

3.12 MENINGOCOCCAL DISEASE

Bacteriology

Meningococcal disease is caused by the bacterium *Neisseria meningitidis* (*N. meningitidis* or the meningococcus), a Gram-negative diplococcus. There are 13 known serogroups distinguished by differences in surface polysaccharides of the outer membrane capsule. Meningococcal serogroups are designated by letters of the alphabet. Globally, serogroups A, B, C, W₁₃₅ and Y most commonly cause disease. Meningococci can be further differentiated by differences in their outer membrane proteins, which are referred to as serotypes and serosubtypes.¹ More recently, molecular typing has been used to further differentiate meningococci. In Australia, serogroups B and C occur most frequently. There is no consistent relationship between serogroup or type and virulence.^{2,3}

Clinical features

Neisseria meningitidis can cause meningitis, septicaemia or a combination of the two. Other localised infections, including pneumonia, arthritis and conjunctivitis, may also occur but are uncommon. Septicaemia, with or without meningitis, can be particularly severe. The overall mortality risk is high (about 10%) despite appropriate antibiotic therapy.

N. meningitidis is carried and transmitted only by humans. There are no known animal reservoirs. Asymptomatic respiratory tract carriage of meningococci is present in about 10% of the population, and the prevalence may be higher when groups of people occupy small areas of living space.²⁻⁸ Recent studies indicate that there may be a number of factors which contribute to the increased risk of contracting meningococcal disease, including exposure to smokers, recent illness, living in crowded conditions and multiple intimate kissing partners.⁴⁻⁸ People with inherited disorders of phagocytosis associated with properdin deficiency or absence of the terminal components of complement, as well as individuals with functional or anatomical asplenia, have an increased risk of meningococcal infection.¹

The disease is transmitted via respiratory droplets, and has an incubation period of between 1 and 10 days, but commonly 3 to 4 days.⁴ The capacity of meningococcal disease to have a fulminant and rapidly fatal course in previously healthy (and usually young) individuals causes it to be greatly feared. Intensive public health follow-up is required after each single case to conduct contact tracing and to institute appropriate public health measures for contacts. As a result of all these factors, this disease causes widespread community alarm and generates significant media interest.⁹

Epidemiology

Meningococci cause both sporadic and epidemic disease throughout the world. Serogroup A disease occurs predominantly in developing populations such as those in Africa and Asia, while serogroup B is the major cause of sporadic meningococcal disease in most developed countries. Serogroup C disease has a more cyclic pattern of occurrence, and increased in incidence in the 1990s in some developed countries such as Australia and the United Kingdom.⁴ Serogroup C meningococci have also been occasionally associated with small clusters of meningococcal disease cases in schools, universities and nightclubs in Australia over the past 10 years.¹⁰⁻¹⁵

As in other temperate climates, meningococcal disease cases occurring in Australia tend to follow a seasonal trend, the majority of cases being reported during late winter and early spring. The overall notification rate of meningococcal disease to the National Notifiable Diseases Surveillance System increased gradually from 1.8 per 100 000 in 1991, to a peak of 3.5 per 100 000 in 2001, but declined to 1.8 per 100 000 in 2005.¹⁶ There are considerable differences noted in the incidence of meningococcal disease between States and Territories, with 5.4 cases per 100 000 notified from the Northern Territory to 1.9 per 100 000 reported for Queensland during 2005.¹⁶ These figures include meningococcal disease cases which were diagnosed on clinical grounds alone, and those cases that were confirmed by laboratory methods such as culture, serology or nucleic acid testing of clinical material. In 2005, 369 cases were reported nationally, of which 345 were laboratory confirmed.^{16,17} The majority of laboratory-confirmed meningococcal cases were serogroup B (73%) and serogroup C (14.5%).¹⁷ There has been a steady decline in serogroup C meningococcal disease among the 0–18 years age group since the 2003 introduction of routine meningococcal C vaccination and catch-up programs in this age group.¹⁸

Meningococcal disease can occur in any age group, but the majority of cases occur in those <5 years of age, with a secondary peak seen in the 15–24 years age group. In Australia, meningococcal disease in the <5 years age group is due predominantly to infection with serogroup B meningococci; very few cases of serogroup C meningococcal disease are now seen in this age group.¹⁷ In the 15–19 years age group, both serogroup B and C disease were seen before the introduction of the meningococcal C conjugate vaccine in 2003.

In contrast to Australia, New Zealand has, over the past 14 years, experienced an epidemic of meningococcal disease which has been almost exclusively associated with a particular strain of serogroup B (B:4:P1.7b,4).^{19,20} Meningococcal disease rates in NZ rose from 1.5 cases per 100 000 during 1989–1990 to 14.5 cases per 100 000 in 2003.¹⁹ A meningococcal B outer membrane vesicle vaccine (MeNZB™), currently being used in New Zealand, is only effective against the serotype and serosubtype of the New Zealand serogroup B strain and is not available in Australia.²⁰

Vaccines

There are 2 different types of meningococcal vaccine: the meningococcal C conjugate vaccines (MenCCV) and the tetravalent meningococcal polysaccharide vaccines (4vMenPV). The differences between these 2 types of vaccines lie in the different way that each vaccine stimulates an immune response.

Other than the New Zealand specific vaccine, there is currently no vaccine effective against serogroup B meningococcal disease although extensive research is being undertaken in this area.

CONJUGATE VACCINES

Meningococcal C conjugate vaccines (MenCCV)

- **Meningitec** – Wyeth Australia Pty Ltd (meningococcal serogroup C–CRM₁₉₇ conjugate vaccine). Each 0.5 mL monodose vial contains 10 µg *N. meningitidis* serogroup C oligosaccharide conjugated to approximately 15 µg of a non-toxic *Corynebacterium diphtheriae* CRM₁₉₇ protein; aluminium phosphate.
- **Menjugate Syringe** – CSL Biotherapies/Novartis Vaccines (meningococcal serogroup C–CRM₁₉₇ conjugate vaccine). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL dose of reconstituted vaccine contains 10 µg *N. meningitidis* serogroup C polysaccharide conjugated to 12.5–25 µg of a non-toxic *Corynebacterium diphtheriae* CRM₁₉₇ protein; 1.0 mg aluminium hydroxide. 5 or 10 monodose packs also available.
- **NeisVac-C** – Baxter Healthcare (meningococcal serogroup C–tetanus toxoid protein conjugate vaccine). Each 0.5 mL pre-filled syringe contains 10 µg *N. meningitidis* serogroup C polysaccharide conjugated to 10–20 µg of tetanus toxoid protein; 0.5 mg aluminium hydroxide. 10 or 20 monodose packs available.

In January 2003, the Australian Government commenced the National Meningococcal C Vaccination Program which provided free MenCCV to all children who turned 1 to 19 years of age during 2003. MenCCV was also added to the National Immunisation Program (NIP) schedule at 12 months of age at that time.

MenCCVs confer protection *only* against serogroup C disease. In these vaccines, an oligo- or polysaccharide antigen is chemically linked (ie. ‘conjugated’) to a carrier protein. Conjugation changes the nature of the antibody response from a T cell-independent to a T cell-dependent response. The T cell help results in improved antibody responses, especially in young children, greater functional activity, and induction of immunological memory, probably resulting in long-term protection.

In the United Kingdom, 98 to 100% of infants given 3 doses of MenCCV in a 2, 3 and 4 month schedule developed protective antibody titres after the third dose,^{21,22} but evidence of waning immunity and vaccine failures led to a booster dose being recommended for children vaccinated according to the 2, 3 and 4 month schedule of MenCCV,²³ which has now been altered to a 3-dose schedule at 3, 4 and 12 months of age.²⁴ In Australia, although some children have received MenCCV before 12 months of age, this was according to a 2, 4, 6 month schedule and there is no evidence of vaccine failure. NHMRC, therefore, does not recommend recall for a booster dose in children *previously* vaccinated before 12 months of age (unless they have inherited defects of properdin or complement, or functional or anatomical asplenia – see ‘Recommendations’ below).

In children >12 months of age, a single dose of MenCCV appears sufficient to induce protective antibody responses. In children 12–18 months of age receiving a single dose of MenCCV, 91 to 100% achieved serum bactericidal antibodies (SBA) titres $\geq 1:8$.²⁵ In older children, seroconversion rates increase with age: 96% of 3-year-olds, 98% of 4–5-year-olds, and 98% of 14–17-year-olds achieved SBA titres $\geq 1:8$ after a single dose.²⁵ In those children aged ≥ 1 year who have received only a single dose of the meningococcal C conjugate vaccine, the duration of immunity and the need for booster doses is not yet known. The Netherlands routinely vaccinates with MenCCV at 14 months of age, and data from 2002 onwards currently indicates that vaccination after the 1st birthday results in longer protection than multiple doses in infancy.²⁶

POLYSACCHARIDE VACCINES

Meningococcal polysaccharide vaccines (4vMenPV)

- **Mencevax ACWY** – GlaxoSmithKline (serogroup A, C, W₁₃₅ and Y meningococcal polysaccharide vaccine). Each 0.5 mL monodose of the reconstituted lyophilised vaccine contains 50 µg of each polysaccharide; lactose. 10-dose vials in packs of 50 contain 0.25% phenol as a preservative. Saline diluent for each vial.
- **Menomune** – Sanofi Pasteur Pty Ltd (serogroup A, C, W₁₃₅ and Y meningococcal polysaccharide vaccine). Each 0.5 mL monodose of the reconstituted lyophilised vaccine contains 50 µg of each polysaccharide; lactose.

4vMenPVs provide protection against serogroups A, C, W₁₃₅ and Y. The vaccine induces antibodies in 10 to 14 days in 90% of recipients >2 years of age. Immunity decreases markedly during the first 3 years following a single dose of vaccine, particularly in infants and young children. However, clinical protection persists for at least 3 years in school children and adults.

The duration of immunity is further complicated by the induction of immunological hyporesponsiveness to the serogroup C component following repeated vaccination with 4vMenPV, as revaccination results in a reduced antibody response compared with the primary immunisation.²⁷ This phenomenon has been noted in both children and adults.²⁸⁻³¹ The demonstration of subsequent hyporesponsiveness has led to the concern that vaccinating low-risk individuals may reduce the effectiveness of revaccination in a subsequent high-risk situation, although this has not been clinically demonstrated. This hyporesponsiveness can be overcome with MenCCV, although additional doses of the conjugate vaccine may be required in young children.^{32,33} There is little response to the serogroup C component of the 4vMenPV before 18 months of age and little response to serogroup A before 3 months of age.^{34,35}

Transport, storage and handling

Meningococcal C conjugate vaccines

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.³⁶ Storage of all MenCCVs should be at +2°C to +8°C. Do not freeze. Protect from light.

The product information for NeisVac-C states that this vaccine can be stored at +25°C for a period of up to 9 months *but must not be returned to the refrigerator*.

Meningococcal polysaccharide vaccines

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.³⁶ Store at +2°C to +8°C. Do not freeze. Protect from light. Reconstituted vaccine should be used immediately but may be stored in the refrigerator at +2°C to +8°C, and must be discarded if not used within 8 hours.

Dosage and administration

Meningococcal C conjugate vaccines

The MenCCV dose is 0.5 mL given by IM injection. Do not mix MenCCV with other vaccines in the same syringe. Experience from the use of the conjugate Hib vaccines suggests that the different brands of the MenCCVs are interchangeable. MenCCVs may be administered simultaneously with other vaccines in the NIP (see 'Variations from product information' below). MenCCVs are registered for use in Australia from 6 weeks of age.

Meningococcal polysaccharide vaccines

The 4vMenPV dose is 0.5 mL, administered by SC injection. 4vMenPVs are approved for use in Australia in children ≥2 years of age, adolescents and adults.

Administration of MenCCV after administration of 4vMenPV

There are limited data available on the length of time that should lapse before administration of MenCCV after giving 4vMenPV. The NHMRC recommends a period of 6 months before the conjugate vaccine is given.^{21,37}

Administration of 4vMenPV after administration of MenCCV

On occasion, both MenCCV and 4vMenPV are recommended (eg. asplenia). If MenCCV is given first, a period of ≥ 2 weeks should lapse before 4vMenPV is given.

Recommendations

Meningococcal C conjugate vaccines

(i) Routine vaccination

It is recommended that a single dose be given to all children at the age of 12 months.

Vaccination before 12 months of age is not recommended, except in infants with inherited defects of properdin or complement, or functional or anatomical asplenia (see (ii) below). Infants, other than those described in the circumstances below, who receive dose(s) of vaccine at < 12 months of age, should be given a further dose at 12 months of age or 4 weeks after the last dose, whichever is later. However, it is not necessary to recall older children who received 3 doses of MenCCV before 12 months of age, as there has been no evidence to date of vaccine failure in infants vaccinated according to a 2, 4, 6 month schedule (see 'Vaccines' above).

(ii) Vaccination of people at high risk for meningococcal disease

The vaccine is also recommended for:

- close (household or household-like) contacts of meningococcal disease cases due to serogroup C, > 2 months of age, who have not previously been vaccinated (refer to 'The early clinical and public health management of meningococcal disease' below),
- control of outbreaks caused by serogroup C (refer to 'The early clinical and public health management of meningococcal disease' below),
- laboratory personnel who frequently handle *N. meningitidis*, who should also receive 4vMenPV,
- those > 6 weeks of age with inherited defects of properdin or complement, or functional or anatomical asplenia. When MenCCV is given to these individuals at < 12 months of age, in addition to a booster dose of MenCCV at 12 months of age, a dose of 4vMenPV is recommended at ≥ 2 years of age.

Under the circumstances as described above, a child under the recommended age of 12 months requiring vaccination should receive doses as follows:

- Infants < 6 months of age require 2 doses of 0.5 mL, given at least 8 weeks apart, followed by a booster dose at 12 months of age.
- Children 6–11 months of age require 1 dose of 0.5 mL, followed by a booster dose at 12 months of age or 8 weeks after the first dose, whichever is later.

Meningococcal polysaccharide vaccines

Routine vaccination with 4vMenPV is not recommended. However, it is recommended in the following situations:

- people who intend travelling to parts of the world where epidemics of group A, W₁₃₅ or Y disease are frequent (a current list of those countries is available from the World Health Organization at either <http://www.who.int/ith> or <http://www.who.int/disease-outbreak-news/>),
- close (household or household-like) contacts, ≥2 years of age, of cases of serogroup A, W₁₃₅ or Y meningococcal disease,
- control of outbreaks caused by serogroup A, W₁₃₅ or Y. A Cochrane review examined the use of polysaccharide vaccine for the prevention of serogroup A meningococcal meningitis. The review assessed 8 randomised controlled trials and the protective effect from the vaccine was consistent across all the trials with a vaccine efficacy of around 95%,³⁸
- laboratory personnel who frequently handle *N. meningitidis*, who should also receive MenCCV,
- those ≥2 years of age with inherited defects of properdin or complement, or functional or anatomical asplenia, who should also receive MenCCV, and
- pilgrims attending the annual Hajj (Saudi Arabian authorities require a valid certificate of vaccination as a condition to enter the country).

A single revaccination with 4vMenPV is indicated for people at continued high risk of infection (such as those living in epidemic areas, and those with impaired immunity as defined above), particularly children first vaccinated before 4 years of age. As antibody levels decline rapidly over 2 to 3 years, revaccination should be given 3 to 5 years later. Data regarding the benefit of subsequent revaccinations with 4vMenPV are unavailable at this time.

Contraindications

Meningococcal C conjugate vaccines

The only absolute contraindications to MenCCV are:

- anaphylaxis following a previous dose, or
- anaphylaxis following any component of the vaccine

Previous serogroup C disease is not a contraindication to administration of MenCCV.

Meningococcal polysaccharide vaccines

The only absolute contraindications to 4vMenPV are:

- anaphylaxis following a previous dose, or
- anaphylaxis following any vaccine component.

Adverse events

Meningococcal C conjugate vaccines

Very common (>10%) adverse events caused by MenCCVs are pain, redness and swelling at the site of injection, fever, irritability, anorexia and headaches. There are some age-related differences in the type of adverse event following vaccination, with systemic adverse events tending to decrease with increasing age, and local adverse events tending to increase with increasing age. Headache is more likely to be reported in the adolescent age group. Serious general adverse events are rare.³⁷

Meningococcal polysaccharide vaccines

Local reactions to 4vMenPV include erythema, induration, tenderness, pain and local axillary lymphadenopathy. However, they are usually mild and infrequent. Fever and chills occur in approximately 2% (common) of young children, and may persist for 48 hours or longer, but significant general adverse events are rare.

The early clinical and public health management of meningococcal disease

Prompt diagnosis and emergency treatment of cases of suspected meningococcal disease are life-saving. If a diagnosis of meningococcal disease is suspected, the patient should be immediately given parenteral (usually IM) penicillin and transferred to hospital. The relevant Public Health Unit must be contacted as soon as possible.⁴

Table 3.12.1: Early clinical management of suspected meningococcal disease

The patient should receive immediate benzylpenicillin (usually IM).	Age <1 year	300 mg benzylpenicillin
	Age 1–9 years	600 mg benzylpenicillin
	Age ≥10 years	1200 mg benzylpenicillin
The patient should be transferred to hospital urgently.		
The relevant Public Health Unit should be notified promptly, so that appropriate public health management can be initiated.		

Guidance on the early clinical and public health management of cases of invasive meningococcal disease has been developed by the Communicable Diseases Network of Australia, and is available at http://www.health.gov.au/pubhlth/cdi/pubs/pdf/mening_guide.pdf.⁴

Contrary to popular belief, a patient with meningococcal disease is not a good transmitter of the disease. Rather, it is carrier(s) passing on the bacteria to other susceptible individuals who may cause further cases of meningococcal disease. Further cases may develop in household contacts in particular. The risk of secondary cases is greatest in the first 7 days, and may persist for many weeks after contact. The public health management of close contacts includes

information, clearance antibiotics and vaccination. Clearance antibiotics should be offered to all identified close contacts regardless of previous vaccination history. Clearance antibiotics are not recommended for healthcare workers unless they were engaged in either mouth-to-mouth resuscitation or were not wearing a mask while intubating a case.

Non-vaccinated close contacts of a proven vaccine-preventable strain of invasive meningococcal disease should be advised in writing by their local Public Health Unit to visit their usual healthcare provider at the next available opportunity to receive the appropriate vaccine.⁴

Antibiotics that reduce or eliminate nasopharyngeal carriage of *N. meningitidis* include ceftriaxone, ciprofloxacin and rifampicin.

- Ceftriaxone is administered as a single IM dose of 250 mg for adults and 125 mg for children <12 years of age. Although it is considerably more expensive, ceftriaxone has a number of advantages over rifampicin: it is more likely to eradicate pharyngeal carriage, it eliminates problems with compliance and it is the preferred chemoprophylaxis for pregnant women.
- Ciprofloxacin in a single oral dose of 500 mg is effective and safe, but it should not be given to children <12 years of age, or to pregnant women.
- Rifampicin is given to children and adults in an oral dose of 10 mg/kg (maximum dose of 600 mg) twice daily for 2 days. The recommended dose for infants <1 month of age is 5 mg/kg twice daily for 2 days. Pharyngeal carriage will be eliminated in 75 to 90% of recipients unless the strain is resistant to rifampicin. The side effects of rifampicin should be explained, including orange-red discolouration of contact lenses, urine and tears, possible interference with the contraceptive pill, and interference with the metabolism of many other drugs including warfarin, phenobarbitone and phenytoin. Rifampicin is not recommended for use in pregnant women.

A potential outbreak of meningococcal disease in an institutional or community setting is a public health emergency needing a rapid response from clinicians and public health practitioners. The decision to control an outbreak with a vaccination program should be made by the appropriate Public Health Unit, following the *Guidelines for the early clinical and public health management of meningococcal disease in Australia*.⁴ If vaccination is indicated and the organism responsible is serogroup C, MenCCV should be used in preference to 4vMenPV.

Use in pregnancy

Meningococcal C conjugate vaccines

Although no clinical study data are available on the use of MenCCV in pregnant women, it is unlikely that it would have any deleterious effect on the pregnancy. Routine pregnancy testing before vaccination is not justified.

Meningococcal polysaccharide vaccines

Studies of vaccination with meningococcal and other polysaccharide vaccines during pregnancy have not documented adverse events in either pregnant women or newborns.^{1,39,40} The number of pregnant vaccinees who received 4vMenPV as reported in the literature is small. A North American study of 109 women who received the 4vMenPV vaccine between 30 and 38 weeks' gestation reported no birth defects.³⁹ A further study of 34 pregnant women in the US who received 4vMenPV during their second and third trimester revealed no teratogenicity and the infants were assessed for 2 years after birth. No developmental abnormalities were detected.⁴⁰

Variations from product information

Meningococcal C conjugate vaccines

The product information for meningococcal C conjugate vaccines state that, under the age of 12 months, either 2 (NeisVac-C) or 3 (Meningitec and Menjugate) doses of vaccine are required. The NHMRC recommends that meningococcal C vaccination is not required before 12 months of age (unless specifically indicated).

The NeisVac-C product information states that the vaccine should not be administered with pneumococcal conjugate vaccine, hepatitis B vaccine and PRP-OMP *Haemophilus influenzae* type b vaccine unless 'medically important'. However, the NHMRC states that the vaccine may be administered simultaneously with other vaccines in the NIP. There have been recent publications citing the coadministration of MenCCV with other combination vaccines and it was found to be immunogenic and safe.^{41,42}

The product information for all 3 conjugate vaccines states that there are no data on the use of MenCCVs in lactating women, whereas the NHMRC does not consider breastfeeding in a healthy woman a reason for not vaccinating.

The Meningitec product information states that an allergic reaction following a previous dose is a contraindication to further doses, whereas the NHMRC states that only an anaphylactic adverse event following a previous dose is a contraindication.

Meningococcal polysaccharide vaccines

The NHMRC recommends revaccination with 4vMenPV within 3 to 5 years of a previous dose in the situations detailed in 'Recommendations' above. The Mencevax ACWY product information states within 2 to 3 years, and the Menomune product information gives no recommended interval before revaccination.

References

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.