Changes to the recommended use of meningococcal B vaccines in people at increased risk of meningococcal B disease

Plain-language summary

Meningococcal disease is a very rare but very serious infection caused by strains of the bacterium called *Neisseria meningitidis*. It can affect people of any age, but most infections occur in young children, older adolescents and young adults. Symptoms appear suddenly and people can die very quickly without medical help. People who survive the disease can have long-term effects, including:

- scarring and loss of fingers, toes, arms or legs
- deafness
- damage to the brain and nervous system.

Vaccination is the best protection against meningococcal disease. There are 2 types of meningococcal vaccines:

- one type of vaccine protects against meningococcal types A, C, W and Y (MenACWY vaccine)
- one type of vaccine protects against meningococcal type B (MenB vaccine).

The recommendations for MenB vaccines are changing. The new recommendations are for a booster dose of MenB vaccine for:

- people who have certain medical conditions that increase their risk of meningococcal disease
- laboratory workers who have ongoing exposure to the bacteria that causes meningococcal disease.

This will give longer-lasting protection to people who are most at risk of disease.

There are no changes to the routine schedule for meningococcal vaccines in people of all ages who are not immunocompromised.

Summary of revised recommendations

The following recommendations are proposed to have updates to their supporting information to recommend a single booster dose of MenB vaccine in people with medical conditions that increase their risk of meningococcal disease, and people with ongoing occupational risk of exposure:

- People with medical conditions that increase their risk of meningococcal disease are strongly recommended to receive MenACWY and MenB vaccines
- Laboratory workers who frequently handle *Neisseria meningitidis* are strongly recommended to receive MenACWY and MenB vaccines

- Any person from 6 weeks of age who wants to protect themselves against meningococcal disease is recommended to receive MenACWY vaccine and MenB vaccine

Background

The Australian Technical Advisory Group on Immunisation (ATAGI) advises the Australian Government on clinical recommendations for vaccinations. ATAGI is proposing changes to the recommendations for the use of meningococcal B (MenB) vaccines.

The proposed changes reflect the current best clinical practice to prevent meningococcal disease. The revised recommendations will be published online in the Australian Immunisation Handbook. Information relating to the GRADE assessment will be published on the National Centre for Immunisation Research and Surveillance (NCIRS) website.

Meningococcal disease

Meningococcal disease is caused by strains of the bacterium called *Neisseria meningitidis*. It spreads when people are in very close contact for a long time with a person who carries the bacterium or is infected.

Invasive meningococcal disease (IMD) is a serious and life-threatening infection. It can affect people of any age. Symptoms appear suddenly and people can die very quickly without medical help. People who survive the disease can have long-term effects including scarring, loss of digits or limbs, deafness, and damage to the brain and nervous system.

Meningococcal disease is very rare in healthy people, but some people have an increased risk of disease. This includes laboratory workers who are in contact with the bacteria that causes meningococcal disease, and people with the following specified medical conditions:

- complement deficiency
- functional or anatomical asplenia
- HIV
- haematopoietic stem cell transplant
- undergoing treatment with a medicine called eculizumab.

There are several subtypes of meningococcal bacteria, which are each given different letters of the alphabet. The main types seen in Australia are B, W and Y.

Meningococcal vaccines

The risk of meningococcal disease can be reduced through vaccination. Different vaccines are needed to protect against the different types of meningococcal disease. In Australia, we have a vaccine for meningococcal B (MenB vaccine) and a combination vaccine for meningococcal A, C, W and Y (MenACWY vaccine). There are 2 brands of MenB vaccine in Australia, called Bexsero and Trumenba.

A primary course of meningococcal vaccines is provided free under the National Immunisation Program (NIP) for certain population groups in the following schedule:

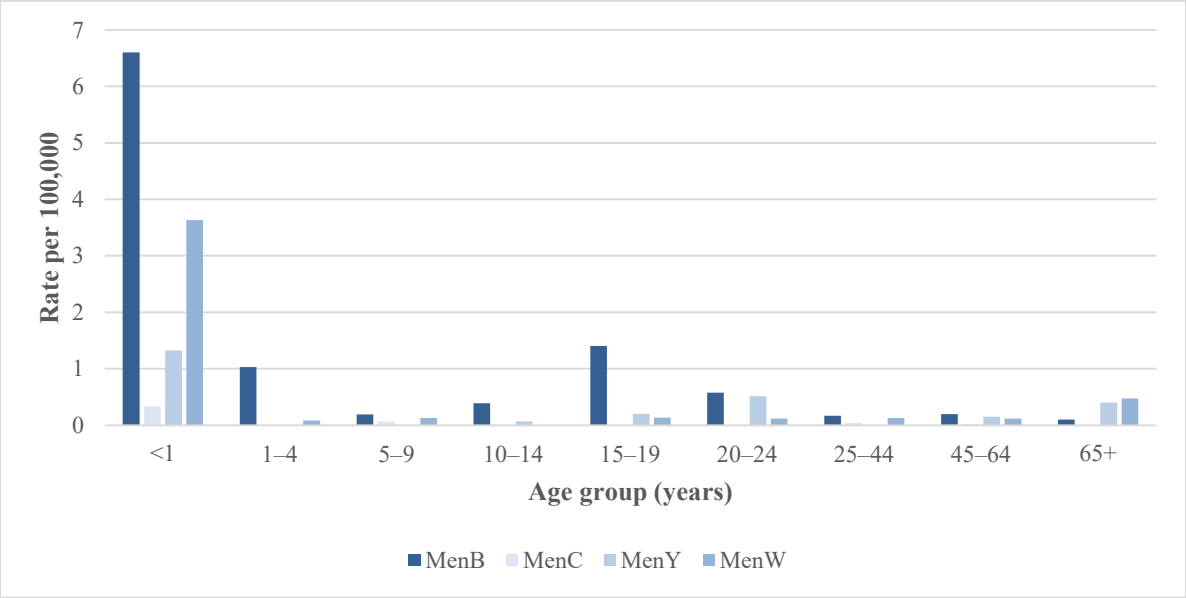
- All children can receive MenACWY vaccine at 12 months of age, and at 14–16 years of age through school programs.
- Aboriginal and Torres Strait Islander children can also receive MenB vaccine at 2, 4 and 12 months of age, with an additional dose at 6 months of age for children with specified medical conditions.
- People of all ages can receive MenACWY and MenB vaccines if they have asplenia or hyposplenia, complement deficiency, or are undergoing treatment with eculizumab.

South Australia also has a state-funded MenB vaccination program, providing free vaccine for all infants at 6 weeks, 4 months and 12 months of age and all students in Year 10.

Rationale for updating recommendations

In healthy people, disease epidemiology suggests that the highest period of risk for MenB disease is in children aged <5 years, with a subsequent peak in adolescents and young adults aged 15–24 years. Numbers of cases have decreased between 2002 and 2020, despite no widespread vaccination program in healthy people.[1-6]

Figure 1 Notification rates of laboratory-confirmed invasive meningococcal disease by age group and serogroup, 2019



Source: Lahra et al.[6]; ABS[7]

In people with certain medical conditions, the risk of invasive meningococcal disease is much higher than in healthy people – up to 10,000 times higher in people with complement deficiency.[8-11] People such as microbiology laboratory workers can be at occupational risk of exposure to *N. meningitidis*.

The Australian Immunisation Handbook recommends booster doses of MenACWY vaccine for people at increased risk or ongoing risk of meningococcal disease, but does not currently include recommendations for booster doses of MenB vaccine.

ATAGI proposes the following changes to the use of MenB vaccines in Australia to help protect people who are at greatest risk of disease.

Recommendations with updated supporting information

The wording of the following recommendations has not changed, but the supporting information has been updated to recommend a single booster dose of MenB vaccine for people at ongoing increased risk of invasive meningococcal disease — that is, people with specified medical conditions and laboratory workers at ongoing occupational risk. The timing of the booster dose depends on the vaccine brand and the person's age when they completed their primary schedule.

Changes to the current recommendations are shown below in red underline and strikethrough.

Recommendation: People with medical conditions that increase their risk of meningococcal disease are strongly recommended to receive MenACWY and MenB vaccines

People with medical conditions specified in List. Specified medical conditions associated with increased risk of invasive meningococcal disease are strongly recommended to receive MenACWY and MenB vaccines.

This includes:

- a full primary course of MenACWY vaccine, with ongoing booster doses
- a full primary course of MenB vaccine, with a single booster dose

People with these specific medical conditions have a higher risk of invasive meningococcal disease. They are recommended to receive extra doses compared with people who do not have these conditions.

The number of doses needed depends on the vaccine brand used and the person's age when they start the vaccine course.

For people aged ≥2 years receiving MenACWY vaccine there is no brand preference: Menveo, Nimenrix or MenQuadfi can be given.

In the case of MenB vaccine, there is no preference for either Bexsero or Trumenba for people aged ≥10 years. For people aged <10 years, Bexsero is the only option as it is the only ~~registered~~ MenB vaccine registered for use in this age group and available in Australia.

Bexsero and Trumenba are not interchangeable for primary or booster vaccines. The same vaccine should be used for ~~both~~ all primary vaccine doses, and the same vaccine should be used for a booster dose.

Regular booster doses are recommended ~~required~~ for MenACWY vaccines. ~~but not~~ A single booster dose is recommended for MenB vaccines.

(Text that is not changing has been omitted here.)

Table. Recommendations for MenB vaccine for people with a specified medical condition that increases their risk of invasive meningococcal disease

Age at start of vaccine course	MenB vaccine brand	Dose requirements for people with a specified medical condition associated with increased risk of meningococcal disease
6 weeks to 5 months	Bexsero	4 doses (8 weeks between doses; 4th dose at 12 months of age or 8 weeks after 3rd dose, whichever is later)
6–11 months	Bexsero	3 doses (8 weeks between 1st and 2nd doses; 3rd dose at 12 months of age or 8 weeks after 2nd dose, whichever is later)
12 months to 9 years	Bexsero	2 doses (8 weeks between doses)
≥10 years	Bexsero	2 doses (8 weeks between doses)
	Trumenba	3 doses (at intervals of 0, 1 and 6 months)
Booster doses for all ages	Bexsero	For people with ongoing increased risk of invasive meningococcal disease who completed the primary series at: • <7 years of age — single booster dose 3 years after completing the primary schedule • ≥7 years of age — single booster dose 5 years after completing the primary schedule
	Trumenba	For people with ongoing increased risk of invasive meningococcal disease, single booster dose 5 years after completing the primary schedule

(Text that is not changing has been omitted here.)

Recommendation: Laboratory workers who frequently handle *Neisseria meningitidis* are strongly recommended to receive MenACWY and MenB vaccines

Laboratory workers who are at occupational risk of exposure to *Neisseria meningitidis* are strongly recommended to receive vaccines against all vaccine-preventable meningococcal serogroups. Specifically:

- 1 dose of MenACWY vaccine
- 2 doses of MenB vaccine

There is no preference for either brand of MenACWY vaccine – Menveo, Nimenrix or MenQuadfi – for laboratory workers.

There is no preference for either brand of MenB vaccine — Bexsero or Trumenba — as a primary course for laboratory workers.

Bexsero and Trumenba are not interchangeable for primary or booster vaccines. The same vaccine should be used for ~~both~~ all primary vaccine doses, and the same vaccine should be used for a booster dose.

Booster doses

People with ongoing occupational risk of exposure ~~risks~~ are recommended to receive:

- a MenACWY booster dose every 5 years

- a single MenB booster dose 5 years after completing the primary schedule

(Text that is not changing has been omitted here.)

Recommendation: Any person from 6 weeks of age who wants to protect themselves against meningococcal disease is recommended to receive MenACWY vaccine and MenB vaccine

(Text that is not changing has been omitted here.)

Booster doses

Healthy people who have completed a primary course of MenACWY or MenB vaccines do not need booster doses.

People at ongoing increased risk of meningococcal disease are recommended to receive booster doses:

- MenACWY — regular booster doses for certain special risk groups. See People with medical conditions that increase their risk of invasive meningococcal disease, Travellers and Laboratory workers
- MenB — a single booster dose for certain special risk groups. See People with medical conditions that increase their risk of invasive meningococcal disease and Laboratory workers

(Text that is not changing has been omitted here.)

Evidence for the updated recommendations

GRADE methods

Evidence on benefits and harms of MenB booster doses was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methods. The primary research question was 'Should people previously vaccinated with a MenB vaccine primary series receive a booster MenB vaccination?' Populations were separated into those at standard background risk of IMD (that is, healthy people with no factors that increase their risk) and those at increased background risk of IMD (due to medical conditions or occupational risk). Studies were included if they used either Bexsero or Trumenba as a booster dose, with a comparator of no booster dose.

The benefits outcomes considered for each vaccine and population were:

- short-term immunogenicity — proportion of participants with hSBA titre ≥1:4 for Bexsero or ≥1:8–1:16 (the lower limit of quantitation [LLOQ] of the assay, depending on the test strain) for Trumenba at 1 month after the booster dose. hSBA titre is a measure of serum bactericidal activity using human complement and is a correlate of protection against clinical disease
- persistence of immunogenicity — proportion of participants with hSBA titre ≥1:4 for Bexsero, or the LLOQ for each test strain for Trumenba, at 12–24 months after the booster dose
- geometric mean ratio (GMR) of antibodies after receiving the booster dose compared with before receiving the booster dose.

The harms outcomes considered for each vaccine and population were:

- local adverse events
- systemic adverse events
- unsolicited adverse events
- severe adverse events
- fever ≥38°C.

The certainty of the evidence for each outcome was determined by assessing the study design, risk of bias, inconsistency, indirectness and imprecision.

GRADE results

Safety and immunogenicity data were included in the assessment from 7 observational studies on Bexsero,[12-18] and 1 observational study on Trumenba.[19]

All studies on booster doses of MenB vaccines were in healthy people, and all studies reported immunogenicity data. There were no studies on clinical outcomes (that is, no studies assessed the risk of meningococcal infection) after vaccination, due to the rarity of the condition. No studies evaluated the effect of booster doses of MenB vaccines in people with medical conditions that increase their risk of meningococcal disease.

Booster dose immunogenicity

Studies showed a moderate effect of a booster dose after 1 month (short-term immunogenicity) using hSBA titre as a correlate of protection. The proportion of study participants with hSBA titre ≥1:4 or the LLOQ at 1 month after a booster dose was 70–100% in infants aged <2 years, and 82–100% in participants aged >2 years. The increase in hSBA titre varied in magnitude depending on the test strain and the degree of waning before the booster dose.[12-19]

Data on persistence of immunogenicity are limited to up to 26 months after the booster. The proportion of study participants with hSBA titre ≥1:4 or the LLOQ was 17–100% after 24 months in infants aged <2 years, 45–100% after 12 months in participants aged ≥2 years, and 58–83% after 26 months in participants aged 12–22 years. The rate of waning of antibody titres appeared to vary by strain, and may be similar to or slower than waning of antibody titres after primary vaccination.[16-19]

GMRs in participants aged <2 years after booster vaccination (compared with before booster vaccination) ranged from 3.25 to 509. In participants aged ≥2 years, GMRs ranged from 4.69 to 525. GMRs also appeared to vary by strain.[14-18]

Certainty of the evidence for immunogenicity was assessed as low for people with standard background risk and very low for people at increased risk. This was due to the absence of studies of boosters in populations at increased risk of IMD, small study sizes, non-randomised observational studies, and evaluation of single-arm data.

There is additional uncertainty in how immunogenicity findings correlate to clinical benefit against serogroup B meningococcal disease. The correlation of hSBA titre ≥1:4 with clinical protection from disease is better established for serogroup C, but there is limited evidence of

its applicability for serogroup B disease.[20,21] However, inferring vaccine efficacy from immunogenicity data has generally been required due to the rarity of this disease. People at increased risk of IMD are likely to consider vaccination worthwhile even when evidence of protection is based only on immunogenicity rather than clinical outcomes.

Booster dose safety

Local and systemic adverse events were very common after a booster dose but were similar to those seen after primary vaccination in vaccine-naive cohorts within the booster studies. Adverse events were mostly mild or moderate in severity.[12-19] No serious vaccine-related adverse events were reported in the booster studies.

Booster dose timing

No studies directly assessed the optimal timing of booster doses.

In the general population, data on vaccine effectiveness suggest that protection against infection after primary vaccination lasts for at least 2 years in infants,[22] and slightly longer in older children and adolescents.[23,24] Immunogenicity data suggest early waning of the proportion with hSBA ≥1:4 or 1:5 (the proposed correlate of protection) from 12–24 months after completion of the primary course in clinical trials.[25,26]

Immunogenicity after primary vaccination with Bexsero is preserved in children with asplenia or hyposplenia, but there is a trend towards lower SBA titres in children with complement deficiency,[27] and decreased serum bactericidal activity of the post-vaccination serum.[28] No evidence is available about the duration of protection after a primary schedule in people at increased medical risk of IMD. The timing of MenB booster doses is recommended to align with the timing of MenACWY vaccine boosters to simplify implementation.

Balance of effects and other considerations

Overall, the GRADE assessment found the balance of effects *was likely to favour* a MenB booster dose for people at standard risk, and *would favour* a MenB booster dose for people at increased risk of meningococcal disease. There is evidence of a moderate effect on protective immune responses, and adverse events occurred at rates similar to those following primary vaccination and were generally non-severe.

All the studies were conducted in healthy participants at standard risk of meningococcal disease and showed a moderate benefit of a booster dose. However, given the very low incidence of meningococcal B disease in the general healthy population, there is insufficient certainty of the benefit for a routine recommendation of booster doses in this population. The recommendation that booster doses are not routinely required in healthy people has therefore not been changed.

For people with medical conditions that increase their risk of meningococcal disease, and for people at ongoing occupational risk of exposure, the benefits of a booster dose are likely to outweigh any risks. This is because of the substantially increased risk of disease in these groups. Data on immunogenicity after primary vaccination with Bexsero show that children who are immunocompromised mount an immune response to the vaccine,[27] and this is expected to also be the case following a booster dose.

The recommended timing of the booster dose (3 years after completing the primary schedule for people aged <7 years, and 5 years after completing the primary schedule for people aged ≥7 years) is in line with data on waning protection after primary vaccination. This also aligns with the recommended timing of booster doses for MenACWY vaccine, which is expected to simplify program delivery.

A single booster dose of MenB vaccine is recommended because the evidence is not sufficient to assess the value of multiple booster doses.

Additional information to be included in the Australian Immunisation Handbook

The proposed updates to the meningococcal chapter of the Handbook will also include updated information on MenACWY vaccines. This is because Menactra (one brand of MenACWY vaccine) is being phased out and is no longer widely available.

MenQuadfi is a newly registered alternative meningococcal vaccine that provides protection against meningococcal disease caused by the meningococcal subgroups A, C, W, and Y. It is registered and suitable for use in people aged ≥12 months. MenQuadfi was licensed for use in Australia in October 2020 and is available on private prescription. It should be administered as a single 0.5 mL injection. Clinical trials have shown that MenQuadfi is a safe and effective vaccine.[29-32]

There is no preference for the use MenQuadfi, Menveo or Nimenrix for the prevention of meningococcal ACWY disease in people aged ≥12 months.

Benefits

There are 2 key benefits from the updated recommendations:

- For people at increased risk of meningococcal disease (as a result of medical conditions or ongoing occupational exposure risk), a booster dose of MenB vaccine is likely to prolong protection against disease.
- Aligning recommendations for MenB vaccine boosters to current MenACWY vaccine boosters will simplify messaging to the public and to immunisation providers. People who require both meningococcal vaccines can receive them at the same time, which will decrease the likelihood of booster doses being missed.

Potential risks

The potential risks that may arise from the updated recommendations include the following:

- Local and systemic adverse events (including injection site redness, tenderness, pain, fever and headache) after a booster dose. These adverse events are generally mild and resolve quickly after vaccination.
- Studies of mixed schedules of Bexsero and Trumenba MenB vaccines have not been conducted. These vaccines should not be regarded as interchangeable. Booster doses must use the same vaccine as used in the primary series. This risk has been mitigated by reiterating this statement in the updated recommendations.

Preference and values

The proposed changes to the use of MenB vaccines are in line with best clinical practice. It is expected that the changes will result in additional protection for people who are most at risk of disease. This is consistent with societal expectations of the best use of vaccines in Australia.

Glossary

A glossary of technical terms is available on the Australian Immunisation Handbook website.

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