



**Australian Government**

**Department of Health**

**Australian Technical Advisory Group on Immunisation  
(ATAGI) Statement**

**Advice for immunisation providers regarding the use of Bexsero<sup>®</sup>  
– a recombinant multicomponent meningococcal B vaccine (4CMenB)**

**March 2014**

- In Australia, the Therapeutic Goods Administration (TGA) included 4CMenB on the Australian Register of Therapeutic Goods on 14 August 2013. The vaccine is registered for use in persons  $\geq 2$  months of age for the prevention of invasive disease caused by serogroup B meningococci. It is available through purchase on the private market. This vaccine is not funded under the National Immunisation Program (NIP).
- Children aged  $< 5$  years, particularly infants aged  $< 1$  year, have the highest incidence of invasive meningococcal disease (IMD) caused by serogroup B meningococci (MenB). A lower, secondary peak in incidence is evident in late adolescence and early adulthood.
- Bexsero<sup>®</sup> (4CMenB) is a recombinant multicomponent meningococcal B vaccine that induces specific bactericidal antibodies against a range of MenB strains. In Australia, based on laboratory tests, about 76% of MenB strains are predicted to be covered by this vaccine, but clinical effectiveness has not yet been shown.
- MenB IMD cannot be prevented by the other meningococcal vaccines currently available in Australia, such as the meningococcal C conjugate and quadrivalent (A, C, W<sub>135</sub>, Y) vaccines, because they target other meningococcal serogroups.
- Based on their higher disease risk, 4CMenB is recommended for these groups:
  - Infants and young children, particularly those aged  $< 24$  months
  - Adolescents aged 15 to 19 years
  - Children and adults with medical conditions that place them at a high risk of IMD, such as functional or anatomical asplenia or complement component disorders
  - Laboratory personnel who frequently handle *Neisseria meningitidis*.
- For infants aged  $< 6$  months, 3 primary doses of 4CMenB plus a booster at age 12 months are recommended. Fewer doses are required for older age groups.
- 4CMenB may be given to infants at the same time as other infant vaccines that are given under the NIP, but must be given at a separate injection site. The 1st dose of 4CMenB may be administered as early as 6 weeks of age to align with the NIP infant schedule.
- In clinical trials, injection site and systemic reactions were very common in children after receiving 4CMenB. Fever was the most notable systemic reaction in children aged 2 to 12 months. Among infants, systemic reactions, including fever and high fever, were more common following 4CMenB when it was given concurrently with other vaccines commonly given to infants, compared to when 4CMenB and other routine vaccines were given separately.
- ATAGI recommends the prophylactic use of paracetamol with every dose of 4CMenB administered to children  $< 2$  years of age, to reduce the probability and severity of fever that may develop following immunisation with 4CMenB. The 1st dose of paracetamol (15 mg/kg per dose) is recommended within the 30 minute period prior to vaccination or as soon as practicable afterwards, regardless of the presence of fever. This can be followed by 2 more doses of paracetamol given 6 hours apart.

## Meningococci and meningococcal disease

Meningococcal disease is caused by the bacterium *Neisseria meningitidis*, also known as meningococcus. While uncommon, invasive meningococcal disease (IMD) is a serious infection which usually presents as meningitis or septicaemia (or both).

Individuals with certain medical conditions are at a higher risk for IMD. This includes persons with anatomical or functional asplenia or deficiencies in the terminal complement pathway. Other risk factors for IMD include exposure to smokers, living in crowded conditions, a history of a preceding illness, and intimate kissing with multiple partners.

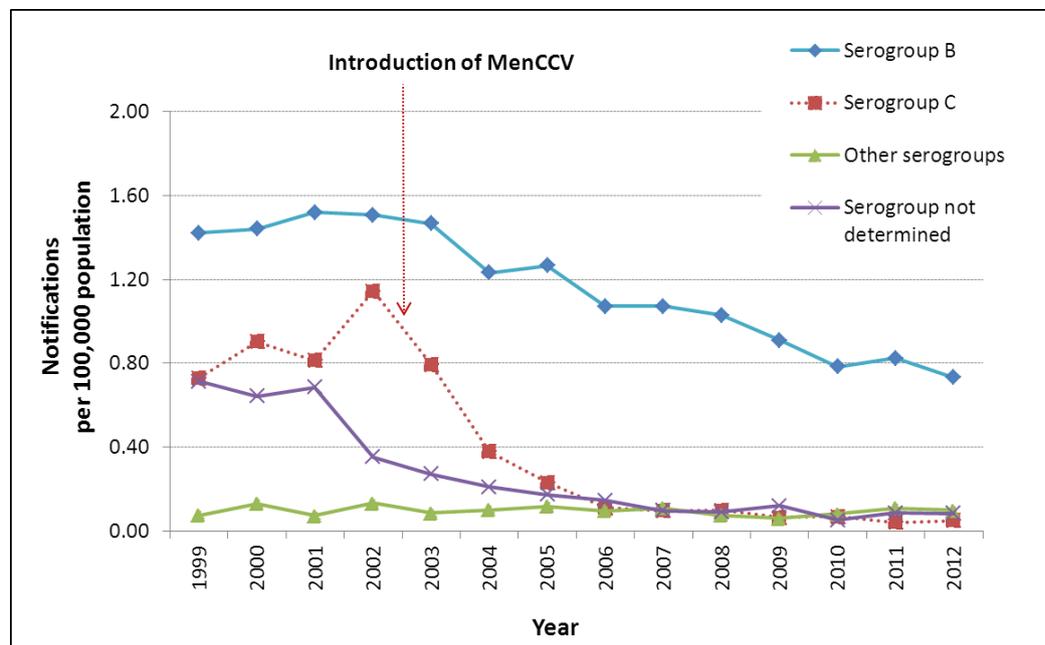
There are several serogroups of meningococci. Globally, serogroups A, B, C, W<sub>135</sub> and Y are the most common causes of IMD. The meningococcal C conjugate vaccine has been used in the National Immunisation Program (NIP) since 2003 and has been highly effective in reducing IMD caused by serogroup C meningococci.

More information regarding meningococcal disease is available in Chapter 4.10 of *The Australian Immunisation Handbook*, 10th edition ([www.immunise.health.gov.au](http://www.immunise.health.gov.au)).<sup>1</sup>

### Invasive meningococcal disease caused by serogroup B meningococci

As shown in Figure 1, serogroup B meningococcus (MenB) has been the predominant serogroup causing IMD in Australia for the past decade, even before, but particularly since, the meningococcal C conjugate vaccine program commenced in 2003. In 2011–2012, MenB IMD represented approximately 84% of all IMD in patients in whom the IMD serogroup was determined.

**Figure 1. Notification rates of confirmed invasive meningococcal disease, by year and serogroup (excluding non-groupable isolates), Australia, 1999–2012\***



\* Data source: National Notifiable Diseases Surveillance System  
MenCCV: Meningococcal C conjugate vaccine

The highest incidence and case fatality rate (CFR) of MenB IMD are observed among children aged <5 years (5.7 cases per 100,000 population in 2006–2011; CFR 4.5%), particularly infants aged <1 year (14.0 cases per 100,000 population; CFR 5.8%). There is a lower, secondary peak in late adolescence and early adulthood (2.8 cases per 100,000 population aged 15–19 years; CFR 2.9%).

It is important to note that IMD disease incidence fluctuates naturally and can be up to several times higher during an epidemic period of IMD. However, a similar age distribution of IMD is typically observed during epidemics.

Notification rates of MenB IMD are higher in young Aboriginal and Torres Strait Islander children aged <5 years, especially infants, compared with non-Indigenous children.

Some studies suggest that severity, mortality and outcome may vary with the serogroup causing IMD and the patient's age. In Australia, mortality among patients with IMD caused by MenB is approximately 5 to 10% and is higher in infants than in older children or adolescents. Approximately 36% of survivors of MenB IMD aged ≤13 years develop long-term sequelae, which can include hearing impairment, impairment in intellectual development, psychological disorders, amputation of limbs or digits, and deficits in executive function and memory.<sup>2</sup>

## Meningococcal B vaccines

Meningococcal vaccines that specifically target a single epidemic MenB strain have been developed and used successfully in several countries, including New Zealand, in response to MenB epidemics. However, they are not suitable for routine use in Australia where there are many different circulating strains of MenB.

Recent MenB vaccine development has focused on antigens that are highly conserved across different MenB strains. Bexsero<sup>®</sup>, a recombinant multicomponent meningococcal B vaccine (4CMenB), was registered for use in Australia on 14 August 2013. The four major antigenic components of the 4CMenB vaccine are:

- Factor H binding protein (fHBP) – 50 µg in each 0.5 mL dose
- Neisserial adhesion A (NadA) – 50 µg in each 0.5 mL dose
- Neisserial heparin-binding antigen (NHBA) – 50 µg in each 0.5 mL dose
- Outer membrane vesicle (OMV) with Por A P1.4, derived from strain NZ98/254 – 25 µg in each 0.5 mL dose.

Other ingredients contained in 4CMenB include aluminium hydroxide, sodium chloride, histidine and sucrose. There may be traces (less than 0.01 µg per dose) of residual kanamycin. The tip cap of the syringe may contain traces of natural rubber latex.

As MenB IMD is a rare disease, it is not feasible to directly assess the efficacy of 4CMenB in randomised clinical trials. Instead, it has been demonstrated that 4CMenB can induce specific bactericidal antibodies in vaccinated subjects.

It should be noted that 4CMenB cannot be expected to provide protection against all circulating MenB strains, since some strains will not express any of the protein antigens contained in the vaccine. Based on laboratory tests, it is predicted that the majority (approximately 76%) of disease-causing MenB strains in Australia express at least one of the vaccine antigens, which would make them susceptible to effective killing by vaccine-induced antibodies.

Meningococcal vaccines that target other serogroups, including the meningococcal C conjugate vaccine and the quadrivalent (A, C, W<sub>135</sub>, Y) meningococcal vaccines, are available – see Chapter 4.10 of *The Australian Immunisation Handbook*, 10th edition.<sup>1</sup>

## Transport, storage and handling

Transport according to the *National Vaccine Storage Guidelines: Strive for 5* (2nd edition).<sup>3</sup> Store in the refrigerator at +2°C to +8°C. Protect from light. Do not freeze.

## Dosage and administration

The dose for 4CMenB is 0.5 mL to be given by intramuscular injection. The number of doses required depends on the age at commencement of the 4CMenB vaccination course (see Table 1).

It is essential that immunisation service providers ensure there is appropriate documentation of all vaccinations in clinical files and personal health records. Vaccination details of children aged <7 years who have received 4CMenB should also be reported to the Australian Childhood Immunisation Register.

4CMenB is registered for use in persons  $\geq 2$  months of age. However, 4CMenB may be given to infants from 6 weeks of age to align with the schedule for other infant vaccines given under the NIP (see *Variations from product information* below).

4CMenB may be administered concurrently, at separate injection sites, with other infant vaccines in the NIP schedule at 2, 4 and 6 months of age. These vaccines include the diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-*Haemophilus influenzae* type b combination vaccine (DTPa-hepB-IPV-Hib, Infanrix hexa<sup>®</sup>), the 13-valent pneumococcal conjugate vaccine (13vPCV, Prevenar 13<sup>®</sup>) and either of the rotavirus vaccines. No significant interference in immunogenicity is expected when these vaccines are administered concurrently with 4CMenB. 4CMenB may be administered concurrently with other vaccines in the NIP schedule at 12 months of age. This includes the measles-mumps-rubella (MMR) vaccine, *Haemophilus influenzae* type b-meningococcal C conjugate (Hib-MenC) vaccine, and 13vPCV or hepatitis A vaccine for those who are recommended to receive these vaccines at this age.

## Recommendations

Based on their higher disease risk, 4CMenB is recommended for:

- Infants and young children, particularly those aged <24 months
- Adolescents aged 15 to 19 years
- Children and adults with medical conditions that place them at a high risk of IMD, such as functional or anatomical asplenia or complement component disorders (see Chapter 4.10 of *The Australian Immunisation Handbook*, 10th edition<sup>1</sup>)
- Laboratory personnel who frequently handle *Neisseria meningitidis*.

4CMenB is also recommended for all children and young adults who wish to reduce their risk of MenB IMD.

The specific OMV-based meningococcal B vaccine previously used in New Zealand, which only targeted the epidemic strain in New Zealand, would not provide protection against a broad spectrum of other MenB strains. Individuals who have previously received this vaccine in New Zealand can receive 4CMenB.

## Recommended schedule of 4CMenB

**Table 1. Recommended schedule of 4CMenB by age group**

Age at commencement of vaccine course	Primary immunisation	Interval between primary doses	Age for booster dose
2 months*	3 doses, delivered at ~2*, 4 and 6 months of age; (intervals ~2 months, at least 1 month)		12 months
3 to 5 months	3 doses	1–2 months	12 months
6 to 11 months	2 doses	2 months	12 months, or 2 months after previous dose, whichever is later
12 months to 10 years	2 doses	2 months	No booster required <sup>†</sup>
11 years and above <sup>‡</sup>	2 doses	1–2 months	No booster required <sup>†</sup>

\* 4CMenB is registered for use in persons  $\geq 2$  months of age; however, the 1st dose of 4CMenB may be administered as early as 6 weeks of age to align with the NIP infant schedule.

<sup>†</sup> The need for a booster dose for this age group is as yet uncertain.

<sup>‡</sup> There are currently no data on the use of 4CMenB in individuals aged over 50 years, however, based on first principles, ATAGI recommends that 4CMenB can be used in older persons who are at high risk of IMD.

### Recommendations regarding use of paracetamol to reduce fever incidence

ATAGI recommends prophylactic use of paracetamol with every dose of 4CMenB administered in children  $< 2$  years of age. This is because of the relatively high incidence of fever, particularly an increased risk of fever (including high fever) in infants who receive 4CMenB concurrently with other NIP vaccines (see *Adverse events* below). The 1st dose of paracetamol (15 mg/kg per dose) is recommended within the 30 minute period prior to vaccination or as soon as practicable afterwards, regardless of the presence of fever. This can be followed by 2 more doses of paracetamol given 6 hours apart, regardless of the presence of fever.

This recommendation is based on results from a clinical trial of 4CMenB, showing that prophylactic use of paracetamol in infancy reduced the incidence and severity of fever without significantly affecting the immunogenicity of either 4CMenB or other vaccines that were given concurrently. This recommendation of prophylactic use of paracetamol has been extended to include young children in the second year of life, to reduce the chance of developing high fever.

If prophylactic administration of paracetamol in this circumstance is not feasible or not given, paracetamol as required for management of fever or other symptoms, such as injection site pain, can be provided at the discretion of parents/carers and according to the recommendations contained in Chapter 2.3 (page 91) of *The Australian Immunisation Handbook*, 10th edition.<sup>1</sup> The dose of paracetamol for an infant or child  $\leq 12$  years of age is 15 mg/kg per dose, up to a maximum of 60 mg/kg per day in four divided doses. However, paracetamol should not be given for more than 48 hours without seeking medical advice.

This recommendation for prophylactic use of paracetamol with 4CMenB administration is an exception to a general recommendation in *The Australian Immunisation Handbook*, 10th edition<sup>1</sup> where routine use of paracetamol at the time of or immediately after vaccination (with any vaccines, other than 4CMenB) is *not* recommended unless fever  $> 38.5^{\circ}\text{C}$  or pain at the injection site develops.

## Contraindications

The only absolute contraindications to 4CMenB are:

- Anaphylaxis following a previous dose of 4CMenB or any other meningococcal vaccine
- Anaphylaxis following any vaccine component.

Previous meningococcal disease, regardless of the serogroup, is *not* a contraindication to administration of 4CMenB.

## Adverse events

Any serious or unexpected adverse event following immunisation should be reported promptly by providers via the appropriate route, as per the reporting protocols of your state or territory.

Parents/carers should also be encouraged to notify their immunisation provider of any untoward medical occurrence that follows immunisation. For more information, refer to Chapter 2.3 of *The Australian Immunisation Handbook*, 10th edition.<sup>1</sup>

## Fever and prophylactic use of paracetamol

### *Incidence of fever following 4CMenB*

Fever was the most notable systemic reaction in both infants and children aged 2 to 12 months in clinical trials. Temperatures were highest 6 hours after vaccination, decreased on day 2, and generally subsided by day 3.<sup>4</sup> The frequency of fever with 4CMenB when given concurrently with other infant vaccines, specifically DTPa-hepB-IPV-Hib and 7-valent pneumococcal conjugate vaccine (7vPCV), was higher than that for other vaccines or 4CMenB alone.<sup>4,5</sup> This was demonstrated in one clinical trial<sup>5</sup> as shown in Table 2.

**Table 2. Proportion (%) of infants reporting fever within 7 days after at least 1 of the 3 infant doses of 4CMenB, by vaccine recipient group**

Axillary temperature	Routine vaccines only	4CMenB only	Concurrent vaccines (routine + 4CMenB)
≥38°C	23–36%	26–41%	51–62%
≥39°C	3–4%	4–8%	10–15%

### *Effect of paracetamol*

Another clinical trial<sup>6,7</sup> in infants has shown that prophylactic use of paracetamol reduced the incidence and severity of fever without significantly affecting the immunogenicity of either 4CMenB or other routine vaccines when these vaccines were given concurrently (Table 3).

**Table 3. Proportion (%) of infants reporting fever with vs without prophylactic paracetamol**

Temperature	Proportion of infants reporting fever	
	With prophylactic paracetamol	Without prophylactic paracetamol
Within 7 days after a dose of 4CMenB		
≥38.5°C	39%	69%
≥39.5°C	3%	8%
Within 6 hours of 1st dose of 4CMenB at 2 months of age*		
≥38.5°C	<15%	>40%
≥39.5°C	Substantially lower with the use of prophylactic paracetamol*	

\* Values estimated from graphs provided as summary of the clinical study results<sup>7</sup>

### ***Booster dose at 12 months of age***

Fever and other systemic reactions are less common following the booster dose at 12 months of age, compared with doses given in infancy. In the large phase 3 clinical trial, temperatures of  $\geq 38^{\circ}\text{C}$  within 6 hours were reported in 32% (248/783) of children when 4CMenB was administered alone; this was similar to when 4CMenB was co-administered with the measles-mumps-rubella-varicella (MMRV) vaccine (31%; 233/761).<sup>4</sup> In the latter group, about 25% also had fever peaking around day 9 after vaccination, characteristic of fever associated with the MMRV vaccine. There is no trial data for co-administration of 4CMenB with either the MMR or Hib-MenC vaccine. It is expected that when 4CMenB is administered concurrently with the MMR and Hib-MenC vaccines at 12 months of age, there could be two periods after immunisation when fever is most likely to occur: firstly within the first 3 days, associated with receiving 4CMenB, and secondly about 5–12 days after immunisation, related to the MMR vaccine.

### ***Other adverse events***

In one phase 3 clinical trial in infants, where 4CMenB was given concurrently with DTPa-hepB-IPV-Hib and 7vPCV at age 2, 4 and 6 months, local reactions due to 4CMenB were common and included injection site tenderness (87% of participants, with 29% being severe), erythema (83%), induration (77%) and swelling (47%). The likelihood of an injection site reaction peaked on the first day after vaccination, and declined substantially by day 2.<sup>4</sup> The commonest systemic reactions were irritability (93%), sleepiness (87%), unusual crying (85%) and change in eating habits (72%). These local and systemic reactions were reported less often following the booster dose of 4CMenB at 12 months of age.<sup>4</sup>

In infants, systemic reactions occurred more often following 4CMenB when it was given concurrently with other vaccines commonly given to infants, specifically DTPa-hepB-IPV-Hib and 7vPCV, compared with when 4CMenB and other vaccines were given separately.<sup>5</sup> Common local reactions at the 4CMenB injection site occurred with similar frequencies regardless of whether the infants received other routine infant vaccines concurrently, but were more likely than reactions at the DTPa-hepB-IPV-Hib injection site in those who did not receive 4CMenB.<sup>5</sup>

In the clinical trials of 4CMenB, other rare adverse events, such as Kawasaki syndrome, were observed following immunisation in a small number of clinical trial participants; however, a causal relationship with 4CMenB has not been established.

Adverse reactions to 4CMenB were less commonly reported among adolescents and adults compared with infants. The most commonly reported reactions for adolescents were injection site reactions (>90%) including pain (86% of 4CMenB vs 60% of placebo recipients), malaise (51% vs 30%) and headache (42% vs 27%). High fever was less common in adolescents (4% reported temperature  $\geq 38^{\circ}\text{C}$ , 1% reported temperature  $\geq 39^{\circ}\text{C}$ ) than in infants.<sup>8</sup>

## **Use in pregnancy and breastfeeding**

Currently, there is no clinical data available on the effects of exposure to 4CMenB during pregnancy. Information on the safety of the vaccine during lactation is also not available. A benefit-risk assessment should be undertaken before making the decision to immunise a pregnant or breastfeeding woman.

## **Variations from product information**

The 4CMenB vaccine is registered for use in individuals 2 months of age and older. However, the 1st dose of infant vaccines in the NIP schedule can be given to infants as early as 6 weeks of age. ATAGI advises that the 1st dose of 4CMenB may also be administered concurrently with other infant vaccines from 6 weeks of age to align with the routine infant schedule. However, there have been no data collected in clinical trials specifically regarding the safety and immunogenicity of 4CMenB when a 1st dose is given at 6 weeks of age. If the 1st doses of these NIP vaccines and 4CMenB are given at 6 weeks of age, the next scheduled doses should still be given at 4 and 6 months of age.

## References

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