaccines in New Zealand

In New Zealand, meningococcal vaccination is not currently part of the routine childhood immunisation schedule. However, these vaccines are recommended and funded to certain special groups with high risk of invasive meningococcal disease (IMD) and to close contacts of cases as part of the National Immunisation Schedule. A funded immunisation programme and immunisation of defined populations may be initiated by the local medical officer of health in consultation with the Ministry of Health in the case of community outbreaks.

**Meningococcal C conjugate vaccine**

NeisVac-C® (Pfizer) is a tetanus toxoid conjugated meningococcal C vaccine (abbreviated MenC-TT). Each 0.5ml dose contains 10µg meningococcal C polysaccharide conjugated with 10-20µg TT protein and adsorbed to the aluminium hydroxide adjuvant. This vaccine is available and funded for certain high-risk infants aged under 2 years.

**Meningococcal A, C, W and Y conjugate vaccines**

Nimenrix® (Pfizer) is a quadrivalent meningococcal vaccine (ACYW-TT). Each 0.5ml dose contains 5µg of each meningococcal A, C, Y and W polysaccharides individually conjugated to 44µg tetanus toxoid protein. It is registered for individuals from age 12 months to 55 years.

Menactra® (sanofi-aventis) is a diphtheria toxoid protein conjugated quadrivalent meningococcal vaccine (ACYW-D). Each 0.5ml dose contains 4µg each of meningococcal A, C, Y and W polysaccharides and approximately 48µg diphtheria toxoid protein conjugated to each polysaccharide. This vaccine is registered in NZ from age 9 months to 55 years. It is
available and recommended as part of the National Immunisation Schedule for high-risk children and adults from 2 years of age.

3.1.2 **High-risk groups**

Two meningococcal conjugate vaccines are funded for specific high-risk groups, namely, MenCCV (NeisVac-C) up to the age of 2 years and ACWY-D (Menactra) from 2 years of age, as of April 2018:(19)

- One dose for close contacts of meningococcal disease case (if vaccine available for relevant group).
- Maximum of two doses for bone marrow transplant patients or following immunosuppression due to steroid or other immunosuppressive therapy for longer than 28 days.
- Up to three doses plus booster doses every five years, as appropriate, for individuals pre and post splenectomy; pre and post solid organ transplantation; with functional asplenia; with acquired or inherited complement deficiency; or who are infected with human immunodeficiency virus (HIV).
- Note: High-risk infants who have received two doses of MenCCV can also receive two doses of MenACWY once they are over the age of 2 years.

Meningococcal conjugate vaccines are also recommended, but not funded, for certain individuals:(14)

- Either MenCCV or MenACWY vaccines are recommended for
  - Laboratory workers regularly handling meningococcal cultures
  - Adolescents and young adults living in communal accommodation, such as hostel, boarding school, military accommodation, correctional facilities or other long-term institutions
- Quadrivalent vaccines are recommended for individuals traveling to high-risk countries as listed by the WHO or before Hajj pilgrimage.

3.1.3 **Other meningococcal conjugate vaccines internationally licensed not in New Zealand.**

Menveo® (GlaxoSmithKline [GSK]) is a quadrivalent meningococcal vaccine conjugated with the non-toxic diphtheria toxin mutant protein cross-reactive material-197 (ACWY-CRM). It is currently approved for use in the US and Australia for children from the age of 2 months, adolescents and adults, but is contraindicated for individuals with hypersensitivity to latex as well as the vaccine active components and excipients.(20)

A combined Hib-MenC tetanus toxoid conjugated vaccine (Mentorix®, GSK) is licensed in Europe and given as a Hib booster in the second year of life.

*Table 8: Summary of meningococcal conjugate vaccines, according to safety data sheets (Medsafe, NZ or licensure in Australia, if not licensed in NZ, as of March 2018)*

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Antigens</th>
<th>Conjugate</th>
<th>Indicated age range</th>
<th>Licensed in NZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeisVac-C</td>
<td>MenC</td>
<td>Tetanus toxoid</td>
<td>From 8 weeks</td>
<td>Y</td>
</tr>
<tr>
<td>Mentorix</td>
<td>Hib-MenC</td>
<td>Tetanus Toxoid</td>
<td>From 6 weeks – 2 years</td>
<td>N</td>
</tr>
<tr>
<td>Menveo</td>
<td>MenACWY</td>
<td>Diphtheria CRM</td>
<td>From 2 months</td>
<td>N</td>
</tr>
<tr>
<td>Nimenrix</td>
<td>MenACWY</td>
<td>Tetanus toxoid</td>
<td>12 months – 55 years</td>
<td>Y</td>
</tr>
<tr>
<td>Menactra</td>
<td>MenACWY</td>
<td>Diphtheria toxoid</td>
<td>9 months – 55 years</td>
<td>Y</td>
</tr>
</tbody>
</table>
3.2 Safety of meningococcal conjugate vaccines

3.2.1 Background and objectives

The safety of meningococcal conjugate vaccines is considered from data obtained during post-licensure clinical studies and vaccine safety monitoring based on reports of adverse events following immunisation (AEFI) through active and passive surveillance. The focus will predominantly be on the safety of quadrivalent MenACWY vaccines as the safety of MenCCVs have been well reported previously. Data around the safety of the African MenA vaccines will also not be considered as they have little relevance to New Zealand.

Recognised reactogenicity will not be considered in detail as these data were published following pivotal, pre-licensure clinical trials and are generally well characterised.

The safety profiles of quadrivalent vaccines using the three different conjugates - the tetanus toxoid (TT), diphtheria toxoid (D) and diphtheria protein CRM conjugated vaccines - are considered individually.

3.2.2 Safety in immunocompetent vaccine recipients

3.2.2.1 Adults and adolescents

**ACWY-TT**

No serious adverse events (SAE) related to the vaccination were reported for up to five years following administration of ACWY-TT vaccine (Nimenrix®) or MenACWY polysaccharide vaccine (Mencevax® ACWY) in Saudi Arabia and the Philippines, as part of a follow-up study of a phase IIb RCT involving 500 healthy participants aged 11-55 years.\(^{(21, 22)}\)

**ACWY-CRM**

For 14 out of 26 predefined events of interest (EOI), no cases were identified for one year after vaccination with ACWY-CRM (Menveo®) in electronic health records. A temporal association was observed between concomitant vaccination with ACWY-CRM and Bell’s palsy (relative incidence 5; 95% CI 1.4-17.8), but no associated risk was detected for ACWY-CRM alone (relative incidence 1.1; 0.2-5.5). The most commonly received concomitant vaccines were human papillomavirus (HPV, 42%), tetanus-diphtheria-acellular pertussis (Tdap, 34%) and influenza vaccine (23%). The cohort study, which included 48,899 vaccine recipients aged 11-21 years, was conducted at Kaiser Permanente South California (KPSC) to assess the vaccine’s safety from 30 September 2011 to 30 June 2013. Specific risk windows (hypothesised time of risk after vaccination) were compared with a self-controlled case series (from end of risk window to up to one year). Further investigation of the association with Bell’s palsy is required since this study was unable to determine if it occurred by chance, was associated with the concomitant vaccines or whether underlying medical history predisposed the vaccine recipients to Bell’s palsy.\(^{(23)}\)

No unexpected findings or patterns of adverse events were identified by a review of reports submitted to the Vaccine Adverse Events Reporting System (VAERS) in the US. Reports of AEFI with ACWY-CRM (Menveo®) vaccine were consistent with pre-licensure data. During the study period (2010-2015), there were 2614 VAERS reports after receipt of this vaccine from individuals aged 2 months to adult. Of these, 67 were classified as serious, including one death that was diagnosed with brain tumour five months after vaccination (medical records were unavailable for review). The two most commonly reported serious adverse events (SAE) were anaphylaxis (seven reports) and five cases of syncope that were reported as serious due to hospital admission for potential concussion sustained during the event. In 53% of reports, ACWY-CRM was administered concurrently with other vaccines and 74%
were adolescents aged 11-18 years. During the analysis period, around 8.2 million doses of this vaccine were administered in the US, which equated to around 0.8 serious reports per 100,000 doses.\(^{(24)}\)

**ACWY-D**

A US-based retrospective, post-licensure safety surveillance self-controlled study found no unexpected safety risks following receipt of ACWY-D (Menactra\(^{\text{®}}\)) vaccine. During 2005-2016, 31,561 patients at Kaiser Permanente Northern California received ACWY-D vaccine (more than 99% were aged 11-55 years and 67.8% and 26.5% were aged 11-16 and 17-18 years respectively). Within a 30-day window post vaccination, there was an increased but low risk of febrile illness (0.38 cases per 1000 person-months). No hospitalisation or pre-specified clinical outcomes were elevated during the 30-day period post vaccination compared with days 60-90, and no pre-specified outcomes were increased during 180 days post vaccination compared with matched controls. It was noted that among the 11-16 years age group, an increase in urticarial events was seen two or more days following vaccination compared with matched controls. Three deaths were not considered vaccine related. Two serious adverse events occurred less than one month following vaccination, one case of new onset type-1 diabetes was noted and one case of new onset juvenile rheumatoid arthritis (both with family histories of these diseases), but were not deemed to have been caused by the vaccine. However, vaccination as a contributor could not be excluded.\(^{(25)}\)

**Conclusions**

- Post licensure, no unexpected adverse events have been identified following administration of ACWY-CRM in children or adults or ACWY-D in adolescents.
- Bell’s palsy was observed following co-administration with other vaccines in adolescents, but no causal effect in relation to ACWY-CRM vaccine has been determined.
- ACWY-D may slightly increase the risk of febrile illness in adolescents, and urticarial events were reported more frequently in 11- to 16-year-olds two or more days after vaccination compared with unvaccinated matched controls.

### 3.2.2.2 Children and infants

No safety concerns were identified following vaccination of children aged 2-10 years with ACWY-CRM (Menveo\(^{\text{®}}\)). A descriptive study analysed the electronic medical records of KPSC members using a validated algorithm to identify 26 predefined EOI and medically-attended SAE up to one year after vaccination. The study included 327 children who received ACWY-CRM between September 2011 and September 2014. This vaccine was given concomitantly with other vaccinations to 80% of the children. Of the 31 children who experienced one or more SAE (94 events in total), none were deemed by medical record review to be vaccine-associated and unrelated injuries or poisoning were most common.\(^{(26)}\)

In children, the most frequently reported AE were related to local reactions, such as injection site swelling and mild fever, or to administration errors. The review of VAERS reports, mentioned in section 3.2.2.1, identified that 33 out of 2614 reports were for children aged 2-23 months and 79 were aged 2-10 years. None of the four SAE per age group were associated with ACWY-CRM vaccination.\(^{(24)}\)

No safety concerns were identified in Italy during a phase II RCT for one dose of either ACWY-CRM (Menveo) or ACWY-TT (Nimenrix) vaccines in 199 healthy toddlers aged 12-15 months (mean 12.7±0.9 months). The frequency of solicited SAE (four reports and two reports, respectively) and at least one solicited AE within seven days of vaccination was comparable between groups (67% vs 63.4%, respectively). Tenderness at injection site was the most common solicited AE. Similar proportions of solicited systemic AEs were reported,
most commonly irritability, sleepiness and change in eating habits between the two vaccines (56.6% and 56.4%, respectively). Fever (≥38°C) was reported for 14.1% of the ACWY-CRM group and 13% of ACWY-TT group; there were no reports of severe fever (≥40°C). No unsolicited AE recorded up to day 29 post vaccination were considered related to the vaccines.(27)

Conclusion

- No new post-licensure safety concerns have been identified following administration of ACWY-CRM or ACWY-TT in any age group.

3.2.2.3 Safety of co-administration with routine vaccines

Various studies have been conducted to examine the safety of quadrivalent meningococcal vaccines when administered concurrently with routine immunisations in infants, young children, adolescents and adults.

A review of clinical trials found that ACWY-TT vaccine could be safely administered concurrently with a range of routine vaccines across a range of age groups.(28)

Likewise, a summary of data from phase III and IV RCTs found no clinically relevant interactions that impacted on vaccine safety following co-administration of ACWY-CRM vaccine with routine vaccines across different age groups. The frequency of post-vaccination AEs was not increased by co-administration with common vaccines in infants (DTaP-IPV-HepB-Hib, MMR, MMRV, PCV), adolescents (Tdap or HPV) and travel-related vaccines in adults.(29)

MenC-CRM

No unexpected changes to the safety profiles of MenC-CRM and MMRV vaccine were reported during a phase IIIb RCT in Italy when these vaccines were given concurrently to healthy children aged 13-15 months. One infant in the MMRV + MenC group reported mild febrile convulsion considered to be related to vaccination on day eight. A second febrile convulsion case, occurring on day 28, was believed to be due to a viral infection not vaccination. The highest incidence of rash occurred in the MMRV + MenC group (27% overall, 1.8% varicella-like and 11.9% measles/rubella-like), compared with 23.2% in the MMRV group (0.6% varicella-like and 9.0% measles/rubella-like) and 8.8% MenC group overall (0.6% varicella-like and 1.2% measles/rubella-like). None of the 12 SAEs reported were causally related to vaccination.(30)

ACWY-TT

An open phase III RCT supported the co-administration of ACWY-TT vaccine with routine childhood vaccines. ACWY-TT was given as a two- or three-dose primary course with routine childhood vaccines to infants aged 2, 3 (for three-dose group only), 4 and 12 months of age and was compared with two doses of MenC-CRM or MenC-TT given at 2, 4 and 12 months. All of the 2095 participants received PCV-10 and DTaP-IPV-HepB-Hib at 2, 3, 4 and 12 months. In all four groups, similar local and systemic symptoms were seen during eight days post vaccination and unsolicited AEs during the 31-day follow-up. One case of epilepsy at seven days post dose three in the ACYW-TT vaccination group was considered vaccine related.(31)

No safety concerns were identified in Mexico and Taiwan when a booster dose of PCV-10 was administered concurrently with ACWY-TT to 363 healthy toddlers aged 12-23 months during a RCT. The children were randomised 2:1:1 to receive either both vaccines together at the first visit, or PCV-10 only then ACWY-TT one month later, or vice versa. All participants had been primed with three doses of PCV-10 as infants. The most frequent solicited AEs were
pain at injection site and irritability, which were similar between all groups. The incidence of fever ranged from 11.0% to 19.8% after each vaccination. No grade 3 unsolicited AE or SAE were considered to be causally related to the vaccinations during a 31-day follow-up period.\(^{(32)}\)

**ACWY-CRM**

Co-administration of ACWY-CRM with routine vaccination was well tolerated in healthy infants aged 2, 4, 6 and 12 months and comparable to administration of the routine vaccines alone (age-appropriate DTaP-IPV/ Hib, HepB, PCV-7 or -13 and MMR). No vaccine-related SAE were observed in either group.\(^{(33)}\)

In two further large phase III clinical trials, no new safety concerns were identified for ACYW-CRM given with routine infant vaccines. The safety of ACWY-CRM was considered in toddlers and infants. The rates of AE were similar across groups, between different infant series schedules and toddler doses, and between the children that received routine vaccines only or with ACWY-CRM.\(^{(34, 35)}\)

**Conclusions**

Meningococcal conjugate vaccines can safely be co-administered with:

- routine infant and toddler vaccines (including DTaP-IPV, HepB, Hib, PCV, MMR, MMRV)
- routine vaccines in adolescents (HPV and Tdap)
- various vaccines in adults

No SAE have been associated with receipt of these vaccines concurrently.

**3.2.2.4 Booster vaccination**

A booster dose of ACWY-TT vaccine had a clinically acceptable safety profile, with no SAE reported during an open-label phase III RCT conducted in Finland. The booster dose was administered four years following one dose of MenC-CRM or ACWY-TT at 12-23 months of age. However, the incidence of unsolicited symptoms was higher in the ACWY-TT group than the C-CRM group (19.2% vs 2.1%), for which injection site reactions accounted for almost half of the vaccine-related symptoms. These local reactions were reported to be consistent with previous studies of this vaccine.\(^{(36)}\)

**3.2.2.5 Exposure in pregnancy**

In a review of VAERS data, there were 14 reports of inadvertent exposure to ACWY-CRM vaccination during pregnancy (10 in first trimester, one each in second and third trimesters). For 13/14 reports, no AE were reported and one reported fever and muscle soreness. For 11/14, no birth outcomes were recorded and three had no complications.\(^{(24)}\)

A recent commentary reviewing a potential role of meningococcal vaccination in pregnancy reported that no increase in adverse events have been associated with meningococcal vaccination in pregnancy, and that the WHO recommends that pregnant women be vaccinated with MenA conjugate vaccine if they are within the target age-range for mass immunisation campaigns. However, data around safety in pregnancy is limited.\(^{(37)}\)

**3.2.3 Use in immunocompromised individuals**

Literature around the safety of meningococcal vaccination of immunocompromised individuals or other high-risk special groups was found to be very limited.

A KPSC electronic record-based descriptive study found that few vaccine recipients (18 out of 327 [5.6%]) aged 2-10 years received the ACWY-CRM vaccine due to functional or
anatomical asplenia and none for persistent complement component deficiencies, despite recommendations. Although no safety concerns were detected for the study population overall, it was unable to draw conclusions around the safety of this vaccine in children with high-risk medical conditions.\textsuperscript{(26)}

\textbf{3.2.4 Summary of vaccine safety}

As summarised in Table 9, no serious safety concerns have been identified associated with vaccination with meningococcal conjugate vaccines. These vaccines are contraindicated for use in individuals with a known hypersensitivity to the vaccine components, including the conjugate proteins.

Most commonly reported adverse events are solicited and associated with previously described vaccine reactogenicity, such as injection site pain and swelling, and systemic reactogenicity, such as headaches and mild fever. These do not increase with concomitant administration with other vaccines. No severe adverse events have been identified as being causally associated with these vaccines in children or adults.

Booster doses of ACWY-TT were associated with increased injection site reactions in children primed with the same vaccine.

A temporal increase in incidence of Bell’s palsy was observed following concurrent administration of ACWY-CRM with Tdap, HPV and/or influenza vaccine, but not when administered alone, to adolescents aged 11-21 years. Further investigation is required to determine whether the apparent increase can be attributed to the vaccines or whether other factors or predispositions were associated with these cases.
<table>
<thead>
<tr>
<th>Age group \ Vaccine</th>
<th>ACWY-TT (Nimenrix)</th>
<th>ACWY-CRM (Menveo)</th>
<th>ACWY-D (Menactra)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants from 2 months</td>
<td>Not licensed &lt;12 months of age in NZ.</td>
<td>No safety concerns – consistent with pre-licensure data.</td>
<td>Not licensed &lt; 2 years of age in NZ</td>
</tr>
<tr>
<td></td>
<td>No safety concerns in RCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One case of epilepsy associated with vaccine dose 3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toddlers from 12 months</td>
<td>No safety concerns, consistent with pre-licensure data</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever (≥38°C) ~13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Injection site reactions more frequent following booster</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children 2 – 10 years</td>
<td>No new data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents and adults</td>
<td>No safety concerns</td>
<td>No concerns, consistent with pre-licensure data.</td>
<td>No concerns, low risk of febrile illness ?urticarial events in adolescents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VAERS reports (0.8 SAE / 100,000 doses) – anaphylaxis and syncope-associated hospitalisation</td>
<td></td>
</tr>
<tr>
<td>Concomitant administration</td>
<td>No safety concerns in infants and toddlers</td>
<td>No concerns in infants and children – consistent with pre-licensure data.</td>
<td>No data identified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>? Bell’s Palsy in adolescents with concomitant vaccines – further evidence need to assess possible predisposition.</td>
<td></td>
</tr>
<tr>
<td>High risk groups</td>
<td>Data limited</td>
<td>Data limited – very low uptake</td>
<td>No data identified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No concerns, but unable to draw conclusions for high-risk children</td>
<td></td>
</tr>
</tbody>
</table>

Table 9: Summary of meningococcal ACWY conjugate vaccine safety
3.3 Immunogenicity of meningococcal conjugate vaccines - overview

3.3.1 Background

Invasive meningococcal disease progresses very rapidly, and prevention relies primarily on the presence of high levels of high affinity bactericidal antibodies. Cellular memory is required to generate high affinity IgG antibodies, but this is secondary to the protection provided by antibodies. Booster doses of vaccine, which reactivate memory cells, maintain protective antibody levels after initial immune priming.

No correlate of protection has been determined due to the rarity of meningococcal disease and therefore immunogenicity is inferred from functional assay titres. Immunogenicity is reported as complement-mediated serum bactericidal activity (SBA) and is a measure of the titre of serum containing group-specific antibody that is required to kill *N. meningitidis* in vitro. This assay determines the survival of meningococci incubated with heat-treated test serum and exogenous human or rabbit complement, and titres are expressed as the dilution of serum required to give 50% bacterial killing (designated hSBA or rSBA titres, respectively).\(^{(1)}\)

Depending on whether human or rabbit complement is used in the SBA assay, the titres of bactericidal activity can differ for individual groups. Careful interpretation is therefore required when making comparisons between immunogenicity data.\(^{(27)}\)

Since meningococcal disease is quite rare, immunogenicity of meningococcal conjugate vaccines, as determined by SBA assays, has been used to infer vaccine efficacy in pre-licensure clinical trials.

This section provides an overview of the reviewed literature published from 2013-2018 around the immunogenicity of meningococcal conjugate vaccines, including MenC and MenACWY vaccines in post-licensure studies. For more study details see section 8.

3.3.2 The effect of conjugate proteins on immunogenicity

Theoretically, the scheduling of different conjugate vaccines on a primary schedule or for high-risk groups can have a beneficial or detrimental influence on immune response to polysaccharide and carrier antigens.\(^{(38-40)}\) Further explanation is provided in section 8.

- A balance needs to be achieved between immunogenicity and clinical effectiveness in these situations.
- Currently, no impact on overall effectiveness has been observed and the possible effect of blunting of immune responses on clinical protection is theoretical.
- Continued disease surveillance is essential to identify any potential issues, particularly for diseases with no correlate of protection such as meningococcal disease and pertussis.
- The same vaccine is recommended to be used throughout a primary course.\(^{(38)}\)
3.3.3 Immunogenicity in children

3.3.3.1 MenCCV

The immunogenicity of MenCCVs has been well studied prior to the scope of this review. A more recent study showed that one-dose priming with MenC-TT in infants either at 4 or 6 months of age was non-inferior to two-dose priming given at the younger ages of 2 and 4 months. Single toddler doses of Hib-MenC do not induce long-lived antibody responses in un-primed children.\(^{(41, 42)}\)

3.3.3.2 MenACWY

More recent information is available for the quadrivalent conjugate meningococcal vaccines than MenCCV, although much of the immunogenicity data was obtained during pre-licensure clinical trials and published before 2014.

Generally, one or two doses of MenACWY vaccines were found to be immunogenic from 12 month of age with seroprotection observed in 79-99% of vaccine recipients after one month.\(^{(27)}\)

One or two doses of ACWY-CRM or –TT induce persistent seroprotective antibodies against groups C, W and Y in children aged 12 months to 10 years. Bactericidal responses against group A are variable and may be an artefact of the type of assay used. Immune memory appears to be induced for all groups since booster responses are induced upon revaccination after five years.\(^{(27, 43)}\)

3.3.3.3 Co-administration with routine vaccinations

In pre-licensure clinical trials, possible interference with the immune response against the pneumococcal serotypes in the CRM-conjugated vaccine PCV-7 was observed when administered with ACWY-D (and implied for PCV-13). Administration of ACWY-D is recommended to be delayed until after the primary course of PCV-13 had been completed in young infants and immunocompromised individuals.\(^{(18)}\) More recent data to confirm this interference was not found during this literature review.

ACWY-TT vaccine can be co-administered with PCV-10, although some immunological interference is possible against TT conjugated vaccine serotype 18C. Pneumococcal booster doses induce good immune responses against all vaccine antigens.\(^{(32)}\)

ACWY-CRM is highly immunogenic against all four meningococcal groups and does not appear to interfere significantly with other primary vaccinations following two or three priming doses (from age of 2 months) plus a booster by 13 months of age.\(^{(34, 44)}\) Catch up doses of ACWY-CRM or –TT induce seroprotection in 79-99% of children aged 12 months to 15 years, following routine vaccination in infancy, were also immunogenic in toddlers.\(^{(34)}\) However, there was insufficient data to conclude what effect concomitant vaccination with PCV-13 and ACWY-CRM has after each priming dose.\(^{(44)}\) In one RCT, slight differences were observed in seroresponse rates to pertussis antigens (pertactin and FIM) and pneumococcal serotypes (6B and 23F) following the post-infant series, but these were not below non-inferiority criteria for immunogenicity.\(^{(33)}\)

Theoretically, the scheduling of different conjugate vaccines on a primary schedule or for high-risk groups can be either beneficial or detrimental to the immune response to vaccine polysaccharides and carrier antigens. A balance needs to be achieved between immunogenicity and clinical effectiveness in these situations. Currently, no impact on overall effectiveness against meningococcal disease or the other vaccines’ antigens has been observed and the possible effect of blunting of immune responses on clinical protection has not been verified. Continued disease surveillance is essential to identify any potential issues,
particularly for diseases with no correlate of protection such as meningococcal disease and pertussis.

3.3.3.4 Booster doses in children

Booster doses of ACWY-TT induced seroprotective responses against all groups when given four years after priming of toddlers with a single dose of ACWY-TT or C-CRM. Booster doses of ACWY-TT alone (36) or concurrently with DTaP were immunogenic in HibMenCY-TT and DTaP- primed toddlers. (45)

The optimum timing of booster doses following priming with ACWY-TT or C-CRM is undetermined in children. Seroprotective antibodies persist for at least four years for groups C, W and Y after priming at 12-23 months. Most primed individuals respond to booster doses given four years later, although the persistence of these antibodies into adolescence is unknown. (36)

3.3.4 Immunogenicity in adolescents and adults

There are few recent publications on the immunogenicity of ACWY-TT vaccine or ACWY-CRM in adolescents or adults. Clinical trial data published prior to 2013 demonstrate good immunogenicity and seroprotective titres in children and adults. (46)

The immunogenicity of ACWY-D has not been widely assessed since licensure and data are limited. Findings reported were also similar to pre-licensure data for different populations. (42)

A single dose of ACWY-TT induces a robust immune response against all groups in more than 72% of healthy adolescents and adults, and may provide protection for at least five years. (22)

This vaccine was also shown to be immunogenic in adults aged 56-103 years, although immune response tended to be lower for those aged 65 year or older. Low levels of anti-TT antibody were also induced in this age group. (47)

3.3.4.1 Co-administration

The immune response to all four meningococcal groups was not affected by concomitant administration of ACWY-CRM with other routine or travel vaccines in adolescents and adults (including Tdap and HPV). (29)

Some immune modulation appears to occur against certain vaccine antigens following co-administration of ACWY-CRM and Td or Tdap vaccines in adults and adolescents, but not with HPV vaccine. Immunogenicity against pertussis and meningococcal groups A and C may be reduced in some individuals, but the clinical relevance on vaccine effectiveness is undetermined. (29)

No recent studies were found that investigated co-administration of ACWY-TT or ACWY-D with other vaccines. Studies conducted prior to 2013 reported no immunogenicity concerns. (48)

3.3.4.2 Booster doses

Booster doses of ACWY-CRM, given three years after primary vaccinations with ACWY-CRM or ACWY-D, induced seroprotective responses in more than 99% of adolescent recipients. (49)

3.3.4.3 Mucosal antibodies

There is evidence of a correlation between vaccine-induced serum IgG and salivary IgG, although salivary antibody is short lived (up to six months post vaccination) and, as
expected for mucosal tissues, IgA-predominant. It is unknown how the presence of salivary anti-meningococcal antibodies relates to carriage and transmission of disease-causing meningococcal strains.\textsuperscript{(50, 51)} Further discussion about the impact of meningococcal vaccines on carriage is provided in section 5.1.2.

### 3.3.5 Immunogenicity in special groups

There is insufficient recent data to comment on the immunogenicity of meningococcal vaccines in high-risk groups. The use of biological therapies may accelerate the waning of seroprotective antibodies leaving some individuals unprotected.\textsuperscript{(52)} Frequent boosters are required to overcome waning seroprotection, although the optimum frequency of booster doses is not established.

Immunosuppressive or immunomodulatory therapies used to treat immune mediated inflammatory diseases or to prevent transplant rejection are likely to affect the immunogenicity of meningococcal conjugate vaccines. Where possible, vaccination is suggested prior to transplantation or commencement of treatment.\textsuperscript{(53)}

Hyporesponsiveness in response to conjugate antigens may be observed in those with prior experience of polysaccharide meningococcal vaccines. Vaccine response rates were lower in some older individuals (over 55 years of age) who had received prior vaccination with polysaccharide vaccines (MenC or quadrivalent).\textsuperscript{(46)}

### 3.3.6 Summary of immunogenicity

Meningococcal conjugate vaccines are immunogenic in all populations following one dose. Duration of antibody protection can be extended by booster doses in primed individuals.

They are generally safe to be given concurrently with routine vaccines, no clinically significant interference has been reported. However, lower antibody responses to some pertussis antigens and some pneumococcal serotypes have been reported.

Although there is no defined correlate of protection for meningococcal vaccines against IMD, clinical protection against IMD is known to be provided predominantly by circulatory antibody, rather than memory cellular responses. Therefore, booster doses are required to maintain seroprotective antibody levels for those at highest risk of IMD.

Data is very limited describing the immunogenicity of these vaccines in high risk groups or that provide recommendations for booster dose frequency.

The findings of this literature review are summarised below in Table 10.
### ACWY-TT (Nimenrix)

<table>
<thead>
<tr>
<th>Age group \ Vaccination</th>
<th>Primary</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants from 2 months</td>
<td>No recent data found</td>
<td></td>
</tr>
<tr>
<td>Toddlers from 12 months</td>
<td>Persistent seroprotection following 1 or 2 doses</td>
<td>Seroprotective response to booster given 4 years after priming with ACWY-TT or ACWY-CRM</td>
</tr>
<tr>
<td>Children 2 – 10 years</td>
<td>Immune memory induced</td>
<td>Timing of boosters not determined</td>
</tr>
<tr>
<td>Adolescents and adults</td>
<td>Data limited</td>
<td>No recent data</td>
</tr>
<tr>
<td></td>
<td>Single dose induces robust response in at least 72% recipients, protection for at least 5 years.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immunogenic in older adults 55-103 years.</td>
<td></td>
</tr>
<tr>
<td>Concomitant administration</td>
<td>Possible immunological interference with PCV-10 serogroup 18C, not observed following PCV-10 booster.</td>
<td>Immunogenic when given concurrently with DTaP booster (in HibMenCY-TT primed toddlers)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No recent data for adults</td>
</tr>
<tr>
<td>High risk groups</td>
<td>Potential hyporesponsiveness against MenC in those with prior experience of MenC-PS vaccinations.</td>
<td>Boosters required – frequency not determined.</td>
</tr>
</tbody>
</table>

### ACWY-CRM (Menveo)

<table>
<thead>
<tr>
<th>Age group \ Vaccine</th>
<th>Primary</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants from 2 months</td>
<td>No recent data</td>
<td></td>
</tr>
<tr>
<td>Toddlers from 12 months</td>
<td>Persistent seroprotection following 1 or 2 doses</td>
<td></td>
</tr>
<tr>
<td>Children 2 – 10 years</td>
<td>Seroprotection last at least 4 years for groups C, W and Y</td>
<td>Optimum timing of booster unknown</td>
</tr>
<tr>
<td>Adolescents and adults</td>
<td>No recent data</td>
<td>Seroprotection in 99% of adolescents primed with ACWY-CRM or ACWY-D</td>
</tr>
<tr>
<td>Concomitant administration</td>
<td>No evidence of significant interference with primary vaccines in infants or other vaccinations in adults and adolescents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Potential interference with pertussis and meningococcal groups A and C, no clinical significance identified.</td>
<td></td>
</tr>
</tbody>
</table>
### ACWT-D (Menactra)

<table>
<thead>
<tr>
<th>Age group\ Vaccine</th>
<th>Primary</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants from 2 - 12months</td>
<td>No data – not licensed under 2 years.</td>
<td>No data identified</td>
</tr>
<tr>
<td>Children 2 – 10 years</td>
<td>Post licensure data limited, one study similar immunogenicity to prelicensure data</td>
<td></td>
</tr>
<tr>
<td>Adolescents and adults</td>
<td>Prelicensure data suggested interference with PCV-7 serotypes</td>
<td>No recent data, no concerns pre-2013</td>
</tr>
<tr>
<td>Concomitant administration</td>
<td>Prelicensure data suggested interference with PCV-7 serotypes</td>
<td>No recent data</td>
</tr>
</tbody>
</table>

Abbreviations: MenC-PS – polysaccharide MenC vaccine, PCV – pneumococcal conjugate vaccine

### 3.4 Effectiveness of meningococcal conjugate vaccines in disease control

Since invasive meningococcal disease is a rare occurrence, except in isolated outbreaks, vaccine effectiveness (VE) is not commonly measured. Very few RCT and post-licensure studies investigate the efficacy, effectiveness or the duration of protection of meningococcal vaccines. In general, the impact of immunisation programmes on the population-wide epidemiology of the disease or on carriage studies are more informative.

#### 3.4.1 Effectiveness of meningococcal C conjugate vaccination

The overall VE of MenCCV vaccination was found to be 98% (lower 95% CI 89%) in a case-control study conducted during a city-wide MenC epidemic in Salvador, Brazil, with a case-fatality rate of 25%. The study concluded that MenCCV was highly effective and rapid uptake through targeted campaigns contributed to the control of the disease. The age groups with the highest attack rates, <5 years and 10-24 years, were targeted in four stages by mass vaccination campaigns during 2010. More than 600,000 doses of MenCCV (MenC-TT then MenC-CRM in the later stage) were administered. The estimated coverage was 92% of targeted population aged <5 years, 80% of those aged 10-14 years, 67% aged 15-19 years and 41% adults aged 20-24 years. Fifty out of 110 laboratory-confirmed MenC cases diagnosed during 2010 were within the targeted age groups and these were matched by age and neighbourhood with 240 controls. Of these 50 cases, 39 had symptoms prior to vaccination campaigns targeting their age groups and 11 were confirmed post campaign. None of the cases had been vaccinated. Out of the controls, 70/240 (29.2%) of controls had been vaccinated with at least one dose of MenCCV, including 50/84 (70.2%) matched with cases from a period after the immunisation campaign.\(^{(54)}\)
3.4.2 Duration of protection

The relationship between vaccine effectiveness, time since MenCCV vaccination and age of vaccination was investigated in Spain.\(^{(55)}\) The duration of effectiveness of MenC vaccination was shown to be longer for those immunised as adolescents than as infants. Ten years after vaccination, VE fell by 50% in children who were vaccinated younger than 1 year, by 9.3% in those vaccinated between the ages of 1-11 years, and no decline in VE was observed for those vaccinated as adolescents aged 12-19 years.\(^{(55)}\)

Out of 345 confirmed MenC cases reported during 2001 and 2013 that were targeted by vaccination programmes in Spain, 125 (36.2%) were deemed vaccine failures. The proportion of vaccine failures in each group decreased with the age at vaccination from 64.0%, to 36.9% and to 3.9% at age <1 year, 1-11 years and 12-19 years, respectively. Vaccine effectiveness decreased from 99% to 48.6% after 10 years in those vaccinated younger than 1 year and from 99.5 to 90.2% in those vaccinated at age 1-11 years; those who were vaccinated at 12-19 years showed no change (0.1% decrease, p = 0.968).\(^{(55)}\)

The overall VE of a single dose ACWY-D given at 11-12 years of age was estimated to be 69% (95% CI 51-80%) up to eight years post vaccination. This finding was based on 161 enrolled cases of group C, W or Y disease identified during 2006 to 2013 (12% of cases compared with 2% of controls had underlying medical conditions).\(^{(56)}\) At one year after vaccination, VE was 79% (49-91%); at years one to three VE was 69% (44-83%); and 61% (25-79%) for years three to up to eight. The VE of ACWY-D against group Y was lowest (51%), which with group C were the major causes of IMD in the US prior to the vaccine introduction. Based on this study, since the period for highest risk of IMD is at 16-23 years, a preferred option chosen by the Advisory Committee on Immunization Practices (ACIP) in the US was to give a second dose at age 16 years (as opposed to a delayed first dose at the age of 14-15 years). This study concluded that, in terms of the number of cases prevented, the impact gained by the booster dose is likely to be limited. In discussion, the authors note that the diphtheria toxoid protein carrier, as compared with other conjugates, may be associated with the reduced long-term protection and was observed with Hib-D vaccines in infants, hence these findings cannot be extrapolated for other MenACWY vaccines.\(^{(56)}\)

3.4.3 Summary of effectiveness

Effectiveness of conjugate meningococcal vaccination against laboratory-confirmed disease is difficult to assess due to the low incidence of cases, even during localised epidemics.

A targeted immunisation campaign demonstrated that MenCCV had 98% effectiveness against MenC disease in young children, adolescents and young adults during a MenC epidemic in Brazil.

The duration of protection of MenCCV depends on the age at which primary vaccination takes place. One study found that when vaccinated with one dose at 12-19 years of age, VE remains virtually unchanged (0.1% decrease) for at least 10 years, whereas in those vaccinated as infants with two or three doses, VE declines by 50% over 10 years.

A single dose of ACWY-D at age 11-12 years maintains 69% VE for up to eight years post vaccination. A second dose given at age of 16 years to extend protection into the high-risk period of early adulthood was recommended by ACIP, but the impact of this booster dose, in terms of the number of cases prevented, is likely to be limited.

The duration of protection for the other MenACWY vaccines was not investigated in the literature.
4 Meningococcal B recombinant vaccines

4.1 Background

Meningococcal B disease has historically been difficult to control through vaccination due to poor immunogenicity, capsular polysaccharide cross-reactivity with ubiquitous human antigens in the brain and antigenic variability of the outer membrane vesicle proteins of the capsular group B bacterium. (3)

Epidemics of MenB disease worldwide are associated with the emergence of hypervirulent strains. (3) As mentioned in the epidemiology section, NZ experienced an epidemic of a particular group B meningococcus strain during 1991-2007, and a specifically designed strain-specific vaccine (known as MeNZB) was successfully used to help bring the outbreak under control from 2004-2008. Other specially designed group B vaccines have been used in Norway and Cuba for national use or outbreak control. (57)

However, isolated outbreaks of group B disease continue to occur and, as described in Section 2.2, group B meningococci remain the most frequent cause of IMD notified in NZ.

Reverse vaccinology and recombinant technology have permitted the development of multi-component meningococcal B (MenB) vaccines. Currently, there is little data on the use of these vaccines beyond licensure clinical trials and several questions remain around their usage, including:

- The extent of the strain coverage
- The effect on other Neisseria species
- Long term antibody persistence and safety
- Whether they are able to reduce transmission and carriage of virulent MenB strains and generate herd immunity

In this section consideration is given to the use of these vaccines in the control of MenB disease. Literature concerning the safety, immunogenicity and impact these vaccines have had in disease control through direct and indirect protection is reviewed for infant immunisation programmes and in adolescents and young adults.

4.1.1 Four-component meningococcal B vaccine

A multi-component meningococcal B vaccine was first licensed in 2013 in Europe and Australia, and has since been licensed in the US, Canada and elsewhere, including South America. (58) As of July 2018, this vaccine has been approved in New Zealand, indicated from 2 months of age. (59)

The four-component vaccine (4CMenB; Bexsero®, GSK acquired from Novartis) consists of three recombinant Neisseria meningitidis group B fusion proteins and detoxified outer membrane vesicles (OMV). The vaccine is predicted to protect against 73-88% of the predominant group B strains. (60)

Further details of the components in 4CMenB are given below: (3)

1. Factor H binding protein (fHbp) was first identified independently by both Chiron Vaccines, designated as ‘genome-derived Neisseria antigen 1870’ (GNA1870), and Pfizer (formerly Wyeth Vaccines), which designated it as lipoprotein LP2086. The binding of fHbp to factor H enables meningococci to survive by down-regulating complement activation in non-immune sera. However, in human serum the binding
site is masked by bound factor H and it is believed that these vaccines induce a response external to this binding site.

2. *Neisseria* adhesion A (NadA) is a fHbp subfamily antigen, which is thought to be related to transport proteins on the meningococcal outer membrane that promote adhesion to epithelial cells. Only 30-40% of group B strains have genes coding for this protein.

3. *Neisseria* heparin binding antigen (NHba) is a surface exposed lipoprotein whose heparin binding was correlated with survival of unencapsulated meningococci in vitro. The contribution of anti-NHba antibodies in the protection elicited by this vaccine is not yet determined.

4. Outer membrane vesicles (OMV) have been used previously in MenB vaccines for isolated outbreaks, as in New Zealand and Norway. Bactericidal antibodies predominantly target specific porin protein, PorA, variants. As used in the MeNZB vaccine, the OMV in 4CMenB is prepared from the NZ98/254 strain, PorA subtype P1.4. It has a role as an adjuvant to enhance the immunogenicity of the recombinant fusion proteins in 4CMenB and to provide some anti-PorA coverage.

Licensed dosing schedules of 4CMenB are outlined in Table 11. The need for booster doses in previously unvaccinated children aged 12-23 months is uncertain. Guidelines in Australia and Canada do not recommend a booster.\(^{61}\)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Primary series</th>
<th>Interval between primary doses</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants, 2-5 months*</td>
<td>3 doses</td>
<td>≥1 month</td>
<td>Yes, one dose at 12-15 months</td>
</tr>
<tr>
<td>Infants, 6-11 months</td>
<td>2 doses</td>
<td>≥2 months</td>
<td>One dose, 2(^{nd}) year of life, ≥2 months after primary series</td>
</tr>
<tr>
<td>Infants, 12-23 months</td>
<td>2 doses</td>
<td>≥2 months</td>
<td>Need not established</td>
</tr>
<tr>
<td>Children, 2-10 years</td>
<td>2 doses</td>
<td>≥2 months</td>
<td>Need not established</td>
</tr>
<tr>
<td>Adolescents and adults*</td>
<td>2 doses</td>
<td>≥1 month</td>
<td>Need not established</td>
</tr>
</tbody>
</table>

* safety or efficacy have not been established under 8 weeks of age or over age of 50 years

Table 11: Licensed dosing schedule for 4CMenB, based on New Zealand licensure (reproduced from Medsafe data sheet, July 2018)

### 4.1.2 Two-component meningococcal B vaccine

A two-component MenB vaccine received accelerated approval in the US in 2014, and was approved in Europe in May 2017 and in Australia in September 2017 for use in adolescents and adults aged 10 years and older. MenB-fHbp (Trumenba\(^{®}\); Pfizer; designated bivalent rLP2086 vaccine in some pre-licensure clinical trials) contains two purified recombinant lipidated fHbp antigens. The vaccine is given as a two- or three-dose series at six months apart or one month after the first dose and then after at least four months.\(^{62}\) Due to an increased risk of fever, it is not approved for children under 10 years of age.\(^{63}\)
4.2 Safety of meningococcal B vaccines

This review will primarily consider post-licensure randomised clinical trial data on AEFI, as available, and not pre-licensure reactogenicity studies. Data on routine use of these vaccines is limited since they have only recently been introduced.

4.2.1 Safety of four-component vaccine (4CMenB)

4.2.1.1 Infants

The risk of adverse reactions, including irritability, changes in eating habits and unusual crying, increased within seven days of vaccination following concomitant 4CMenB immunisation with routine vaccines in infants (from 2 months of age). During a phase III observer-blind RCT, 2302 (93%) out of 2478 infants who received 4CMenB were administered anti-pyretic medication as compared with 471/659 (71%) who received routine vaccines alone and 325/490 (66%) who received MenC conjugate vaccine concurrently with routine vaccines. The rate of medically-attended fever was similar for each group (2%, 2% and 3%, respectively). No increase in reactogenicity was observed when the 4CMenB booster was co-administered with MMRV or alone at 12 months of age.(64)

Using Public Health England’s national syndromic surveillance systems, including daily consultation data from general practitioner electronic patient records, presentations for all-cause fever in infants were investigated for 12 months following the introduction of 4CMenB immunisation in England. Fever was identified using 72 predefined Read codes describing fever, pyrexia or febrile convulsions in infants aged less than 1 year from September 2015 to August 2016 and was compared with the two previous years’ historical data.(65)

- The daily average for all-cause fever consultations was higher during 2015-2016 than for the same periods prior to the introduction of 4CMenB: 11.18 vs 9.55 and 7.58 per 100,000 during 2013-14 and 2014-15, respectively.
- The incidence risk ratio (IRR) for infants aged 7-10 weeks (age of dose one) was 1.6-fold higher than previous years and 1.5-fold higher than for infants aged 15-18 weeks (age of dose two; p<0.05 for both).
- No significant difference was observed for infants aged 0-6 and 11-14 weeks (i.e. pre-vaccination ages and age for dose two of routine vaccines without 4CMenB, respectively).(65)

Based on this study, it was estimated that there would be an additional 1825 GP consultations (95% CI 328-3088) annually across England for all-cause fever in the 4CMenB vaccine-eligible cohort of around 776,000 infants. Prophylactic paracetamol is recommended prior to and following 4CMenB vaccinations in infants. Emergency department admissions and wider health service usage (such as health advice line consultations) were not assessed in this study.(65)

A retrospective study showed a significant increase in AEFI presenting at EDs in the UK at 2 and 4 months of age, following 4CMenB vaccination.(66) The study examined the frequency of infants aged 1-6 months presenting to EDs in the UK due to AEFI post-vaccination with 4CMenB. An increase in the annual rate of AEFI (probable or possible onset within 48 hours of vaccination) in the Oxford University Hospitals NHS trust emergency departments was observed:

- AEFI increased from an average of 12 per year prior to the introduction of 4CMenB (during 2013-2015) to 38 in the year following its introduction (2015/16).
At 2 months of age, the rates of AEFI significantly increased from 1.03 per 1000 immunisation episodes to 3.4 (p<0.001) and from 0.14 to 1.13 at 4 months of age (p=0.005).

No increase was seen at 3 months of age, when no doses of 4CMenB were scheduled (p=0.380).

The increase in presentations was also associated with increased AEFI-related hospital admissions, invasive investigations and intravenous antibiotic use.(66)

A prospective audit of ED presentations in Northern Ireland identified 35 out of a total of 1413 attendances of infants aged 30-180 days were due to symptoms occurring after primary vaccinations, representing an estimated 0.8% of the vaccinated population within the catchment area. Of these infants, 30 presented after their first 4CMenB dose and five after the second dose. Paracetamol was reportedly administered to 33 of the infants, as recommended to parents. All of the cases were finally diagnosed as being AEFI by exclusion. The authors concluded that infants presenting with fever following immunisation with 4CMenB pose a diagnostic challenge for ED paediatricians, but there is a need for education around AEFI to allow clinical judgement to be used to avoid unnecessary investigations and hospital admissions.(67)

Conclusions

- 4CMenB vaccination is associated with increased risk of fever, irritability and changes in feeding behaviour in infants younger than 12 months.
- The rates of AEFI presenting at ED increased significantly following routine 4CMenB vaccination of infants (from 1.03 to 3.4 per 1000 immunisations at 2 months of age).
- Prophylaxic paracetamol is recommended prior to routine vaccinations that include 4CMenB.
- Education of ED paediatricians is required to avoid unnecessary invasive investigations and hospital admissions of infants presenting to ED with fever after receiving 4CMenB.

4.2.1.2 Toddlers

The rates of fever were lower in 2-year-old vaccine-naïve toddlers than younger toddlers at 12 months. Injection site tenderness and erythema was reported in more than half of toddlers receiving primary or booster doses of 4CMenB and increased with the number of doses received. The reactogenicity of 4CMenB was examined in an extension of a phase III study that administered the vaccine as either a booster dose in previously vaccinated infants at 12 months of age or as a primary catch-up in vaccine-naïve toddlers aged 12 months or 2 years in Europe. (68)

Local major reactions were erythema (58-77% of injections, 1-13% severe [>50mm]) and tenderness was reported in 56-57% of toddlers receiving their first vaccinations at 12-13 months of age; 10% of tenderness was reported as severe (crying when limb was moved). The rates of tenderness increased with subsequent doses: 66-67% were reported to have any tenderness and 16-18% had severe after the second dose; following third dose any tenderness and severe was reported in 94% and 18% of recipients, respectively. In 2-year-olds, the rate of severe tenderness was 10-18% following the first and second doses. Severe tenderness was transient and resolved the day following vaccination.(68)

The highest rate of fever (≥38°C) was seen six hours after vaccination in 37% and 46% of vaccine-naïve toddlers at 13 months or with concomitant MMRV at 12 months, respectively.
The rates of fever and paracetamol use were lower for the older toddlers receiving their first dose at 2 years. Only two cases had a transient fever of ≥40°C in toddlers and one case in a two-year-old occurred several days post vaccination. The rates of fever in toddlers was non-significantly lower than reported for infants. The authors suggested that the body weight ratio to dose of OMV in the vaccine could be associated with the greater reactogenicity in the youngest infants and toddlers.(68)

4.2.1.3 Adults

There is very limited post-licensure data around adverse events associated with 4CMenB vaccination in adolescents and adults.

The safety of three doses of 4CMenB, one of which was administered concurrently with ACWY-CRM vaccine, was investigated in public health laboratory workers aged 23-55 years (mean 34 years) in the UK. Local injection site reactions were reported by all 4CMenB recipients, compared with less than a quarter of ACWY-CRM-only recipients, with higher rates of erythema and induration following 4CMenB. Pain was the most frequently reported local reaction and 16% reported severe pain following each dose. When both vaccines were given concurrently, nausea and headache were most frequently reported; these AE reduced with consecutive 4CMenB doses. Over 40% of recipients reported using pain relief following the first dose of ACWY-CRM/4CMenB, and fewer following the second and third 4CMenB doses. The authors suggested that, as for infants, prophylactic paracetamol be recommended for adults prior to receiving 4CMenB.(69)

Conclusions

Due to an increased risk of fever in young children, it is recommended to administer paracetamol prophylactically prior to immunisation with 4CMenB.

- General mild to moderate systemic adverse events have been observed within a week of 4CMenB immunisation of infants.
- The rates of injection site tenderness and erythema were higher in toddlers than in infants and increased with the number of doses given (94% of 2-year-olds receiving third doses had injection site tenderness).
- The rates of fever in toddlers tended to be lower, but not significantly, than for infants.
- Awareness of the risk of adverse events following immunisation with 4CMenB could avoid unnecessary invasive investigations and hospital admissions of vaccinated infants presenting with fever to emergency departments.

Although the post-licensure literature is limited, local and systemic adverse responses have also been recorded in adults.

- When administered concurrently with ACWY-CRM, injection site pain was reported for all recipients and 16% reporting severe pain following each dose.
- Nausea and headache were the most frequent systemic responses in adults and more common after the first dose of 4CMenB with ACWY-CRM compared with the second and third doses of 4CMenB.

4.2.2 Safety of two-component vaccine (MenB-fHbp)

The post-licensure data on the safety on MenB-fHbp is even more limited than 4CMenB, since it has only more recently been licensed – first in 2014 in the US and then in the European Union in May 2017. A brief review of the pre-licensure safety data is provided below.
Due to the high fever rates (64-90%) observed during early clinical trials following vaccination of infants with MenB-fHbp vaccine, the use of this vaccine in infants was discontinued and it was not licensed for children younger than 10 years.\(^3\),\(^70\)

In a review of pivotal clinical trial data following the first licensure of the two-component MenB-fHbp vaccine, the most common systemic adverse reactions reported in adolescents and adults aged 11-25 years were mild to moderate fatigue, headache and muscle pain, including when administered concurrently with HPV4 vaccine.\(^71\)

Across seven RCT, 24.5% of recipients reported non-serious adverse events within 30 days of vaccination after any dose. Three SAE were considered vaccine-related – one hospitalisation for fever and vomiting following the first dose, another hospitalised with severe vertigo, chills and headache following the second dose, and one case of anaphylaxis after the third dose. The vaccine was generally considered well tolerated in this age group.\(^71\)

A subsequent review of published RCT data found MenB-fHbp to be moderately reactogenic, but generally well tolerated in adolescents and adults, with most adverse events being mild to moderate. Fever (≥38°C) was more common after dose one than doses two or three.\(^72\)

### 4.2.3 Summary of meningococcal B vaccine safety

Both of meningococcal B recombinant vaccines are associated with mild to moderate injection site and systemic reactions, and are moderately reactogenic.

Due to the increased risk of high fevers in young children, MenB-fHbp vaccine is not approved for use in children aged younger than 10 years. In adults and adolescents, mild to moderate pain and inflammation at the injection site and systemic responses, including headaches and nausea, have been identified.

The use of 4CMenB vaccine routinely in infants from 2 months of age in the UK will provide further information about the reactogenicity and long-term safety of this vaccine. Currently, prophylactic paracetamol is recommended prior to receipt of this vaccine to help to reduce the risk of febrile seizures and medically-attended fevers in young infants.

Toddlers experienced more injection site reactions and transient tenderness than infants, which increased to 94% of recipients by the third dose. In adults, this vaccine is associated with injection site pain, headaches, muscle ache and nausea. Prophylactic paracetamol may also be recommended for toddlers and adults to reduce pain following each dose.

An awareness in emergency departments of the adverse events associated with 4CMenB, in particular fever, is likely to prevent unnecessary or invasive investigations and hospital admissions to determine the source of the fever in young vaccinated infants.

No long-term safety data or SAE observed during licensure clinical trials have been identified by this literature review.

### 4.3 Immunogenicity of meningococcal B vaccines

As for MenACWY vaccines, due to the low incidence of meningococcal B disease globally, immunogenicity rather than efficacy was used in clinical trials as a measure of responsiveness to these vaccines. Serum bactericidal antibody titres inferred protection against a manufacturer-selected panel of three or four group B strains.

These strains do not necessarily represent wild-type virulent strains and have a known susceptibility or high expression of vaccine antigens. Inconsistent or composite endpoints used in the pre-licensure studies make interpretation difficult. Subsequently, further studies
have combined these data with bactericidal antibody data against additional disease-causing isolates, and with data on the expression and cross-reactivity with antigens of circulating disease-causing strains.\(^{(3)}\)

The generation of bactericidal serum IgG antibodies is the most frequent measure of immunogenicity. It is unknown what part cellular or mucosal immune responses may play in the protective response to these vaccines.

Due to these limitations, both pre- and post-licensure immunogenicity data for both of the recombinant MenB vaccines is reviewed in this section for the relevant age groups.

### 4.3.1 Immunogenicity of four-component 4CMenB vaccine

#### 4.3.1.1 Infants

Bactericidal antibody levels declined by pre-school age in children primed with 4CMenB as infants. A pre-licensure immunogenicity study was conducted in the UK to examine the presence of bactericidal antibodies in 4CMenB-primed infants (at 2, 4, 6 and 12 months) before and after the pre-school booster at age 40-44 months. Participants also received routine doses of DTaP-IPV vaccine and MMR at the final study visit. A decline in the proportions of infants with bactericidal antibody was observed from 13 months of age (from 100%, 93% and 96% to 65%, 76% and 41% for the strains fHbp, NadA and NZ98/254 [PorA], respectively). However, it is unclear whether these differences between strains reflects persistence of efficacy or different susceptibilities of the strains tested to the bactericidal assay. Of the participants who were primed and boosted with 4CMenB, 86-100% achieved bactericidal antibody titres of $\geq 1:4$ for all except one strain.\(^{(73)}\)

Reduced infant schedule (two primary doses) and two-dose catch-up schedules of 4CMenB are immunogenic and potentially would provide adequate seroprotection against MenB, assessed in an open label phase IIIb clinical trial. Infants (n=754) were randomised to receive the vaccine as a 2+1 (two-dose) schedule at 3.5, 5 and 11 months or 6, 8 and 11 months, or as a 3+1 (three-dose) schedule at 2.5, 3.5, 5 and 11 months. Two catch-up doses were given two months apart to children aged 2-10 years who had not received a primary series (n=404). Across all groups post primary vaccination, 98-100% of infants developed seroprotective serum bactericidal activity (hSBA) titres $\geq 1:4$ for fHbp, NadA and PorA, and 48-77% had antibody titres $\geq 1:4$ for the NHba reference strain. In the catch-up group, 95-99% of children developed hSBA titres $\geq 1:4$ for all four vaccine components.\(^{(74)}\)

#### 4.3.1.2 Children and adolescents

A systematic review and meta-analysis was conducted by Flacco et al in 2018 to assess the immunogenicity of 4CMenB against four reference MenB strains 30 days and six months after the primary immunisation course or primary course plus booster.\(^{(75)}\) Although after 30 days, seroconversion rates were high or adequate for all strains, after six months seroconversion rates declined to below 50% for two strains (<50% for M10713 and <35% for NZ98/254 strains). Booster doses enhanced seroconversion ($\geq 93\%$ for all strains). Long-term immunogenicity of NZ98/254 was suboptimal following booster doses. The clinical significance of these findings in terms of vaccine coverage is unknown.\(^{(75)}\)

#### 4.3.1.3 Adults

There is limited data around the immunogenicity of 4CMenB in adults. Only one study was identified that assessed immunogenicity in just 14 laboratory workers in France, in which seroprotection did not appear to be long-lived. However, the numbers were deemed too small to be presented here.\(^{(76)}\)
4.3.1.4 Co-administration with meningococcal conjugate vaccine in infants

Concomitant administration of 4CMenB in infants with MenCCV and PCV-10 induced robust immune response against reference MenB strains and no clinically relevant interference was seen against the MenC immune response. As part of a phase IIIb RCT, 251 healthy infants were randomised to receive either 4CMenB and MenC-CRM or MenC-CRM alone at 3, 5 and 12 months of age together with PCV-10 vaccine (at 3, 5, 7 and 12 months). The immunogenicity against MenC following co-administration was found to be non-inferior to MenCCV alone. A robust immune response was seen against MenB with 95-97% of infants achieving hSBA titres ≥1:4 against fHbp, NadA and PorA test strains after the completion of the primary series. The proportion of infants with hSBA titres ≥1:4 against NHba test strains was 70% following both the primary series (95% CI 58-79) and booster (95% CI 58-80). The immunogenicity for pneumococcal serotypes was not reported.\(^7\)

4.3.1.5 Co-administration with meningococcal conjugate vaccine in adults

Data from a small UK study in healthcare workers supported the use of co-administration of meningococcal vaccines in a healthcare setting. SBA titres increased against ACWY and diverse MenB strains (including four wild-type strains from the UK) in 95-100% and 90-100% of 38 healthcare workers (mean age 34 years, range 23-55 years), respectively, following vaccination with 4CMenB (three doses) and one concomitant dose of ACWY-CRM with dose one of 4CMenB. However, since this group had been recommended meningococcal vaccination, high proportions of participants had protective SBA titres pre-vaccination (61-84% and 61-87%, respectively) and the study did not include a vaccine-naïve control group.\(^6\)

Conclusions

- Use of 4CMenB in a 2+1 schedule in infants is immunogenic and is likely to provide early-life protection against MenB disease.
- Preschool booster doses are likely to be required to maintain seroprotective levels of bactericidal antibodies in childhood.
- A robust response is seen when 4CMenB is co-administered with MenCCV to infants.
- Long-term seroprotection against NZ98/254 strain in adolescents may be suboptimal following booster doses. It is unclear whether this is clinically significant in terms of strain coverage.
- Co-administration with 4CMenB and MenACWY vaccines is likely to provide good protection to laboratory workers against circulating strains of meningococcal disease.

4.3.2 Immunogenicity of two-component MenB-fHbp vaccine

4.3.2.1 Adolescents and young adults

A 2018 review of pivotal phase III clinical trials reported that strong immune responses against diverse test strains were elicited by MenB-fHbp in children and adolescents aged 10-18 years and young adults aged 18-25 years (seroconversion defined as an at least four-fold increase in hSBA titres at one month after third dose). Evidence that this vaccine can provide broad coverage against MenB was seen when immune sera were tested against additional strains. Further clinical trials found that antibody titres increased with each dose and that the geometric mean titres were higher when there was a longer interval between the first and second dose (six months vs two or four months).\(^7\)
The patterns of antibody persistence following two or three primary doses of vaccine were similar for up to 12 months. Antibody titres declined within the first 6-12 months then plateaued. At 48 months after the final primary series dose, hSBA titres above the lowest level of quantification were observed in 18.0–58.6% of participants (strain dependent). At one month following a single booster dose given after approximately four years, at least 91.9% of participants had hSBA titres at or above the lowest level of quantification for each of the test strains. No differences in responses to booster doses were observed when primed with two or three doses.(72)

Data is limited for use of this vaccine in adults older than 25 years. Only one study in laboratory workers found consistency with pivotal trials, but the numbers involved were too small to present here.(78)

### 4.3.2.2 Co-administration with other vaccines

Non-inferiority in immunogenicity was shown in a series of RCT in which MenB-fHbp was given concomitantly with Tdap-IPV and HPV4 in adolescents. Although the non-inferiority criterion was not met for HPV-18, clinical effectiveness was likely to be retained since high rates of seroconversion were observed (≥99% for all four HPV vaccine antigens).(72)

In phase II RCT in the US, the immunogenicity of MenB-fHbp vaccine met all the non-inferiority criteria when MenB-fHbp was given concomitantly with Tdap and ACWY-D compared with alone in 2648 healthy adolescents aged 10-12 years. The adolescents received either MenB-fHbp + Tdap + ACWY-D, Tdap + ACWY-D or MenB-fHbp alone. The immune response was assessed using hSBA against two MenB test strains expressing vaccine-heterologous fHbp variants, rSBAs against MenACWY. After doses two and three of MenB-fHbp + Tdap + ACWY-D, seroprotective hSBA titres were observed for 62.3-68.0% and 87.5-90% of recipients, respectively.(79)

**Conclusions**

- Men-fHbp vaccine induces strong bactericidal immune responses against test strains of MenB when given alone or concurrently with other routine vaccinations in adolescents and young adults.

- Broad coverage has been suggested.

- The duration of protection following priming or booster doses has not been investigated as yet.

### 4.3.3 Summary

A limitation of extrapolating immunogenicity data to clinical effectiveness for MenB vaccines is the selection of the test strains. Much of the clinical trial data on which licensure of these vaccines was based use the same set of test strains. It is less well known how these vaccines work against a wider range of circulating or emergent MenB strain variants.

Both vaccines induce strong bactericidal antibody responses against the reference strains across all licensure age groups - in infants (4CMenB only), adolescents and adults.

Questions remain around the longevity of the antibody. Booster doses appear to be required, at least in young children, to maintain antibody titres following a two- or three-dose primary series with 4CMenB. Currently, data suggest that these responses are short-lived. For children under the age of 4 years, this may provide sufficient protection during the time of highest risk.

For adults and adolescents, these vaccines are immunogenic and are likely to provide at least short-term protection against group B meningococcal not otherwise available. This may
be sufficient to overcome high-risk periods, such as overseas travel and communal living, but timing of the adolescent doses is likely to require careful consideration. No literature was identified around the use of these vaccines in individuals at increased risk of meningococcal disease.

4.4 Effectiveness of meningococcal B immunisation

Due to the rarity of the disease in the general population and the recent addition of these recombinant vaccines to immunisation programmes, very few studies have been conducted to investigate the effectiveness of MenB vaccines against meningococcal B disease. As mentioned above, these vaccines have been licensed based on pivotal clinical trial safety and immunogenicity data.

4.4.1 Using immunogenicity data to predict vaccine effectiveness

As part of a systematic review, Harder et al (2017) investigated hSBA titre as a correlate of protection to predict vaccine effectiveness against MenB disease compared with observed effectiveness, and concluded that hSBA response can predict protection against MenB moderately well for a period of one or two years following two vaccine doses in older children and adults, or three doses in children age under 2 years.\(^{(80)}\)

The review included data from 19 studies that assessed the use of OMV-based MenB vaccines during outbreaks from 1987-2009 in six countries (including the MeNZB OMV component used in 4CMenB). Comparison between predicted and observed VE was possible for five outbreaks. One study conducted in NZ in children aged 16-24 months, found that hSBA results correlated with protection against MenB disease. This was based on the proportion of vaccinees with an at least four-fold increase in seroprotective antibody titre rather than those achieving a predefined titre. Further evidence is required based on studies using both recombinant MenB vaccines (4CMenB and MenB-fHbp).\(^{(80)}\)

4.4.2 Effectiveness of 4CMenB in infants

Since the 4CMenB vaccine has only recently been introduced to routine childhood schedules, there is limited data on the effectiveness of infant vaccination against invasive group B disease.

Two-dose vaccine effectiveness was shown to be 82.9% (CI 24.1-95.2) against all MenB cases in the UK between Sept 2015 and June 2016 in infants eligible for routine vaccination. The priming schedule consisted of two doses at 2 and 4 months, with opportunistic catch-up for 3 and 4-month olds. Coverage was 95.5% for dose one and 88.6% for two doses by 6 months of age. The effectiveness against MenB, evaluated from cases diagnosed between September 2015 and June 2016, was 82.9% (95% CI 21.1-95.2) for two doses. A 50% IRR reduction was observed in vaccine-eligible cohort (37 vs average 74 cases; IRR 0.50 [CI 0.36-0.71]; p=0.0001) in the first 10 months of the programme, compared with the pre-vaccine period, irrespective of infant vaccination status or predicted MenB strain coverage.\(^{(81)}\)

4.4.3 Effectiveness through herd immunity and carriage

An important role of meningococcal vaccination is to reduce carriage of virulent strains and to induce herd immunity to protect those most vulnerable to the disease, in whom immunisation may not provide adequate protection.

Currently, there is limited post-licensure data to assess the herd immunity effectiveness. Although these recombinant subunit vaccines may behave differently to conjugate vaccines, according to modelling data this type of MenB vaccine has the potential to have a similar
magnitude of effect as the conjugate vaccines, even when vaccinating the adolescent carrier population only.\(^{(58)}\) This has not yet been observed through real life usage.

### 4.4.4 Summary of meningococcal B vaccine effectiveness

Due to the relatively short time that these recombinant vaccines have been available and the rarity of meningococcal disease, there is limited data around the effectiveness of MenB vaccines or immunisation programmes.

In the UK, the risk of MenB disease was halved in vaccine-eligible infants compared with the pre-vaccination period irrespective of vaccination status and, over 10 months, vaccine effectiveness following two doses was 82%.

Meningococcal conjugate vaccines have demonstrated disease control by reducing carriage and inducing herd immunity. However, such benefits have not yet been observed with these recombinant MenB vaccines.

## 5 Impact of meningococcal immunisation programmes

### 5.1 Impact of meningococcal C and ACWY immunisation programmes

Routine meningococcal C vaccinations have been widely introduced worldwide, including in Australia, Canada, the UK, most European countries, and parts of Africa and the Middle East, where they have had significant impact on meningococcal C disease. In recent years, however, many countries have observed an increase in group W and Y cases and have subsequently introduced quadrivalent MenACWY vaccines to replace or augment infant meningococcal C programmes and to target adolescents in whom meningococcal carriage and transmission of \(N.\) meningitidis is highest.

#### 5.1.1 Direct protection

Circulating bactericidal antibodies are crucial for protection against invasive meningococcal diseases; immune memory alone is not adequate to prevent IMD due to the rapid progression of the infection. Seroprevalence data showed that infants immunised with single or multiple doses plus a booster in the second year of life did not have sufficient antibody levels to maintain bactericidal protection into adolescence, affecting the direct protection and herd immunity in the older age-groups.\(^{(82)}\)

##### 5.1.1.1 Targeting infants and toddlers

In the three years following the introduction of a MenC vaccination in Brazil, the incidence of MenC disease declined by 65% (95% CI 20.5-84.7) among children aged <1 year, from 9.50 confirmed cases/100,000 in 2010 to 3.03 in 2013; and by 46.9% (14.6-79.1) from 3.68 to 0.89/100,000 in children aged 1-4 years, according to an observational population-based study of surveillance data conducted between 2001-2013. Two doses of MenCCV were recommended at 3 and 5 months with a booster at 12-15 months. A single catch-up dose was available at 12-23 months during the first year of the programme in 2010. The impact of vaccination varied between regions. Three regions achieved 95% coverage in the first year.\(^{(83)}\)

Following an increase in the number of MenW cases in Chile, a MenACWY immunisation programme was introduced in 2012 that initially targeted children aged 9 months to <5
years with ACWY-CRM. One dose of ACWY-TT became mandatory for all children ≥1 year in January 2014. However, the number of cases of MenW disease is increasing in children aged 9 months to 5 years.\(^\text{(84)}\)

### 5.1.1.2 Targeting adolescents

Adolescents are at increased risk of meningococcal disease due to high levels of bacterial carriage. Older adolescents and young adults (16- to 23-year-olds) are at risk of invasive disease due to lifestyle factors, such as smoking, which damages the nasopharyngeal mucosa; communal living in University residences, backpacker hostels, correctional facilities and military barracks; and greater intimacy.

In the UK, a booster dose of MenCCV was introduced in 2013 at age 13-14 years, and a university entrance ‘fresher’ booster was recommended for a limited period for students aged <25 years as a catch-up for those who did not receive the earlier adolescent booster. In 2015, the adolescent and ‘fresher’ MenC boosters were replaced by a MenACWY conjugate vaccine in response to an increase in group W disease in the UK and elsewhere.\(^\text{(82)}\)

### 5.1.1.3 Targeting combined age groups and catch-up campaigns

Due to the success of the MenCCV campaign, cases of invasive group C disease are rare in the UK (one case out of 116 meningococcal cases in infants aged <1 year during 2015-2016).\(^\text{(85)}\) The infant priming doses were gradually removed as herd immunity against MenC was established through catch-up vaccination of older children, adolescents and young adults. With herd immunity established by also targeting adolescents and young adults up to 24 years of age, the childhood schedule was changed in 2013 to a single priming dose at 3 months of age, plus 12-month booster using a combination Hib-MenC-TT vaccine, and MenACWY is given at 14 years of age (year 9 of school).\(^\text{(82)}\) See section 6.1.4 for further details of the UK programme changes.

The national MenC immunisation programme in Australia was introduced in 2003 as a single dose of MenCCV given at 12 months of age, with catch-up for all children from the age of 2-19 years. Individuals aged 1-4 and 15-19 years were specifically targeted for vaccination. Catch-up was completed for most children in 2014. Coverage reached 93% in 1-year-olds and 70% for the catch-up cohorts.\(^\text{(86)}\)

Ten years following the implementation of MenCCV in Australia (from January 2003 to end of December 2012), the population-wide incidence of group C IMD had declined by 96% (95% CI 94-98) to 0.4 cases per million in vaccinated cohorts and 0.6 cases per million in unvaccinated cohorts. Prior to this, the annual incidence rate of MenC across Australia was 13 cases per million in 2000-2002. In Victoria and Tasmania, incidence had declined from 21.5 cases to three per million in 10 years. Vaccine coverage for one dose at 12 months was 93% and 70% for catch-up cohorts aged 2-19 years. Overall coverage from 2003 to 2012 for the 1984-2011 birth cohort was estimated to be 76% and over six million vaccine doses were administered. This single dose strategy with catch-ups appears to have resulted in a near elimination of MenC disease in all age groups (vaccinated and unvaccinated) and there was no evidence of vaccine failures in the decade since programme introduction. An independent reduction (55%) in group B disease was also observed over the same time period; this is likely to be due to the natural pattern of group B disease.\(^\text{(86)}\)

During a MenC outbreak in the Brazilian state of Bahia, two immunisation strategies were implemented in early 2010: across the state, a routine MenCCV immunisation programme targeted children younger than 5 years (doses at 2, 4 and 12-15 months or one dose for children aged 1-5 years); in the state capital, Salvador, the programme included a catch-up campaign for individuals aged 10-24 years. Additionally, in late 2010, MenCCV was included...
in the national immunisation schedule for children aged <2 years across Brazil (without catch-up).

An observational, ecological study analysed data collected during 2007-2013 to compare the impact of these two strategies on meningococcal disease, as summarised in Table 12. In Salvador, significant reductions in incidence rates of MenC were seen across all age groups, including those too old to have been vaccinated. A virtual disappearance of MenC was observed in 2015. In the rest of Bahia, excluding Salvador, no herd protection was observed and within five years of the introduction of the immunisation programme significant impact on MenC disease was only seen among vaccine-eligible children.\(^{(87)}\)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Salvador Pre-vaccine period Rate</th>
<th>Salvador Post-vaccine period Rate</th>
<th>RR (95% CI)</th>
<th>p value</th>
<th>Bahia (without Salvador) Pre-vaccine period Rate</th>
<th>Bahia (without Salvador) Post-vaccine period Rate</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 4</td>
<td>5.45</td>
<td>0.73</td>
<td>0.11</td>
<td>&lt;0.0001</td>
<td>0.78</td>
<td>0.24</td>
<td>0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>5 - 9</td>
<td>3.91</td>
<td>1.11</td>
<td>0.28</td>
<td>0.28</td>
<td>0.15</td>
<td>0.27</td>
<td>0.76</td>
<td>0.203</td>
</tr>
<tr>
<td>10 - 19</td>
<td>3.05</td>
<td>0.7</td>
<td>0.23</td>
<td>0.39</td>
<td>0.23</td>
<td>0.19</td>
<td>0.76</td>
<td>0.48</td>
</tr>
<tr>
<td>20 - 39</td>
<td>1.92</td>
<td>0.78</td>
<td>0.39</td>
<td>0.39</td>
<td>0.23</td>
<td>0.19</td>
<td>0.76</td>
<td>0.389</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>1.01</td>
<td>0.45</td>
<td>0.44</td>
<td>0.44</td>
<td>0.15</td>
<td>0.11</td>
<td>0.76</td>
<td>0.389</td>
</tr>
<tr>
<td>Total</td>
<td>2.13</td>
<td>0.67</td>
<td>0.31</td>
<td>0.31</td>
<td>0.33</td>
<td>0.22</td>
<td>0.67</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Rate – average annual incidence per 100,000 population; RR – relative risk

Table 12: Incidence rates of MenC disease by age group in Bahia, Brazil, pre and post vaccination periods (reproduced with permission, Evellyn do Macedo et al, 2017)

Conclusions

Although immunisation of infants has a positive impact on disease in those age groups, the presence of bactericidal antibodies is required to control meningococcal disease and meningococcal carriage. To maintain antibody levels, booster doses are required every five years. This is important for high-risk groups, but not feasible for universal immunisation programmes.

- Children primed in infancy require booster doses in the second year of life and in adolescence require high antibody levels to be maintained during times of high risk for disease.
- The best mechanism for control across the two main age groups of high disease incidence (infants and adolescents) is herd immunity, which prevents the spread of the infection.
- Herd immunity can be achieved with conjugate vaccines by controlling the carriage of disease in adolescent and young adult age groups.

Once herd immunity is established, with less circulating infection direct protection of infants is no longer essential – as has been achieved for MenC in several countries (and MenA in Africa).
5.1.2 Impact on meningococcal carriage and herd immunity

High levels of mucosal antibodies reduce the risk of invasive disease (direct protection) by reducing nasopharyngeal carriage and prevent transmission from asymptomatic carriers to the population (indirect protection).

Meningococcal carriage is most frequent in young adults, from around 24% to approaching 100% of those living in closed or semi-closed groups such as University residences and military barracks.\(^{(84)}\)

Several challenges have been identified when studying carriage. Most studies have been observational and conducted in conjunction with extensive vaccination campaigns or outbreaks in which seasonal variation or variability in sampling methods and group analyses complicate interpretation. Few RCT have been conducted with nasopharyngeal carriage as a predefined endpoint. Low baseline carriage rates are also reported that result in insufficient statistical power.\(^{(88)}\)

5.1.2.1 Meningococcal C carriage

The impact of MenC conjugate vaccination leading to reduction in MenC carriage and herd protection was presented in a review by the Global Meningococcal Initiative.\(^{(84)}\) In the UK, a year following the introduction of the MenC vaccination programme to adolescents, there was a 71% reduction observed in MenC carriage in immunised individuals aged 15-19 years and an 81% reduction in year two (2001).\(^{(84)}\) Prior to the introduction of MenC vaccination in adolescents and young adults, these age-groups accounted for 25% of carriage rates.\(^{(82)}\)

Indirect protection was also observed, with a 67% reduction in attack rate amongst unvaccinated children during 2001 and 2002. The importance of building herd protection through adolescent and ‘catch-up’ MenC vaccination campaigns, with high vaccine uptake, has also been demonstrated in Europe, Australia and Canada. The exact ages targeted by these campaigns varied between countries due to different socioeconomic and lifestyle behaviours that affect transmission (ages associated with close physical contact and smoking, for example).\(^{(84)}\)

5.1.2.2 Meningococcal W and Y carriage

Following the significant rise in group W disease (specifically a 2013-strain W:cc11 IMD) in the UK, MenACWY vaccination was introduced in 2015 for adolescents (age 14-18 years) and for university entrant students under 25 years of age with the aim of reducing meningococcal carriage.

After just two months following the introduction of the MenACWY adolescent/fresher boosters, a small study demonstrated a 39% decrease in MenY carriage and 36.2% decrease in combined CWY carriage in university students.\(^{(82)}\)

However, a cross-sectional study conducted alongside a campus-based vaccination programme of new entrant students at the University of Nottingham, UK, found that vaccine-induced immunity did not have a significant impact on carriage of hypervirulent W:cc11 as compared with MenY. It was suggested that this immunity may have developed too slowly to prevent acquisition of MenW but not MenY strains. The study implied that possible differences in the duration of MenW and MenY carriage in vaccinated individuals may facilitate the risk of spread of MenW to unvaccinated populations. Further studies are required to determine any differences in carriage duration between these strains.\(^{(89)}\)

Previously reported findings from this University-based study showed that despite vaccine coverage of 71%, the carriage of MenW increased substantially from 0.7% in September 2015 to 8% in March 2016. No change in MenY carriage was detected. Of the 50 MenW
carriers, 36 (72%) had received ACWY vaccine before or during university registration (similar to overall coverage rate in first-year student cohort). Widespread colonisation was observed at the second and third sampling points, and 21 (91%) of MenW carriers identified at the final sampling time point in March 2016 had been vaccinated at least five months prior to sampling.\(^{(90)}\)

**Conclusions**

The impact that MenACWY vaccines have had on carriage of MenW is not as great as observed for MenC (or MenA) conjugate vaccines and transmission appears to continue in vaccinated young adults. Data is limited around MenY carriage following MenACWY vaccination.

**5.1.3 Summary**

Meningococcal immunisation programmes using conjugate vaccines have made significant impacts on the epidemiology of meningococcal C disease (and MenA in Africa, data not presented here) in countries that have implemented these programmes. This has been achieved by targeting both infants and young children (under 4 years of age) to prevent disease, and targeting adolescents or young adults to provide individual protection and herd immunity.

In recent years, group Y and hypervirulent group W strains have become more prevalent. Meningococcal immunisation programmes are now targeting adolescents with the quadrivalent MenACWY conjugate vaccines.

Conjugate vaccines, MenC and MenACWY, have an impact on carriage of vaccine-group meningococci and play an important role in disease control through herd immunity. However, the timing of vaccination is likely to be important to prevent acquisition of the infection before late adolescence when disease risk is greater.

The ability of MenACWY to reduce carriage of hypervirulent MenW strains and their role in herd immunity against these strains is unclear. Strain differences in carriage behaviour may facilitate the spread of hypervirulent strains to unvaccinated populations. It appears that targeting of adolescents with these vaccines provides direct protection, but is probably less effective in preventing transmission.

**5.2 Impact of meningococcal B immunisation programmes**

**5.2.1 Meningococcal antigen typing system**

The impact of meningococcal B immunisation programmes is likely to depend on the scope of the vaccine to prevent circulating strains of MenB. The meningococcal antigen typing system (MATS) is used to estimate the coverage of 4CMenB vaccine.

MATS is a qualitative and quantitative enzyme-linked immunosorbent assay (ELISA) system used to determine whether MenB isolates are potentially vaccine-preventable and to estimate vaccine coverage. This system quantifies fHbp, NHba and NadA expression of individual MenB isolates with the ability of 4CMenB-induced antibodies (pooled from post-vaccination sera) to recognise these proteins on each isolate. This information is combined with PorA genotyping to MATS-type the isolate. An isolate that is vulnerable to bactericidal killing by these antibodies against one or more antigen and above predetermined threshold limits, or that possesses homologous PorA (P1.4), is described as MATS-positive and thereby is predicted to be vaccine-preventable.\(^{(91)}\)

In developing this system, it was found that isolated MenB strains exceeding the ELISA threshold value for any of the three vaccine antigens had more than 80% probability of
being killed by immune serum in an SBA assay. Strains positive for two or more antigens had a 96% probability of being killed.\(^{(92)}\)

MATS coverage is a prediction of the proportion of MenB isolates that would be killed by post-vaccination sera. For example, MATS predicted that 78% of 1052 group B isolates collected from patients across Europe during 2007/8 would be killed by post-vaccination sera.\(^{(91)}\) The MATS predicted strain coverage of 4CMenB on strains circulation in Canada during 2006-2009 was estimated to be 66% (46-78%). Of these strains, 26%, 29% and 11% were covered by one, two or three vaccine antigens, respectively.\(^{(93)}\)

A need to monitor antigen expression and diversity, in countries with 4CMenB programmes in particular, was identified as temporal changes in MATS coverage are likely. To estimate coverage by 4CMenB on IMD isolates before the introduction of 4CMenB to the infant schedule in the UK, the invasive MenB isolates collected from cases in England, Wales and Northern Ireland during 2014/15 were compared with those collected in 2007/08. Over this time, the number of MenB IMD cases fell from 1123 to 44 cases (61% decrease). Of the isolates, fewer were estimated by MATS to be covered by 4CMenB in 2014/15 than in 2007/08 (66% vs 73%), reflecting changes in the circulating strains (particularly in ST-269 clonal complex strains). MATS coverage changed with age and geographical region.\(^{(91)}\)

This study also identified an association between MATS-positive strains and more severe disease, suggesting that immunised infants may be better protected from severe disease caused by strains covered by the vaccine. It was noted that this is an unsurprising finding since the antigens selected for the 4CMenB are known virulence factors.\(^{(91)}\)

### 5.2.2 Meningococcal B immunisation

The use of 4CMenB during an outbreak in Quebec, Canada was associated with a decrease in incidence of group B IMD in all regions following a mass vaccination in 2015/16 of people aged from 2 months to 20 years in the particularly affected region of Saguenay-Lac-Saint-Jean. Prior to the immunisation campaign, the rate of IMD caused by one clone (ST296) was 3.4/100,000 person-years during 2006-2013 in that region. Using MATS, it was predicted that 95% of ST296 strain-isolates collected in Canada during 2006-2009 would be covered by 4CMenB vaccine.\(^{(94)}\)

Out of the 59,000 targeted Saguenay-Lac-Saint-Jean residents, 82% had been immunised (ranging from 47% in 17- to 20-year-olds to 94% in 2- to 5-month-olds) and no cases of MenB IMD were reported in the vaccinated population. There were three unvaccinated cases, two adults and one visiting child. Following vaccination, the variable-adjusted relative risk for MenB IMD was 0.22 (95% CI 0.05-0.92; \(p=0.04\)). The incidence of group B IMD decreased in all other regions of Quebec, although sporadic cases continued. These findings supported recommendations for the use of 4CMenB vaccine to control outbreaks of clones covered by this vaccine.\(^{(94)}\)

#### 5.2.2.1 Possible cross-protection effect of 4CMenB on non-group B meningococci

Since the components of 4CMenB are also expressed on non-capsular group B meningococci, there is a potential for protective antibodies to be induced against multiple capsular groups, including groups Y and W, that are increasing in prevalence.

A study in the UK demonstrated potent hSBA antibodies in children immunised with 4CMenB against hypervirulent W:cc11 isolates. After the booster dose, hSBA titres against six MenW isolates were similar to those seen among adolescents who had received a single MenACWY dose and higher than after primary immunisation. However, the role of 4CMenB in herd immunity and meningococcal carriage is undetermined and the study findings supported
implementation of both adolescent MenACWY and infant MenB immunisation programmes.(95)

A potential role for cross-reactive antigens was identified by ‘Bexsero Antigen Sequencing Types’ (BASTs). Whole genome sequencing was used to analyse 3,073 IMD isolates obtained during 2010-2016 prior to the introduction of routine 4CMenB infant immunisation in the UK (isolates collected during 2015 were not considered affected by the vaccine as few infants had been immunised by that time). In 2015-16, 85/238 (35.7%) of group B isolates showed exact matches to at least one 4CMenB component and 149/238 (69.3%) of isolates had potentially cross-reactive antigens. For group C, the numbers of exact matches varied each year depending on the predominant clonal complex; for example, in 2014-15, 3/23 (13.0%) had exact matches and 25/34 (91.3%) had potentially cross-reactive antigen matches with BAST. Group W isolates showed the highest proportion putatively cross-reactive variants. In 2015-16, 185/197 isolates (93.9%) potentially matched the vaccine antigens, and hence there was a likely role for cross-reactive antigens. Only one MenW isolate out of 571 (0.2%) had an exact match to a 4CMenB component (fHbp1). For group Y, 3/104 isolates in 2015-16 showed exact matches and 3/104 (2.9%) had potential cross-reactive antigen matches.(96) The estimated MATS coverage for IMD isolates from the UK during 2014-15 was 66% (95% CI 52-80%). It was noted, however, that the presence of cross-reactivity and levels of expression of antigenic variates alone does not directly measure susceptibility to bactericidal killing.(96)

Conclusions

- Meningococcal B immunisation programmes using 4CMenB have shown protection during MenB outbreaks.
- Temporal changes in antigenicity and vaccine coverage need to be monitored.
- Strains covered by 4CMenB are associated with more severe disease in infants.
- Additional protection against other meningococcal disease, including group W and Y, may be provided.
- Cross-protection has not been established enough to negate the benefit of MenACWY vaccines for adolescents. Concurrent programmes against MenB and MenACWY in infants and adolescents are recommended.

5.2.3 Impact of immunisation on meningococcal B carriage and herd immunity

5.2.3.1 Carriage of pathogenic and commensal flora

The potential impact of 4CMenB vaccination in Spain on asymptomatic carrier strains (including non-virulent strains) collected from children aged 4-19 years was shown to be mediated by NHba expression, particularly on encapsulated MenB strains. Of the 20,527 children sampled, 11% were found to be N. meningitidis carriers (highest rate was 31% in 17- to 19-year-olds). This study was conducted after the introduction of the national MenC vaccination programme and carriage of MenC strains had declined significantly. A 60-carrier strain panel was selected for study, out of which 20 were group B. Immunological cross-reactivity between fHbp expression on oropharyngeal-carried strains was around 10% compared with 75% for NHba expression. It was suggested that a NHba-containing vaccine could impact on both potentially pathogenic strains and on commensal flora of other Neisseria species.(97)
5.2.3.2 Meningococcal B carriage

The OMV component of 4CMenB has been suggested to play a role in herd immunity. A carriage study was conducted during a MenB outbreak in Normandy, France, among subjects aged 1-25 years. During this time, a parent vaccine of the MeNZB OMV vaccine, MenBvac, was used to control the MenB outbreak. In early 2008, only children ages 1-7 years had been vaccinated and around one third had received at least one dose of MenBvac. Only 17 out of 1082 children (1.6%) were found to be carriers of *N. meningitidis*, none of which carried the epidemic clone (one had been vaccinated and 16 were unvaccinated). The numbers were too small to demonstrate a meaningful protective MenBvac effect against carriage of any meningococcal strains.\(^{(98)}\)

The impact of MenB vaccination, with 4CMenB and Men-fHbp vaccines, on the carriage of MenB was assessed in university students in the US following a MenB outbreak in 2015 in Oregon. No participants carried the outbreak strain and carriage of other strains was stable with time (at 11-17%). It was noted that low prevalence of MenB carriage limited the power to detect associations between vaccination and carriage.\(^{(99)}\)

Soeters et al also observed that these vaccines did not have a rapid impact on meningococcal carriage and, in the context of an outbreak response, were unlikely to provide herd protection.\(^{(99, 100)}\) During an outbreak at a university in Rhode Island, US, meningococcal carriage prevalence remained stable (20-24% any meningococcal bacteria, 4% any MenB). Five mass vaccination campaigns were conducted during 2015 and 2016 of students and staff aged 25 years or younger (3525/3745 [94%] received the first dose of MenB-fHbp). No reduction in carriage or group B acquisition was observed over time or with more MenB-fHbp doses – only one student was identified to carry the outbreak strain after receiving two doses of vaccine. It was concluded that MenB-fHbp does not rapidly reduce meningococcal carriage or prevent MenB acquisition, which therefore reinforced the need for high immunisation coverage to protect individuals.\(^{(100)}\)

A phase III RCT study in the UK was unable to show a specific effect of 4CMenB on the carriage of capsulated group B strains. The study investigated the effect of meningococcal vaccination on meningococcal carriage rates in 2954 university students (mean age 19.9 years). Participants were randomised to receive either two doses of 4CMenB one month apart, one dose of ACWY-CRM plus a dose of placebo (with adjuvant), or two doses of a control vaccine (Japanese encephalitis vaccine).\(^{(101)}\) The findings were:

- At baseline around one third of students carried *N. meningitidis*.
- One month after the second vaccination, no significant difference was noted between 4CMenB and control groups in the prevalence of carriage of disease-related MenB.
- Significantly lower carriage prevalence was observed between 4CMenB and control for meningococcal carriage of non-vaccine related strains.
- Both the MenACWY and 4CMenB vaccines significantly reduced meningococcal carriage during one year of follow-up.
- ACWY-CRM had a vaccine-group effect and 4CMenB had a broader effect.

It was suggested that administering the vaccine during the peak time for carriage may have been too late to prevent acquisition and that the greatest effect on reducing carriage may be obtained by initiating vaccination in early rather than late teens.\(^{(101)}\)

Mucosal and non-hSBA responses may be more critical for the disruption of carriage by 4CMenB than by conjugate vaccine. Both 4CMenB and ACWY-CRM induce robust immune responses against group B reference strains and groups C and Y, respectively, in university
students from one month and up to 12 months following vaccination. Carriage in groups prior to vaccination was associated with higher SBA titres at baseline, however, no correlations were found between carriage and hSBA titres post vaccination.\textsuperscript{(102)}

The South Australian Meningococcal B Herd Immunity Study, 'B Part of It', involving students in school years 10-12 (age 15-18) is underway in South Australia to investigate MenB carriage and the effect of two doses of 4CMenB vaccine on carriage in adolescents (clinical trial reference NCT03089086).

Conclusions

- In general, carriage of disease-associated MenB strains is low even during outbreaks, making such studies challenging.

- The OMV component of 4CMenB may play a role in preventing colonisation and reducing carriage of a broader range of meningococci than capsulated group B strains, although evidence is limited.

- Other cross-reactive vaccine antigens, such as NHba, have been suggested to be important in preventing carriage of virulent and non-virulent strains N. meningitidis.

- Since MenB-fHPb has only recently been licensed, literature on its role in carriage is limited.

- The effect on carriage following 4CMenB vaccination appears to be delayed and likely not to have an impact during an outbreak. It was suggested that a potentially greater impact on carriage may be achieved by vaccinating prior to acquisition.

5.2.4 Summary of meningococcal B vaccine impact

Meningococcal B vaccines have been more recently introduced than conjugate vaccines and data on their impact is limited. These vaccines have been used successfully to target adolescent and young adult populations during localised epidemics, although in these outbreak situations, they did not have a rapid effect on disease-causing strain carriage and were unable to establish herd immunity.

The UK was the first country to routinely administer 4CMenB to infants as part of the routine schedule, although as of March 2018, no literature was found that considers the impact of the immunisation programme on meningococcal disease control.
6 International policy and practice

6.1 Review

This section provides a review of the meningococcal immunisation practices and recommendations internationally. This review has been restricted to immunisation schedules and policies in Australia, Canada, selected European countries, the UK and the US. Regional variations between provinces, states and territories have not been individually reviewed.

The recommendations of the Global Meningococcal Initiative for meningococcal disease were discussed in 2015. Those most relevant to NZ were: (84, 103)

1. Country-specific approaches to prevent IMD by vaccination are needed due to disease variation.
2. Country-specific meningococcal policy should be based on local epidemiology and economic considerations.
3. Travellers to high-risk areas should be vaccinated against IMD.
4. Vaccines against all clinically relevant groups (A, B, C, W, X and Y) should be developed.
5. Conjugate vaccines should replace polysaccharide vaccines whenever cost, availability, licensing and immunisation policy allow. Polysaccharide vaccines are recommended where conjugate vaccines are not available.
6. Laboratory-based surveillance for IMD should be strengthened to determine the true burden of disease.

6.1.1 United States

The current recommendations from the US Advisory Committee on Immunization Practices on meningococcal vaccination, as of March 2018, are summarised below. ACIP does not recommend routine vaccination against meningococcal disease for children aged 2 months to 10 years.

6.1.1.1 MenACWY

As published in June 2014, ACWY-CRM (Menveo) vaccine is only recommended as an option for infants aged 2–23 months who are at increased risk of IMD. High-risk infants are recommended to receive four doses at 2, 4, 6 and 12 months of age. (104) These include infants with:

- Persistent complement component deficiencies (i.e. C3, C5-9, properdin, factor D and factor H).
- Functional or anatomic asplenia, including sickle cell disease.
- Healthy infants in communities with a meningococcal disease outbreak for which vaccination is recommended.
- Those travelling to or living in areas where meningococcal disease is hyperendemic or epidemic (such as countries in the sub-Saharan African meningitis belt and during Hajj and Umrah pilgrimages).

Alternative options for the above groups are ACWY-D (Menactra) at 9 and 12 months, excluding those with asplenia due to potential interference of PCV-13 immunity, or Hib-MenCY-TT at 2, 4, 6 and 12–15 months (not for children travelling to endemic regions).
Booster doses with a MenACWY conjugate vaccine are recommended three years after the primary series and every five years thereafter.

ACIP recommends that individuals aged 2 months or older and infected with HIV should receive meningococcal conjugate vaccine routinely with an age-appropriate MenACWY vaccine: age 2-23 months ACWY-CRM; ACWY-D not before 2 years of age and concomitantly or before DTaP.\(^{(105)}\)

### 6.1.1.2 Meningococcal B

#### High risk groups

For adults and children aged from 10 years, ACIP recommends MenB vaccination for those at increased risk of group B IMD, including:\(^{(106)}\)

- Individuals with persistent complement component deficiencies
- Those with anatomic or functional asplenia
- Microbiologists routinely exposed to isolates of *Neisseria meningitidis*
- Persons identified as at increased risk because of a MenB disease outbreak

Other groups are included in the MenACWY recommendations but are not included in the MenB vaccination recommendations. MenB vaccine is not recommended for people who travel to countries with high incidence of meningococcal epidemics, since in these countries group B disease is not generally endemic.

ACIP does not state a preference between 4CMenB or MenB-fHbp vaccines, but emphasises that these vaccines are not interchangeable.

#### Adolescents

ACIP conducted a review of the burden of group B IMD among adolescents, young adults and college [university/tertiary education] students and found that the incidence of group B disease is stable and low in adolescents and young adults aged 11-23 years, with around 50-60 cases per year and 5-10 deaths reported. More than 80% of these cases were in the 16-23-year age group. The estimated incidence of MenB disease in college students was similar to or lower than all 18- to 23-year-olds and non-college students (0.09 vs 0.14 and 0.21/100,000, respectively). It was estimated that routine vaccination for adolescents (age 11, 16 or 18 years) is likely to prevent around 15-29 cases and two to five deaths, and vaccination of college students only would prevent approximately nine cases and one death annually.\(^{(107)}\)

ACIP advised that MenB vaccine series may be administered to adolescents and young adults aged 16-23 years to provide short-term protection against most MenB strains, with a preferred age of 16-18 years. Routine use of MenB vaccines for those at risk of IMD is recommended, including during outbreaks of group B disease and on college campuses.\(^{(107)}\)

Changes were made in May 2017 to the ACIP recommendations around MenB-fHbp vaccine dosage.\(^{(108)}\)

- For persons aged ≥10 years at increased risk of group B disease, three doses should be given at 0, 1-2 months and 6 months to provide earlier protection and to maximise short-term immunogenicity. A third dose is not necessary if the gap between first and second dose is more than six months.

- For adolescents aged 16-23 years not at increased risk, two doses given six months apart is sufficient. [If a second dose is given <6 months after first, then a third dose is required at least four months after second dose].
6.1.2 Canada

Meningococcal disease in Canada is mostly associated with groups A, B, C, W and Y and the highest incidence is in infants. (109) A universal programme is recommended:

- Healthy children are recommended to routinely receive one dose of MenC conjugate vaccine at 12 months of age or younger depending on provincial schedules (some include a dose at 2 or 4 months). If not previously immunised, children less than 5 years should receive MenCCV and this should also be considered for those aged 5-11 years. On an individual basis, 4CMenB may be considered from 2 months of age to protect against group B IMD.

- Adolescents are routinely recommended one dose of MenCCV or MenACWY at 12 years (depending on local meningococcal strain epidemiology) and as young adults, even if they were previously vaccinated as an infant or toddler. Also, 4CMenB is recommended on an individual basis for protection against relevant group B strains.

- MenACWY and 4CMenB are recommended for children and adults with increased risk of IMD. Periodic booster doses of MenACWY are also recommended for these groups. High risk groups include:
  - Persons with functional or anatomical asplenia
  - Persons with congenital complement, properdin, factor D or primary antibody deficiencies
  - Persons with acquired complement deficiency due to treatment with a terminal complement inhibitor such as eculizumab
  - Travellers to areas with high rates of endemic meningococcal disease or transmission
  - Laboratory personnel at risk of exposure to N. meningitidis
  - Military personnel at increased risk of IMD
  - HIV positive individuals, especially if HIV was acquired perinatally

- Meningococcal vaccines (MenCCV, MenACWY-CRM or 4CMenB, depending on disease strain) are recommended for outbreak control and post-exposure management from 2 months of age.

6.1.3 Australia

The recommendations around meningococcal immunisation are under review with the Australian Technical Advisor Groups on Immunisation (as of December 2017) and have been undergoing public consultation. (110-112)

Immunisation is recommended for:

MenCCV (as a single dose)

- All children aged 12 months (routine since 2003, funded at 12 months as Hib-MenC)
- Refugees under 20 years

MenACWY

- All adolescents aged 15-19 years (in certain states ACWY-TT, Nimenrix, is funded)
- People travelling overseas to high-risk countries or mass gatherings (e.g. Hajj pilgrimage)
• Laboratory workers exposed to meningococci
• Individuals with medically increased risk (see below)

MenB (4CMenB)

• All children under 2 years (with prophylactic paracetamol, from 6 weeks of age – two or three doses plus booster at 12 months, depending on age at start)
• Adolescents aged 15-19 years (a school-based clinical study is underway providing funded vaccine in South Australia)
• Young adults living in communal residences (military barracks, dormitories)
• Individuals with medically increased risk of IMD (see below)

Individuals with increased risk of IMD are recommended both MenACWY (with booster three years after first two doses [or three doses for infants aged<6 months and booster at 12-18 months], then every five years) and MenB vaccines (two doses, or three doses for infants aged <6 months). These include:

• Defects in or deficiency of complement components, including factor H, factor D or properdin deficiency
• Current or future treatment with eculizumab (a monoclonal antibody directed against complement component C5)
• Functional or anatomical asplenia
• HIV infection, regardless of stage of disease or CD4+ count
• Haematopoietic stem cell transplant

In September 2017, the Therapeutic Goods Administration registered MenBfhbp (Trumenba) and MenACWY-CRM (Menveo).

6.1.4 United Kingdom

The UK MenC immunisation programme started in 1999 as a three-dose priming schedule with MenC conjugate vaccine (at 2, 3 and 4 months). It was found to provide short-term direct protection (VE 97%), but effectiveness fell significantly to 68% more than a year after immunisation. A two-dose priming schedule with MenC conjugate vaccine (at age 3 and 4 months) and a Hib-MenC booster at 12 months (2+1) was introduced, but was not sufficient to maintain long-term direct protection due to waning immunity.\(^{(82)}\)

When the MenC programme was introduced, catch-up was also provided for all children up to 18 years of age and it was the indirect protection that provided greater disease control. With herd immunity established by further targeting adolescents and young adults up to 24 years of age, the childhood schedule was changed in 2013 to a single priming dose at 3 months of age, plus 12-month booster using a combination Hib-MenC-TT vaccine.\(^{(82)}\)

From August 2015, the UK introduced targeted vaccination programmes for 13- to 18-year-olds, particularly targeting school leavers aged 17-18 years, to try to combat the increase in cases of the hypervirulent MenW cc11 strain.\(^{(113)}\) Three cohorts were sequentially included: those born September to August 1996-1997, 1997-1998 and 1998-1999. All cohorts remain eligible for MenACWY vaccination until the age of 25 years. MenACWY vaccination is also offered to older students up to 25 years as part of a ‘freshers’ programme for new entrant university students who may have missed these programmes.\(^{(114)}\)
In September 2015, the UK was the first country to introduce 4CMenB vaccine to its national infant immunisation programme, which provided a reduced two-dose primary schedule (as opposed to three).\(^{(60)}\)

In 2016, the schedule was changed to a single dose of Hib-MenC vaccine at 12-13 months and provided an adolescent booster of MenACWY vaccine at around the age of 13 years to maintain herd immunity.\(^{(85)}\)

As of September 2017, the UK immunisation schedule routinely includes meningococcal vaccination to provide protection against group C, ACWY and B meningococcal disease for infants and adolescents.\(^{(115)}\)

- MenB – 4CMenB is given at 8 and 16 weeks of age with a booster at 1 year (1st birthday or soon after).
- MenC – combined Hib/MenC conjugate vaccine is administered at 1 year with 4CMenB, PCV-13 and MMR.
- MenACWY - one dose of ACWY-TT or ACWY-CRM is given to adolescents at age 14 years (school year 9) with Td-IPV.

High-risk groups are recommended Hib/MenC, MenACWY and MenB vaccination. These include: individuals with asplenia or splenic dysfunction (including sickle cell disease and coeliac disease) and complement disorders (including those receiving complement inhibitor therapy).

### 6.2 Summary

A summary of the international meningococcal immunisation recommendations schedules is provided in Table 13.\(^{(116-118)}\)

In general, those deemed at high risk are similar between countries. These are individuals with:

- Functional or anatomic asplenia and splenic dysfunction, including sickle cell disease
- Congenital or acquired complement deficiencies and disorders
- Haematopoietic stem cell/bone marrow transplant recipients
- Laboratory workers exposed to meningococcal cultures and isolates
- Travellers to regions with high rates of meningococcal disease and transmission, including sub-Saharan Africa and Hajj or Umrah pilgrims
- HIV infection

Meningococcal vaccines are also recommended for adolescents and young adults living in communal residences, including military barracks, university residences, correctional facilities and dormitories. During community disease outbreaks, close contacts and infants are also recommended strain-appropriate vaccines.
Table 13: Summary of international immunisation recommendations for meningococcal vaccines, as of 2017 (adapted from European Centre for Disease Protection and Control and country specific websites)

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine given</th>
<th>Age of vaccination</th>
<th>Number of doses</th>
<th>Special recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>USA</strong></td>
<td>ACWY-D (Menactra)</td>
<td>11-12 years and 16 years (from 9 months)</td>
<td>Two</td>
<td>Younger age for special groups</td>
</tr>
<tr>
<td></td>
<td>ACWY-CRM (Menveo)</td>
<td>From 2 months</td>
<td>One</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4CMenB (Bexsero)</td>
<td>Adolescents at increased risk (min age 10)</td>
<td>Two 1 month apart</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MenB-fHbp (Trumenba)</td>
<td>Clinical discretion age 16-23 years</td>
<td>Two 6 months apart</td>
<td>3 doses special groups and outbreak</td>
</tr>
<tr>
<td>*<em>Canada</em></td>
<td>MenC</td>
<td>2 or 4, 12 months or just 12 months</td>
<td>One or two</td>
<td>MenACWY and 4CMenB recommended for high risk groups from 2 months of age</td>
</tr>
<tr>
<td></td>
<td>MenACWY</td>
<td>School age 12-14, where available</td>
<td>One</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4CMenB</td>
<td>Not part of routine schedule</td>
<td>Two</td>
<td></td>
</tr>
<tr>
<td>*<em>Australia</em></td>
<td>Hib-MenC (Menitorix)</td>
<td>12 months – national programme</td>
<td>One</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACWY-TT* (Menactra)</td>
<td>Year 10 (age 15 years), catch-up 16-19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACWY-CRM (Menveo)</td>
<td>2-6 months or 7-11 months</td>
<td>Three or Two</td>
<td>Recommended for those with increased medical or occupational risk</td>
</tr>
<tr>
<td></td>
<td>ACWY-D* (Nimenrix),</td>
<td>From 12 months</td>
<td>Two</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4CMenB (Bexsero)</td>
<td>15-18 years</td>
<td>Two 3 plus booster</td>
<td>SA only, MenB vaccine herd immunity study, year 10, 11 and 12 Recommended children &lt;2 years, adolescents, and for those with increased medical or occupational risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>From 6 weeks, 4 and 6 months (not funded)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td>Hib-MenC (Menveo or</td>
<td>12-13 months</td>
<td>One</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nimenrix)</td>
<td>14 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MenACWY (Menveo or</td>
<td>Catch-up 2-17 years</td>
<td>One</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nimenrix)</td>
<td></td>
<td></td>
<td>Catch-up for those age 10-25 who haven’t received MenC or first year attending University Born between Sept 1996 – Aug 1999</td>
</tr>
<tr>
<td></td>
<td>4CMenB (Bexsero)</td>
<td>2, 4, 12-13 months</td>
<td>2+1</td>
<td></td>
</tr>
<tr>
<td><strong>Germany</strong></td>
<td>MenC</td>
<td>12-23 months</td>
<td>One</td>
<td></td>
</tr>
<tr>
<td><strong>France</strong></td>
<td>MenC (NeisVac-C)</td>
<td>5 and 12 months</td>
<td>1+1</td>
<td>Mandatory in infants Special groups – MenACWY and 4CMenB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Catch up 2-24 years</td>
<td>One</td>
<td></td>
</tr>
<tr>
<td><strong>Ireland</strong></td>
<td>MenC-CRM (Menjugate)</td>
<td>6 months and 11-12 years</td>
<td>1+1+1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hib-MenC</td>
<td>13 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4CMenB</td>
<td>2, 4, 12 months</td>
<td>2+1</td>
<td></td>
</tr>
</tbody>
</table>

* Varies by territory/state/region
7 Options for New Zealand

7.1 Background

Meningococcal immunisation is not routinely provided in New Zealand, as of 2018. Meningococcal conjugate vaccines are available for the prevention of group A, C, W and Y invasive disease, and funded for certain high-risk groups, contacts of an index case and during isolated epidemics at the discretion of the local medical officers of health and the Ministry of Health. The group B vaccines are recent additions to the global market and questions remain around their routine use and role in disease control. However, data is emerging from Australia and the UK around routine programmes. As of June 2018, two quadrivalent MenACWY conjugate vaccines (Menactra® and Nimenrix®) and one MenC conjugate (NeisVac-C) vaccine are approved in New Zealand. In July 2018 (since the preparation of this review), the four-component MenB, 4CMenB (Bexsero®) was approved by Medsafe. Group B is the most frequent cause of IMD in New Zealand.

Based on the preceding reviewed literature, this section will consider options for the scheduling and target populations of meningococcal vaccines in New Zealand. It will also consider the placement of the recently licensed group B recombinant vaccine, 4CMenB (Bexsero®) and ACWY-CRM (Menveo®), which is not currently licensed in New Zealand. No literature considering cost-effectiveness or cost-benefit has been reviewed or taken into account in this section.

7.2 Universal programmes

7.2.1 Meningococcal conjugate vaccines

7.2.1.1 Infants and toddlers

To help reduce the incidence of meningococcal disease in infants, direct and indirect protection can be provided by MenC and MenACWY conjugate vaccines. In NZ, early increases in group W and Y disease is apparent in older adults (aged over 40 years), although group W cases have been reported in infants.

There is a steady background of group C disease across all age groups. The average annual rate is 0.3/100,000 in NZ with the highest rate in infants (1.7/100,000), for which either a MenCCV or MenACWY conjugate vaccine could provide protection. However, this is rate is much lower than the rate of MenB infection in infants (13.9/100,000).

Depending on ongoing group prevalence, a single dose of MenC conjugate vaccination in infancy with a booster in the second year of life may therefore be sufficient to provide protection against MenC IMD in children younger than 2 years of age, if it is considered. Little advantage of additional group cover is likely to be provided currently by routine quadrivalent vaccine for this age group and greater protection against IMD would be afforded with MenB vaccination and herd immunity from adolescents against MenC.

A single toddler dose induces a longer lasting immune response than priming doses alone in younger infants, the antibody responses of a single toddler dose of Hib-MenC is not long-lived in unprimed children. A single toddler dose alone is unlikely to be sufficient to prevent disease in young children until circulating disease in NZ is diminished through herd immunity, which potentially could be provided through adolescent meningococcal vaccination.
Conclusions

- To reduce meningococcal disease in infants, a catch-up campaign for all children would better support an infant programme against MenC or MenACWY by providing herd immunity.
- Currently, there is little evidence of a role for MenACWY or MenC vaccination in infants in NZ.
- A decision to add routine MenACWY vaccination to the infant schedule would depend upon incidence of MenW and Y in children under 2 years of age and whether adolescent MenACWY vaccination can provide supportive herd immunity through limiting transmission.

7.2.1.2 Booster doses in children

Bactericidal antibodies play an important role in protecting against IMD by neutralising the infection before it has a chance to rapidly spread in normally sterile body systems. Antibody-driven immunity post vaccination tends to wane within 3-5 years. Booster doses are required to maintain high levels of antibodies to provide individual protection into mid-childhood.

The optimum timing of booster doses following priming with ACWY-TT or MenC-CRM is undetermined in children. Seroprotective antibodies persist for at least four years for groups C, W and Y after priming at 12-23 months. Most (95-100%) primed individuals have seroprotective antibodies one year after booster doses given at age 5-6 years, although the persistence of these antibodies into adolescence is unknown as yet.\(^{(36)}\)

Conclusion

- Booster doses are required to maintain seroprotective antibody levels until transmission has been interrupted.

7.2.1.3 Adolescents and young adults

A strategy focussed on routine vaccination of adolescents may have profound and long-lasting impacts on meningococcal disease, despite the challenges of reaching this age-group.\(^{(8)}\)

Asymptomatic carriage of meningococci is common, but the dynamics of transmission and carriage have not been identified. It is known that adolescents and young adults are at the highest risk for carriage acquisition and transmission, have a high incidence of disease, and as such, play an important role in the epidemiology of IMD, as previously illustrated in Figure 2.\(^{(8)}\)

As presented in section 2.2, the overall rate of IMD in NZ in 15- to 19-year-olds is 3.3 per 100,000 compared with the total rate of 1.6 per 100,000 annually and is particularly high for group C disease (1 vs 0.3 /100,000 annually) and group B (1.3 vs 0.9/100,000, annually).

There are two key advantages of immunising adolescents against meningococcal disease with conjugate vaccines, namely:

- Direct protection is provided to an age-group at high risk of IMD
- Vaccination of adolescents also provides herd immunity to younger or more at-risk individuals by reducing the rate of carriage and transmission

Single or multiple doses of MenCCV in infancy plus a booster in the second year of life induced insufficient antibody levels for bactericidal protection to be maintained into
adolescence, affecting the direct protection and herd immunity in this older age-group.\textsuperscript{(82)} The duration of effectiveness of MenCCV vaccination has been shown to be longer when immunised as adolescents rather than as infants.\textsuperscript{(55)}

A single dose of ACWY-D provides protection to the majority of 11- to 12-year-olds until early adulthood, but around one third may not be fully protected after more than three years. A second dose in late adolescence (age 16-19 years) may be required to extend protection during high-risk periods.\textsuperscript{(56)} However, these findings cannot be extrapolated for the other MenACWY vaccines and no further literature was found for these.

### 7.2.2 Concomitant routine vaccination

#### 7.2.2.1 Infants and toddlers

During pre-licensure clinical trials, the immunogenicity against three out of seven vaccine-type pneumococcal polysaccharides was less when ACWY-D (Menactra\textsuperscript{(®)}) was given concurrently with PCV-7 than PCV-7 alone. Since licensure, it has been recommended that this meningococcal vaccine only be given once the primary series for PCV has been completed in infants, to children from 2 years of age and to older individuals at high risk of invasive pneumococcal disease, although the vaccine is licensed from 9 months of age.

ACWY-TT (Nimenrix\textsuperscript{(®)}) has been demonstrated in clinical trials to be immunogenic when administered concomitantly with DTaP-IPV-HepB/Hib and PCV-10 in infants starting at 6 weeks of age. In individuals aged at least 12 months, ACWY-TT can be given concurrently with HepA, HepB, MMR, MMRV, PCV-10 or influenza vaccines. Whenever possible, in toddlers aged 12-23 months, ACWY-TT should be given concomitantly with, or at least one month prior to, a tetanus toxoid-containing vaccine dose, to minimise any potential conjugate protein interference.\textsuperscript{(17, 119)} However, in PCV-10 primed infants, concomitant administration with ACWY-TT does not appear to interfere with the seroprotection against TT-conjugated pneumococcal serotypes.\textsuperscript{(32)} Note however, that this vaccine is licenced from 12 months of age.

ACWY-CRM (Menveo\textsuperscript{(®)}) has been shown to be immunogenic in infants (from 2 months of age) and young children. There is no evidence of clinically relevant interference with concurrently administered primary immunisations.\textsuperscript{(23)} ACWY-CRM has not been investigated with PCV-10 as used in the NZ routine childhood schedule.

**Conclusions**

- Questions remain around the protective value of MenACWY vaccines for young infants in NZ.
- Any effect that the conjugate proteins may have on priming for other conjugate vaccines, such as certain PCV serotypes, is unclear.
- Any interference may not be clinically relevant and may depend on the disease types in circulation.

#### 7.2.2.2 Adolescents and adults

Concomitant vaccination with ACWY-CRM and routine vaccines, such as Td or Tdap or HPV, does not significantly alter the immunogenicity of these vaccine antigens in healthy individuals.\textsuperscript{(29)}
7.2.3 Meningococcal B vaccines

Recombinant 4CMenB vaccine is likely to provide good protection against vaccine-preventable strains, predicted to be around 76% of circulating group B strains in Australia.\(^{(111)}\) Cross-protection against other groups may also occur, but has yet to be confirmed.

The duration of protection and the ability of 4CMenB to reduce carriage and provide herd immunity is unknown currently.

7.2.3.1 Infants

Introducing 4CMenB to the NZ schedule is likely to provide protection for infants against group B disease. MenB disease is seen most frequently in infants under the age of 1 year. In NZ, the average annual rate of for MenB disease is 13.9 /100,000 in infants younger than 1 year (compared with total rate of 0.9/100,000).

The UK and Ireland are the only countries that have introduced 4CMenB to the reduced infant schedule (at 2, 4 and 12 months of age). Australia and Canada recommend this vaccine, but it is not funded, for infants from 6 weeks or 2 months of age, particularly for high-risk infants. No current literature was found that provided data around the effectiveness of this approach.

Adverse events, in particular fever and injection site pain, would require careful monitoring and may affect uptake. Education of health professionals, particularly in emergency departments, around the likely responses to this vaccine is likely to prevent unnecessary investigations and hospitalisation of infants. Prophylactic paracetamol is advised to reduce discomfort and fever risk.

7.2.3.2 Adolescents

In the US, recommendations for MenB vaccination (with either 4CMenB or MenB-fHbp) target adolescents (from 10 years of age). Since there is likely to be low uptake as MenB is not a significant cause of IMD in the US and there is uncertainty around the role of MenB recombinant vaccines in preventing transmission, it is unknown what impact targeting adolescents will have on IMD in the US.\(^{(8)}\)

Since MenB cases have been increasing in this age group, routine immunisation of adolescents may at least provide direct protection, particularly to those in communal accommodation.

7.3 High-risk groups

Case-fatality rate for MenC and MenW IMD is highest in older adults, and as such warrants vaccination of high-risk groups with MenACWY vaccines.

Due to variability in the influence that conjugate vaccine carrier proteins have on vaccine immunogenicity, it is recommended that those with poorer immune responses in particular, such as young children and immunocompromised individuals, receive the same MenACWY vaccine throughout an immunisation course.\(^{(38)}\)

No data is available on the use of MenB vaccines in high-risk individuals.

There is limited data on co-administration of MenACWY vaccines with other vaccines in immune-deficient individuals. The clinical relevance of any potential interference is undetermined and, when vaccines are given concurrently compared with individually, immune responses are not more likely to fall below protective thresholds.
7.3.1 High-risk infants

Immunisation with MenACWY conjugate vaccine is likely to provide greater benefit to infants with increased risk of IMD than MenC vaccine alone. However, the only vaccine licensed younger than 9 months of age is ACWY-CRM (Menveo), which is unavailable in NZ.

Since MenB incidence is higher in infants than in the other groups, high-risk infants may benefit from 4CMenB where it is not provided as part of the routine immunisation schedule. This vaccine was licensed in NZ in July 2018 and its role on the schedule has not yet been determined.

7.3.2 Occupational risk

Individuals at increased risk of exposure to meningococcal isolates, such as laboratory workers, are recommended to receive MenACWY and MenB vaccination (where available) to provide broad coverage. The duration of protection of both of these vaccines is undetermined and booster doses are likely to be required frequently (five-yearly) to maintain seroprotective antibody levels. Data is limited around the role of these vaccines in groups with occupational risk.

7.3.3 Travellers and mass gatherings

Hajj pilgrims have been associated with outbreaks of meningococcal disease and those travelling to Mecca, Saudi Arabia, are recommended to receive MenACWY vaccination prior to attending the Hajj or Umrah pilgrimages. Polysaccharide vaccine provides short-lived protection for such travellers, but has limited role in prevention of carriage acquisition. It is therefore suggested that MenACWY conjugate vaccine may help to reduce further transmission during mass gatherings or from returning travellers. However, as mentioned, the impact of MenACWY conjugate vaccination on the hypervirulent MenW strain (W:cc11) carriage is uncertain.\(^{(8, 89)}\)

Other travellers, particularly young adults residing in backpacker accommodation with potentially higher-risk lifestyles, are at risk of being exposed to virulent meningococcal strains not seen in NZ. MenACWY vaccination is highly recommended.

7.4 The role for herd immunity

The immunisation of major age groups that are \textit{N. meningitidis} carriers – adolescents and young adults - has been shown to provide herd immunity to protect young children and older adults against vaccine-group meningococci. In all countries that introduced MenCCV vaccination to infants and toddlers, with a catch-up campaign for all children, an indirect effect on unvaccinated individuals was seen. However, this was not apparent in countries that did not include catch-up of older children and adolescents.

Although catch-up campaigns may have an initial impact, this is not sustained unless vaccination of adolescents is included on the immunisation schedule to reduce circulating disease transmission.

\textbf{Meningococcal ACWY}

Initial evidence does not appear to show that MenACWY vaccines prevent carriage and potentially reduce transmission of hypervirulent MenW strains. Currently, there is insufficient data to determine whether the adolescent-only MenACWY vaccination in the UK will impact on overall disease incidence for W and Y disease in particular.\(^{(8, 89)}\) Therefore, targeting those aged 16-25 years is likely to provide greater direct benefit, as well as indirect protection against MenC and possibly MenY.
Carriage of MenW has also been shown to be highest in the most affected age groups, in infants and older adults, rather than adolescents.\(^{(12)}\)

**Meningococcal B**

Early data appear to suggest that recombinant meningococcal vaccines have a limited ability to provide herd immunity when given in late teens or early adulthood. For example, MenB-fHbp did not reduce meningococcal carriage or rapidly prevent MenB acquisition when provided during a college outbreak in the US. Therefore, a high coverage was required to protect individuals.\(^{(100)}\) Likewise, administering 4CMenB vaccine during the peak time for carriage is unlikely to prevent acquisition. Potentially, a greater reduction in carriage could be achieved by initiating vaccination earlier in adolescence, prior to acquisition, rather than late teens or early adulthood.\(^{(101)}\)

The South Australian Meningococcal B Vaccine Herd Immunity Study (B Part of It) being conducted by the University of Adelaide aims to provide data on MenB carriage and 4CMenB vaccination in students aged 15-18 years (Australian school years 10-12) in South Australia, where the incidence of MenB IMD is high.\(^{(120)}\) Recruitment is ongoing, primary outcome data is estimated to be collected by mid-2018 and the study completion is anticipated for June 2020.

**Conclusions**

- Adolescents are a source of transmission as well as being at high risk of IMD.
- Careful consideration of the emerging data may help to inform the most effective age at which to vaccinate adolescents against meningococcal disease.
- The role of MenACWY conjugate vaccines in providing herd immunity against type W and Y disease is unclear.
- The ability of MenB vaccines to reduce transmission is also unknown.

**7.5 Summary**

Meningococcal conjugate vaccines are effective both for direct protection against invasive meningococcal disease of A, C, W and Y serotypes and to reduce oropharyngeal carriage. Maintenance of circulatory bactericidal antibodies is necessary for long-term protection and, as seroprotective antibody levels wane after 3-5 years, booster doses are required to achieve adequate protection. This is particularly important for those at greatest risk of disease, such as infants, teenagers and young adults, and individuals with medically or occupationally increased risk of disease.

Herd immunity is the best mechanism for disease control across the two main age groups of high disease incidence and transmission, i.e. infants and adolescents, and for older adults.

**Meningococcal ACWY**

The age and number of priming doses of meningococcal conjugate vaccines necessary to directly control meningococcal disease depends upon IMD incidence and whether NZ choses to adopt a catch-up programme at the start of a meningococcal immunisation programme to gain herd immunity control, rapidly. A decision to add routine MenACWY vaccination to the childhood schedule would depend upon incidence of MenW and Y in children under 2 years of age and whether adolescent MenACWY vaccination can provide supportive herd immunity by limiting transmission.
As found with MenCCV programmes, infant-only vaccination was not effective in controlling disease, catch-up and adolescent immunisation strategies were also required to prevent circulation. At the start of an immunisation programme, priming of infants would be required with one or two doses while disease circulation is high, followed by a booster dose in the second year of life. Simultaneous immunisation of adolescents is likely to achieve herd immunity to reduce carriage rates of disease-causing strains. The most effective strategy to gain herd immunity quickly is a mass catch-up campaign for all children and adolescents, alongside the routine doses.

Hypervirulent MenW strains appear to behave differently to other meningococcal groups. Indirect protection against MenW strains may be best achieved prior to acquisition of this infection, i.e. vaccination in early rather than late adolescence, therefore, a catch-up campaign would be more beneficial.

Herd immunity may not achievable through adolescent doses alone and MenACWY vaccine would be required for direct protection in 15-20 year-olds. Infant and toddler doses of MenACWY could be necessary to provide direct protection to those age groups, if herd immunity was not effective against group W disease.

**Meningococcal B**

Recombinant MenB vaccines are relatively new to the market and there is limited data on their role in IMD disease control, particularly as part of routine immunisation programmes. The use of 4CMenB vaccine in infants, in a two-dose schedule with a toddler booster, is likely to provide the best protection for this high-risk age group.

Two doses of 4CMenB for adolescents at around 15-18 years is likely to provide protection during late adolescence and, depending on the duration of protection, into early adulthood. To date, a role in providing indirect/herd immunity is unclear. The South Australia ‘B Part of It’ study is anticipated to provide further data.

The four-component MenB vaccine, 4CMenB, seems to offer wider coverage against MenB strains than two-component MenB-fHbp vaccine, and early data suggests cross-protection with other meningococcal strains, such as MenW. This has not yet been confirmed.

**Potential programme**

With this in mind, the broadest coverage against meningococcal disease in young children is likely to be best achieved with both 4CMenB and MenACWY on the childhood schedule in the second year of life.

Since group B IMD incidence is greatest in infants, 4CMenB in infants would provide greater protection to children aged under 2 years of age. A question that remains is at which age would it provide the greatest protection if two doses (and with or without a booster) were given - in the second year of life, from 6 months of age or younger?

A role for MenACWY is not clear. Routine vaccination with MenCCV alone in infants is unlikely to provide broad or long lasting benefit against IMD and there is currently no evidence that the extra group coverage provided by MenACWY is necessary in this age group. Either ACWY-TT (Nimenrix) or ACWY-CRM (Menveo) would be the most appropriate vaccines, since ACWY-D (Menactra) is unsuitable under the age of 2 years due to potential interference with pneumococcal primary series.

A dose of MenACWY vaccine in early or mid-adolescence is likely to provide herd immunity, at least against MenC and MenY, to provide broader protection to the ages of highest risk (including older adults).
For high risk groups, MenACWY is likely to provide direct protection against these groups. There is insufficient data to comment on a role for 4CMenB in such groups. ACWY-CRM (currently unlicensed in NZ) would be suitable for high risk infants if groups W and Y became more prevalent in infants younger than 12 months.

Policy decisions are likely to be better informed as further data becomes available, particularly on the effect of MenACWY vaccines on herd immunity, the scope of protection provided by 4CMenB when given during infancy or in adolescence, and the duration of protection data for both.
8 Immunogenicity of meningococcal conjugate vaccines - in detail

As an addition to the summary provided in section 3.3, this section will review the published literature from 2013-2018 covering the post-licensure study immunogenicity data of meningococcal conjugate vaccines, in more detail, including MenC and MenACWY vaccines.

8.1.1 Effect of conjugation on vaccine immunogenicity

The type and quantity of conjugated carrier proteins and the way they are conjugated can influence the immunogenicity of meningococcal conjugate vaccines. The polysaccharide to protein ratio can also influence immunogenicity. Although the conjugated protein has an influence on immunogenicity of meningococcal conjugate vaccines, other formulation factors can influence their profile.\(^{(38)}\)

Due to this variability, Bröker et al (2016) recommend that when more than one dose of a conjugate vaccine is required to complete primary immunisation - as for infants, young children and immunocompromised individuals - the same vaccine be used throughout the course and vaccine exchange be avoided.\(^{(38)}\)

As well as inducing T cell-dependent immune response against the meningococcal polysaccharides, the carrier proteins can induce a carrier-specific response.\(^{(38)}\) The responsiveness against both the vaccine polysaccharides and the carrier antigen can be influenced by the timing of vaccines containing tetanus or diphtheria antigens, or influence the immunogenicity of other conjugated vaccines, such as Hib or pneumococcal vaccines.

Immunity to vaccine carrier proteins in co-administered vaccines can modify the immune response to vaccine antigens, referred to as carrier priming. When specific T cells induced by one vaccine have a heightened response to the same antigen in another vaccine, immune enhancement can occur, thereby augmenting the effect of co-administered vaccines.\(^{(39, 40)}\)

Conversely, suppression can occur. Immunity to a polysaccharide antigen conjugated to a carrier protein can be suppressed by pre-existing immunity to that carrier protein, termed carrier-induced epitopic suppression (CIES). When there is a lower frequency of vaccine antigen-specific B cells than carrier-specific clones, an overload of carrier antigen will be rapidly presented to the T cells by the dominant carrier-specific B cells. This results in an impaired antibody response to the vaccine antigen (polysaccharide). The decrease in polysaccharide response is proportional to the intensity of the immune response to the carrier, such that a low ratio of hapten (antigen of interest, such as polysaccharide) to carrier protein results in CIES and carrier overload may suppress immunity in primed individuals.\(^{(40)}\)

As reviewed by Pobre et al (2014), a study in the UK found that in children aged 1-17 years, prior administration of a tetanus-containing vaccine lowered the immunogenicity of MenC-TT, although meningococcal antibody levels remained above the seroprotective threshold. When co-administration was compared with consecutive administration in adolescents, the findings were inconclusive: one RCT found non-inferiority between ACWY-D and Tdap given concomitantly or sequentially; another RCT, in which MenC-TT was given together with or one month after Td, found that the immune response was higher when the vaccines were given concurrently than separately. MenC-CRM administration appears to work both ways – boosting both the anti-diphtheria and anti-MenC polysaccharide responses.\(^{(40)}\)
8.1.2 Immunogenicity in immunocompetent individuals

8.1.2.1 ACWY-TT vaccine in adults and adolescents

A systematic review and meta-analysis by Pellegrino et al in 2015 concluded that the immunogenicity of ACWY-TT was high for all groups tested and at least as immunogenic as the other licensed meningococcal vaccines (defined as rSBA titre ≥1:8). (46)

Four studies, out of a total of 15 RCT reviewed, compared the immunogenicity of ACWY-TT vaccine with C-CRM in vaccine recipients aged from 12 months to over 56 years and one study of ACWY-D in recipients aged 10-25 years. One dose of ACWY-TT induced a robust immune response in all age groups. A large variation in response rates and rSBA titres were observed between age groups and groups (in particularly A and C) across the different trials, although the clinical significance was not determined and further studies are required. (46)

Hyporesponsiveness against group C to booster doses was observed in some individuals aged over 55 years, which was thought to be associated with prior doses of polysaccharide MenC vaccine. (46)

One reviewed study reported that a single dose of ACWY-TT induced seroprotective antibody titres (rSBA ≥1:128) against all four groups in 93% of adult participants aged 56 years or older with varied meningococcal immunisation histories. Across all groups, the vaccine response rate was at least 76%. However, when the magnitude of the response was analysed, it was found to be significantly lower in the ACWY-TT recipients than the polysaccharide vaccine (MenPS) recipients in terms of vaccine response rate against group A (76.6% vs 91.7%, respectively) and rSBA geometric mean titres against groups A and C. Recipients with pre-existing rSBA titres ≥1:128 responded less well to ACWY-TT than those who were initially seronegative. VR rates were lower in participants age >65 years. Around one quarter of participants had received one dose of MenPS vaccine more than five years previously. The clinical significance was not determined. (47)

A phase IIb open-label RCT concluded that a single dose of ACWY-TT could provide protection for at least 72% of healthy adolescents and adults for at least five years post vaccination. The study assessed the immunogenicity and antibody persistence following one dose of ACWY-TT vaccine in 500 adolescents and adults aged 11-55 years in the Philippines and Saudi Arabia compared with an ACWY polysaccharide vaccine (Men-PS) randomised 3:1. Pre-specified non-inferiority criteria were met in terms of the rSBA titres. At one-month follow up, 82.7-96.3% of ACWY-TT recipients and 69.7-91.7% of Men-PS recipients had responded to each vaccine group. By year three, rSBA titres of ≥1:128 and ≥1:8 were retained in at least 82.9% and 99.1% of ACWY-TT recipients respectively, compared with 86.7% and 80.2% of the Men-PS group. (21) In a five-year follow-up of this study that included 404 of the original participants, rSBA titres of ≥1:128 and ≥1:8 against groups A, C, W and Y ranged from 64.9-86.3% and 71.6-90.0% in ACWY-TT recipients compared with 21.0-68.6% and 24.8-74.3% in the Men-PS vaccine group, respectively. (22)

ACWY-TT was shown to be immunogenic in adults aged 56 years to 103 years. Vaccine response rates tended to be lower in adults who were older than 65 years, compared with 56-65 years. This was less pronounced than following polysaccharide vaccination for groups A, C and Y. Following a single dose, vaccine response rate was ≥76% (against group A 76.6%, group C 80.3%, group W 77.5% and group Y 81.9%), and ≥97.4% of recipients achieved rSBA titres of ≥1:128 against all four groups at one month after vaccination with ACWY-TT as compared with ≥95.5% of those who received MenACWY polysaccharide vaccine. The vaccine also induced low levels of anti-TT antibodies in this population.
(proportion with titres of $\geq 0.1$ IU/ml increased from 6.3% pre-vaccination to 28.1% post-vaccination).\(^{(47)}\)

**Conclusions: ACWY-TT immunogenicity adolescents and adults**

- Vaccine response rate to one dose of ACWY-TT in recipients aged over 56 years was 76%.
- Possible hyporesponsive due to prior experience with polysaccharide menC vaccinations. Clinical significance not determined.
- Antibody protection against all groups maintained for up to 5 years for 72% - 90% of recipients.

**8.1.2.2 ACWY-CRM in adults and adolescents**

In Russia, a single dose of ACWY-CRM was reported to be immunogenic and comparable between children aged 2-10 years, adolescents aged 11-17 years and adults aged from 18 years. At one month after vaccination, hSBA titres $\geq 1:8$ were detected in 89% (83-93%) of participants against group A, 84% (78-89%) against group C, 97% (93-99%) against group W and 88% (82-92%) against group Y.\(^{(121)}\) Similar findings were reported in children and adults from 2 to 75 years of age in India.\(^{(122)}\)

Likewise in Korea, seroprotection rates with hSBA titres $\geq 1:8$ were observed in 79%, 99%, 98% and 94% of recipients against groups A, C, W and Y, respectively.\(^{(123)}\)

**8.1.2.3 ACWY-D vaccine in children and adults**

The only study that assessed immunogenicity of ACWY-D had similar findings to previous pre-licensure studies in different populations.\(^{(42)}\)

In vaccine-naïve children and adults in India (aged 2-55 years), seroprotective antibody titres ($\geq 1:8$) were observed at 30 days post vaccination in 91–100% of all participants, and across all the groups, 68-97% of participants achieved a four-fold increase in GMT (titres for MenC antibodies were lower in children aged 2-11 years).\(^{(42)}\)

**Conclusions: immunogenicity of ACWY vaccines in immunocompetent individuals**

The immunogenicity of MenACWY vaccines has generally been well characterised in pre-licensure clinical trials.

- The immunogenicity of ACWY-TT was high for all groups tested and at least as immunogenic as the other licensed meningococcal vaccines.
- A single dose of ACWY-TT induces a robust immune response against all groups in more than 72% of healthy adolescents and adults and provides protection for at least five years.
- Vaccine response rates were lower in adults aged over 65 years and some individuals aged over 55 years who had received prior vaccination with polysaccharide vaccines (MenC or quadrivalent).
- Recipients with pre-existing rSBA titres responded less well to ACWY-TT than those who were initially seronegative. The clinical significance was not determined.

**8.1.2.4 Immunogenicity in infants and children aged younger than 10 years**

**Meningococcal C**

A phase IV study conducted in the UK and Malta with 509 infants (aged 6-12 weeks) concluded that toddler-only schedules rely on herd immunity to protect infants and young...
children and that a single priming dose of MenC vaccine did not reduce the post-booster antibody titres. The study compared a single dose priming dose of MenC-CRM at 3 months of age plus a booster Hib-MenC-TT at 12 months with two-dose priming at 3 and 4 months plus booster; a single dose of MenC-TT vaccine plus booster; or a single toddler dose of Hib-MenC-TT. Infant priming with single MenC-TT plus a Hib-MenC-TT booster induced a more robust antibody response than one or two doses of MenC-CRM. Without infant priming, bactericidal antibody was not well maintained at 24 months following a single dose of Hib-MenC-TT at 12 months.\(^\text{(124)}\)

### 8.1.2.5 Meningococcal C-TT in infants – single priming dose

The immunogenicity of a single priming dose of MenC-TT (NeisVac-C) was found to be non-inferior to two priming doses in infants in Spain and Poland. Infants were randomised to receive a single dose of MenC-TT at 4 or 6 months of age or two-dose priming at 2 and 4 months, followed by a booster at 12-13 months. Pre-booster, 78.0% and 90.7% of infants had seroprotective antibody titres following single dose priming at 4 or 6 months respectively, compared with 67.8% of infants who received two priming doses, and both met non-inferiority criteria of 10%. The geometric fold increase from baseline was significantly higher in the 6-month single dose group than 4-month dose or two-dose groups (20.2 [95% CI 16.9-24.1]; 8.8 [7.4-10.6] and 7.1 [5.8-8.7], respectively). In all groups, 99.0% of infants showed rSBA titres ≥1:128 at one month following the booster dose.\(^\text{(41)}\)

### 8.1.2.6 Meningococcal ACWY in children

The immunogenicity of ACWY-CRM or –TT vaccines were found to have comparable immunogenicity profiles at one month post vaccination in a phase II study in 202 toddlers aged 12-15 months. At six months post vaccination, substantial antibody titres persisted for groups C, W and Y, whereas for group A, hSBA titres declined in both groups and rSBA titres remained high (proportion with hSBA titre ≥1:8: 30% in ACWY-TT group and 65% in ACWY-CRM group). This difference appears to be related to the assay used rather than the bactericidal ability of the antibodies; although hSBA and rSBA strongly correlate for group C, it is not the case for groups A, W and Y and samples lacking hSBA activity are often positive by rSBA.\(^\text{(27)}\)

A multi-centre study found that around half the children vaccinated at 2-10 years of age had seroprotective antibodies after five years against meningococcal groups C, W and Y (proportion with hSBA titre ≥1:8: group A 7-22%; group C, 32-57%; group W, 74-83% and group Y, 48-54%). The children had been initially vaccinated with one or two doses of ACWY-CRM at 2-5 years or one dose at 6-10 years and were compared with age-matched, unvaccinated controls. There was little difference in antibody persistence after five years between the children primed with one or two doses. Booster responses were demonstrated in 98-100% of previously vaccinated children against all four groups in all three vaccinated study groups.\(^\text{(43)}\)

**Conclusions: immunogenicity in children**

- One dose priming with MenC-TT in infants aged 4 or 6 months was non-inferior to two dose priming at the younger ages of 2 and 4 months.
- One or two doses of ACWY-CRM or –TT induce persistent seroprotective antibodies against groups C, W and Y in children aged 12 months to 10 years.
- Bactericidal responses against group A are variable and may be an artefact of the type of assay used – booster responses demonstrated that immune memory appears present upon re-vaccination after five years.
8.1.3 Immunogenicity of co-administration with other vaccines

8.1.3.1 Coadministration infants and children

**Meningococcal C**

Following co-administration of MMRV and MenC-CRM vaccine to healthy toddlers aged 13-15 months in Italy, seroprotection against MenC was achieved in 98.3% of infants, compared with 99.3% in the MenC-CRM-only group. At 42 days post vaccination, seroconversion rates were 99.3%, 94.5%, 100% and 99.7% for measles, mumps, rubella and varicella respectively in the MMRV+MenC group, and 99.4%, 93.2%, 100% and 100%, respectively, in the MMRV-only group. Predefined non-inferiority was achieved for all vaccine antigens.\(^{30}\)

The immune response to MenC was non-inferior following two or three doses of ACWY-TT vaccine when compared with two doses of MenC-TT or MenC-CRM (at 2, 4 and 12 months). All vaccines were administered concurrently with routine PCV-10 and DTaP-IPV-HepB/Hib at 2, 3, 4 and 12 months as part of a phase III RCT, conducted in Estonia, Germany and Spain. Robust rSBA and hSBA titres were observed against vaccine groups following a booster dose with ACWY-TT.\(^{31}\)

**Meningococcal ACWY**

During pivotal clinical trials, it was reported that when ACWY-D vaccine was co-administered with PCV-7 (CRM conjugated pneumococcal vaccine) in infants aged 9-12 months, non-inferiority criteria were not met for pneumococcal IgG titres against three out of seven pneumococcal serotypes (4, 6B, 18C). A similar effect was implied for PCV-13, since it contains the same serotypes and conjugate as is used in PCV-7. It was subsequently recommended that ACWY-D only be given once children had completed their primary PCV series.\(^{18}\)

Concomitant administration of PCV-10 and ACWY-TT in healthy toddlers aged 12-23 months was supported by an open RCT conducted in Mexico and Taiwan. Non-inferiority criteria comparing concomitant and separate administration of these vaccines given one month apart were met for all four meningococcal groups and for nine out of 10 pneumococcal serotypes (except 18C which is TT conjugated). One month after ACWY-TT vaccination, 97.5% of toddlers had rSBA titres $\geq 1:128$ for all meningococcal groups. Prior to the booster dose, 75% of participants had anti-pneumococcal antibody concentrations of $>0.2\mu g/ml$ (51% for group 1). Following PCV-10 booster, $\geq 96\%$ and $\geq 92.9\%$ of toddlers had antibody concentrations $>0.2\mu g/ml$ and opsonophagocytic activity titres $\geq 1:8$, respectively. An increase in seroprotective anti-tetanus antibody was also observed in all groups following vaccination with ACWY-TT (from 94.6-100% to 100% post vaccination).\(^{32}\)

A phase III RCT assessed the immunogenicity of ACWY-CRM when administered with routine vaccines from 2 months of age. Healthy infants ($n=900$) in Argentina and Colombia were randomised 1:2 to receive routine vaccines alone or concomitantly with either two primary series doses of ACWY-CRM at 2 and 6 months or three doses at 2, 4 and 6 months plus a booster dose at 12 or 16 months, respectively. All groups received routine vaccines at 2, 4 and 6 months as per the immunisation schedule (DTaP-IPV-HepB, Hib-TT, PCV-7 and rotavirus). For immunogenicity at one month post infant series, the immune response was similar for groups C, W and Y (proportion with hSBA titres $\geq 1:8$ after two and three doses: 94-99% and 97.8%, respectively). A greater proportion of participants who received three primary doses had hSBA titres $\geq 1:8$ against group A than those who received two doses (89% vs 74%, respectively). A month after the full primary/booster series, 94-99% had seroprotective antibody levels at 13 months of age following the two-dose plus booster series and 95-100% following the three-dose plus booster series at 17 months of age. Non-
inferiority was achieved for each of the routine vaccine antigens, including pneumococcal antigens, at 7 months and 13 months. The study concluded that ACWY-CRM was immunogenic when given as a 2+1 or 3+1 infant schedule and did not interfere clinically with concomitant vaccines.\(^{(34)}\)

As part of the same RCT, toddlers who only received routine vaccines in their first year were administered ACWY-CRM as catch-up doses at 12 and 15 months of age. Of these toddlers, 97-100% had seroprotective antibodies to each of the four meningococcal groups.\(^{(34)}\)

In an RCT conducted in the US and Canada, 751 infants were randomised to receive three doses (at 2, 4, and 12 months) or four doses (at 2, 4, 6, and 12 months) of ACWY-CRM with PCV-13 and routine vaccinations, PCV-13 with routine vaccinations, or routine vaccines alone. One month after four-dose series of ACWY-CRM, 96% had hSBA titres ≥1:8 against group A and 99% against groups C, W and Y. The four-dose and three-dose series both met the predefined criteria for immune response sufficiency and three doses were found to be non-inferior to four doses. At seven months, following two or three doses of concomitant ACWY-CRM and PCV-13, non-inferiority was met for most pneumococcal serotypes, but not met for serotypes 3 and 5 in two-dose group and 19A after three doses ACWY. Due to potentially insufficient sample sizes, a further pooled analysis was conducted combining two- and three-dose data, in which non-inferiority criteria were met for all PCV-13 serotypes, requiring further investigation. At 13 months (following three or four doses of vaccine), immune responses to PCV-13 antigens were non-inferior to those in the routine vaccine group.\(^{(44)}\)

The immunogenicity of ACWY-CRM was assessed in an RCT in the US, Canada and Australia, in which 529 healthy infants were vaccinated at 2, 4, 6 and 12 months concomitantly with age-appropriate routine vaccines (DTaP-IPV/Hib, HepB, PCV-7 or PCV13 and MMR). Highly immunogenic responses were observed against all four meningococcal groups without clinically relevant interference to the routine immunisations. Following the three-dose infant series (ACYW-CRM and routine vaccines group), 76%, 94%, 98% and 94% of infants had hSBA titres ≥1:8 against groups A, C, W and Y, respectively. Slight differences were observed in the post-infant seroresponse rates for pertussis antigens pertactin and FIM and for pneumococcal serotypes 6B and 23F, but these met the geometric mean concentration ratio non-inferiority criteria.\(^{(33)}\)

**Conclusions: co-administration with routine vaccines in children**

- **Since licensure, it has been recommended that vaccination with ACWY-D be delayed until after the primary course of PCV-13 has been completed in young infants and immunocompromised individuals. This was based on pre-licensure clinical trial data that showed potential interference in the immunogenicity of some of the PCV-7 and PCV-13 serotypes (CRM-conjugated pneumococcal vaccines).**

- **ACWY-TT vaccine can be co-administered with PCV-10. Although interference is possible with TT conjugated PCV vaccine serotype 18C, the clinical relevance is unknown. Pneumococcal booster doses induce good immune responses against all vaccine antigens.**

- **Three or four doses of ACWY-CRM are highly immunogenic against all four meningococcal groups and do not appear to interfere significantly with other primary vaccinations by 13 months of age.**

- **There is insufficient data to conclude what effect ACWY-CRM has after each priming dose when given with PCV-13, although for PCV-7, there was no significant effect following three primary doses.**
8.1.3.2 Co-administration in adults and adolescents

One review found that the immune response to all four meningococcal groups was not influenced by concomitant administration of ACWY-CRM with Tdap and HPV in adolescents or travel vaccines (rabies, Japanese encephalitis, hepatitis B and A) in adults. Analysis of five phase III and IV open-label RCTs found no clinically-relevant immunological interference following co-administration of ACWY-CRM with Tdap and HPV in adolescents aged 11-25 years or travel vaccines in adults aged 18-64 years. Co-administration of ACWY-CRM with routine vaccinations was supported in all age groups.[29]

The proportion of adolescents with anti-diphtheria antibodies ≥1.0 IU/ml at one month was statistically higher following co-administration with ACWY-CRM and Tdap compared with routine Tdap alone (94% vs 85%). However, non-inferiority was not uniformly met across studies against pertussis antigens in adolescents. In one study, non-inferiority was not met for the proportion of participants with a four-fold increase in pertussis toxin antibody (76% in the ACWY-CRM+Tdap group and 81% in the Tdap only group) or for pertactin antibody (84% vs 91%, respectively), although the clinical relevance was unclear.[29]

A Korean study found that tetanus-diphtheria (Td) booster vaccination given three days prior to meningococcal vaccination influenced the immunogenicity of ACWY-CRM vaccine in military recruits. Although the meningococcal vaccine was immunogenic against all groups in all participants, those that received ACWY-CRM alone had significantly higher post immunisation antibody responses to A and C groups than those who receive Td and then ACWY-CRM.[125]

No studies published since 2014 were found that considered the immunogenicity of ACWY-TT when given concurrently with other vaccines. A review of studies published prior to 2013 reported on two studies, one of which found that co-administration of hepatitis A/B vaccine and ACWY-TT was immunologically non-inferior to each vaccine given alone in 11- to 17-year-olds. Another study reported acceptable seroconversion rates for all vaccine antigens following co-administration with seasonal influenza vaccine to 18- to 55-year-olds in Lebanon and Philippines.[48]

Conclusions: co-administration in adolescents and adults

- Some immune modulation appears to occur against certain vaccine antigens with co-administration of ACWY-CRM and Td or Tdap vaccines in adults and adolescents, but not HPV.
- Immunogenicity against pertussis and meningococcal groups A and C may be reduced in some individuals, but the clinical relevance on vaccine effectiveness is undetermined.
- There are few recent publications on the immunogenicity of ACWY-TT vaccine. Clinical trial data published prior to 2013 appear to demonstrate good immunogenicity and seroprotective titres when administered to children and adults.

8.1.4 Booster doses

8.1.4.1 Booster doses in toddlers

Booster doses of ACWY-TT or MenC-CRM induced persistent seroprotective antibody titres in 95-100% of children. The immunogenicity and antibody persistence of booster vaccination with ACWY-TT or MenC-CRM vaccines was evaluated in Finland, four years after 293 toddlers were primed in a previous study with one dose of ACWY-TT or MenC-CRM at 12-23 months of age. Prior to the booster, 28.8%, 73.2%, 80.6% and 65.4% of children primed with ACWY-TT had maintained hSBA titres ≥1:8 against groups A, C, W and Y, respectively. In
the MenC-CRM group, 46.9% had hSBA titres ≥1:8 against group C. At one year post booster, 97.4% of the ACWY-TT group and 97.8% of the MenC-CRM group had group C hSBA titres ≥1:8. Booster doses also induced seroprotective titres against each A, W and Y groups in all participants in the ACWY-TT group. By one year after the booster dose, 95.5% had hSBA titres ≥1:8 against group A and 100% against groups W and Y. Follow-up for up to 10 years is planned to evaluate the potential adolescent benefit of a booster dose given at age 4-6 years in those primed at 12-23 months.(36)

It was concluded that ACWY-TT could be given as a booster and co-administered with DTaP to toddlers primed as infants with HibMenCY-TT and DTaP-containing vaccines.(45) All participants had hSBA ≥1:8 for groups C and Y and 96.1% or more had hSBA 1:8 titres for groups A and W at one month following a booster vaccination with ACWY-TT at age 12-15 months or ACWY-TT plus DTaP at 15-18 months (primed as infants at age 2, 4 and 6 months with HibMenCY-TT).(45)

This study also found that non-inferiority was met for diphtheria, tetanus and pertussis filamentous haemagglutinin antigens, but not for pertussis toxoid or pertactin, between those co-administered ACWY-TT and DTaP or DTaP alone. However, the pertussis antibody levels were above the level reported to be clinically efficient. The study concluded that ACWY-TT could be given as a booster and co-administered with DTaP to toddlers primed as infants with HibMenCY-TT and DTaP-containing vaccines.(126) HibMenCY-TT (MenHibrix®) vaccine was discontinued in 2016 due to low demand. Hib-MenC-TT (Mentorix®) is available in New Zealand.

8.1.4.2 Booster doses in adolescents

A phase III RCT found that ACWY-CRM could be used to boost adolescents three years after primary vaccination with either ACWY-CRM or ACWY-D vaccines. At three years after primary vaccination with ACWY-CRM, hSBA titres ≥1:8 against groups C, W and Y were shown in 64%, 82% and 65% of participants, respectively (n=367), and 28% for group A. Significantly more ACWY-CRM recipients had seroprotective titres against W and Y than the ACWY-D recipients. Following a booster dose of ACWY-CRM, 99-100% of participants had hSBA titres ≥1:8 against all groups irrespective of primary vaccination.(49)

**Conclusions: booster doses**

- Four years after priming of toddlers with ACWY-TT or MenC-CRM, booster doses of ACWY-TT induced persistent seroprotective responses against all groups.
- Booster doses of ACWY-TT alone or concurrently with DTaP were immunogenic in HibMenCY-TT and DTaP-primed toddlers.
- No clinically relevant differences in anti-pertussis antibody levels were observed when ACWY-TT was co-administered with DTaP in toddlers.
- Booster doses of ACWY-CRM induced seroprotective responses in more than 99% of recipients regardless of priming with ACWY-CRM or ACWY-D.

8.1.5 Immunogenicity in special groups

Very few recent publications were identified that investigated the immunogenicity of meningococcal vaccines in individuals at high risk of invasive meningococcal infection or immunocompromised individuals.

Evidence of interference from ACWY-D on PCV-7 (and PCV-13) immunogenicity for certain serotypes was reported during pre-licensure clinical trials. It is recommended that ACWY-D
is given at least four weeks after PCV-13 to individuals at high risk of meningococcal and pneumococcal disease, such as those with asplenia.\(^{(14, 18, 127)}\)

The long-term kinetics of the antibody response to meningococcal C vaccination was investigated in patients with juvenile idiopathic arthritis in the Netherlands. The study found that MenC IgG antibodies waned with time, but at 4.2 years after vaccination were estimated to be at similar levels to healthy controls. Treatment with biologicals after vaccination, but not methotrexate, accelerated antibody waning, leaving some patients unprotected and requiring re-vaccination. During a nationwide catch-up campaign conducted in 2002, children aged 1-19 years were vaccinated with MenC-TT vaccine (NeisVac-C). The study included 127 patients (aged 8.9±3.7 years at time of vaccination) and 1527 healthy controls (aged 9.1±5.1 years).\(^{(52)}\)

The immune response to non-conjugate polysaccharide and conjugated MenACWY vaccines was assessed in patients who had received solid organ transplant (n=10 and 5, respectively, median age 56 years). Following vaccination, 40% and 50% of patients respectively mounted a seroprotective immune response (defined as hSBA titre ≥1:4). Half of the patients in the conjugate vaccine group had seroprotective antibodies against one group; one patient had seroprotection against two groups. All these patients planned to travel to Sub-Saharan Africa during the epidemic season and would not otherwise have been considered at high risk of meningococcal disease. It was concluded that meningococcal vaccination be considered prior to transplantation.\(^{(53)}\)

As mentioned above, hyporesponsiveness to group C was observed in adults aged over 55 years when given booster doses of ACWY-TT. This may have been a consequence of receiving prior doses of MenC polysaccharide vaccine.\(^{(46)}\) This is a plausible scenario for adults with life-long high risk of IMD who may have been given MenC-PS, historically.

**Conclusions: special groups**

- Immunosuppressive or immunomodulatory therapies used to treat immune-mediated inflammatory diseases or to prevent transplant rejection are likely to affect the immunogenicity of meningococcal conjugate vaccines.
- Where possible, vaccination is suggested prior to transplantation or commencement of treatment.
- Frequent boosters are required to overcome waning seroprotection.
- Hyporesponsiveness in response to conjugate antigens may be observed in those with prior experience of polysaccharide meningococcal vaccines.

**8.1.6 Effect of bactericidal and mucosal antibodies on meningococcal carriage**

Following the immunisation of university students in the UK with ACWY-CRM or four-component meningococcal B vaccine (4CMenB – as described in section 4), no correlation was observed between changes in carriage rates of MenC, Y or B strains and post-vaccination hSBA titres in a phase III RCT. Both vaccines were seen to be highly immunogenic at two months and up to at least 11 months after vaccination, and 95% of ACWY-CRM recipients had hSBA ≥1:8 against group Y. Carriage of groups A and W were too low to be detectable. Higher carriage rates of group C, Y and disease-associated group B were observed among participants who had high hSBA titres ≥1:8 at baseline, prior to vaccination.\(^{(102)}\)

The role and induction of mucosal antibodies in preventing acquisition and carriage of meningococci have not been studied as much as serum bactericidal antibody titres. One study conducted in the UK and published in 2000 showed that, although both vaccines
induce anti-MenC polysaccharide-specific salivary IgA, MenCCV induced significantly higher salivary IgG than polysaccharide MenC vaccine in children aged 11-17 years, and that these titres correlated with serum IgG titres. IgG and IgA mucosal antibodies in the saliva declined significantly by six months post vaccination.\(^{(50)}\)

A more recent study, conducted in the Netherlands and published in 2018, also found that serum antibody correlated with salivary antibody titres for MenA, C, W and Y polysaccharides following vaccination of healthy adolescents with MenACWY-TT. After both primary and booster vaccination, salivary IgA levels declined significantly to pre-vaccination levels after one year.\(^{(51)}\)

However, neither of these salivary antibody studies assessed any changes in meningococcal carriage. Further discussion about the impact of meningococcal vaccines on carriage is provided in section 5.1.2.

**Conclusions: mucosal antibodies**

There is evidence of a correlation between vaccine-induced serum IgG and salivary IgG, although salivary antibody is short lived (up to six months post vaccination) and, as expected for mucosal tissues, IgA-predominant. It is unknown how the presence of salivary anti-meningococcal antibodies relates to carriage and transmission of disease-causing meningococcal strains.

- Serum IgG titres correlate with salivary IgA and IgG levels but have not been correlated with meningococcal carriage.
- Salivary antibodies decline rapidly, within one year, post vaccination.
- The role of mucosal antibodies in preventing meningococcal carriage has not been studied.
9 Methodology for review

9.1 Objectives

This review was commissioned by the New Zealand Ministry of Health and aims to inform policy decisions around the use and potential benefit of meningococcal vaccination as part of the New Zealand National Immunisation Schedule. This is a review of evidence-based, peer-reviewed literature published from January 2014 to December 2018 concerning the use of meningococcal vaccines. The focus is on post-licensure studies and clinical trials for conjugate and recombinant vaccines available in New Zealand and internationally. It is not a systematic review and does not include cost-effectiveness or cost-benefit analyses.

9.2 Literature search strategy

9.2.1 Medline search terms and strategy

Medline (OVID)

1. Keyword MeSH – meningococcal vaccines [focus, all sub-headings] = 2310
2. Limit English, humans, 2013-current (04Dec17) = 678
3. 2 AND immunogenicity.ab = 136 – removed 54 duplicates = 109
4. 2 AND safety.ab = 119, removed duplicates from import = 33 new
5. 2 AND effectiveness = 70, minus 20 duplicates in import and 32 in full library = 44

1. Keyword MeSH - Immunization programs [focus, all sub-headings] = 6048
3. Keyword MeSH – meningococcal vaccines [focus, sub-headings admin & dosage, immunology, therapeutic use] = 1535
5. 2 AND 4 = 30, selected 21, removed duplicates = 14

1. Title ACWY = 31
3. Selected 1

PubMed

Meningococcal vaccines (MesH) and immunocompromised
Limit 5 years [prior to 20Feb18], English, humans = 5

9.2.2 Cochrane Library search terms and strategy

No recent Cochrane reviews were found.

9.2.3 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. All duplicates were removed from the final library. Additional literature searches were conducted during January–March 2018.
Additional to the published articles and included in the reference sources are book sections, MedSafe datasheets, fact sheets and web pages from New Zealand and international government sources.

9.2.4 Final EndNote Library 282 journal articles

Where systematic reviews and/or meta-analyses were available the preceding literature has been excluded from the review, unless further details were obtained directly from the preceding literature.

9.3 Participants/populations

This review is predominantly focussed on meningococcal immunisation of age groups at highest risk of disease. The vaccines are primarily provided for infants younger than 2 years of age and adolescents or young adults aged 10–25 years.

Where literature was available, other individuals at increased risk of meningococcal disease were considered. This includes individuals with immunosuppression who are at increased risk from meningococcal disease and certain high-risk groups who are eligible for funded vaccine, across all age groups. Other groups at increased risk of exposure or invasive disease are recommended but not eligible for funded vaccine. These include laboratory workers and travellers to countries with high rates of meningococcal disease incidence or epidemics.

9.4 Study designs

The studies included in this update are meta-analyses, systematic reviews, reviews, randomised controlled trials, case-control studies, case reports and observational studies using database matching.
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