Australian Government

Department of Health

Australian Technical Advisory Group on Immunisation

Public consultation on changes to the recommended use of meningococcal and *Haemophilus influenzae* type B vaccines

The Australian Technical Advisory Group on Immunisation (ATAGI) is consulting with stakeholders on proposed changes to the meningococcal vaccination recommendations for inclusion in *The Australian Immunisation Handbook*, with an intention to submit the recommendations to the National Health and Medical Research Council (NHMRC) for its approval under section 14A of the *National Health and Medical Research Council Act 1992*.

This draft includes new recommendations and the rationale for the proposed changes.

You are invited to make a submission on the draft recommendations by 6 May 2018.

In particular, ATAGI is seeking comments on the following:

- Are there additional potential benefits, harms or unintended consequences which could arise from the proposed changes to the use of meningococcal vaccines, not already outlined, and how likely are they to occur?
- Are there additional clinical or implementation considerations which need to be outlined?

Should you require additional information please contact ATAGI Secretariat on atagi.secretariat@health.gov.au.

Summary

The Australian Technical Advisory Group on Immunisation (ATAGI), which advises the Australian Government on clinical recommendations for vaccinations, is proposing changes to the recommendations for use of meningococcal and *Haemophilus influenzae* type B vaccines.

The proposed changes reflect the current best clinical practice to prevent invasive meningococcal disease and will be published in *The Australian Immunisation Handbook* online (http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10-updates).

Meningococcal disease is a serious infection caused by meningococcal bacteria. In Australia, five serogroups of meningococcal bacteria are found. ATAGI has been monitoring the epidemiology of meningococcal disease in Australia and observed that:

serogroup A	is currently extremely rare, but has historically been significant
serogroup B	is endemic and has been an important cause of disease for several decades
serogroup C	was more common around 15 years ago, but was controlled through the introduction of a nationally-funded meningococcal C vaccination on the National Immunisation Program since 2003
serogroup W	is a new strain which has become more common in Australia
serogroup Y	was previously rare, but is now also becoming more common

Several state and territory governments have introduced vaccination programs for adolescents, including through schools, particularly for protection against the emergence of meningococcal W and Y.

Given changes to the epidemiology of meningococcal disease and recognising the new programs available through states and territories, ATAGI has reviewed the meningococcal chapter of *The Australian Immunisation Handbook*.

Rationale

The Therapeutic Goods Administration has recently registered:

- Trumenba for protection against meningococcal B in individual ≥10 years;
- Menveo for use among infants and toddlers 2–23 months of age for protection against meningococcal A, C, W and Y;
- Menactra for use among infants and toddlers 9–23 months of age for protection against meningococcal A, C, W and Y.

There is no single meningococcal vaccine in Australia which can protect against all 5 serogroups. Vaccines are available for protection against:

- meningococcal B – the meningococcal B (MenB) vaccines: Trumenba and Bexsero
- meningococcal A, C, W and Y all at the same time – the meningococcal ACWY (MenACWY) vaccines: Menactra, Menveo, Nimenrix
- meningococcal C only – NeisVac-C (serogroup C alone) and Menitorix (combination that also protects against *Haemophilus influenzae* type b; *Hib*).

The review of the meningococcal chapter has prompted a review of the *Haemophilus influenzae* type B (Hib) chapter recommendations, as meningococcal C vaccination on the National Immunisation Program is currently given as a combination vaccine with *Hib*.

The vaccines are able to be used in different age groups and in different dosing schedules. A full list of vaccines and their details is provided in Attachment 1.

Recommendations

A **ATAGI proposes that the current recommendation in *The Australian Immunisation Handbook* regarding the use of MenC and *Hib* vaccination in children aged 12 months is revoked. Existing recommendations regarding meningococcal vaccination using MenB and MenACWY vaccines, respectively, are retained, as shown in Attachment 2.**

New and expanded recommendations for meningococcal vaccines are summarised in Recommendation B and for the *Hib* vaccine in Recommendation C below.

B **ATAGI proposes the following NEW expanded recommendations for the use of meningococcal vaccines in Australia.**

1. Anyone who wants to protect themselves against meningococcal disease can be vaccinated with MenB and MenACWY vaccines.
2. All children aged 2–23 months (<2 years) are recommended to receive MenACWY vaccines (according to an age-based dose schedule as shown in Table 1).
    - Children who have received MenACWY vaccination before 12 months of age should also receive at least one dose of MenACWY vaccine at 12 months of age (refer to Table 1).
3. Adolescents aged 15–19 years are recommended to receive a single dose of MenACWY vaccine.
4. Three MenACWY vaccines are available (Nimenrix, Menveo and Menactra) and recommended for use for protection against serogroups A, C, W and Y. However, among people ≥2 years, if more than one MenACWY vaccine brand is available, a single dose of Nimenrix or Menveo is preferred to a single dose of Menactra.
5. Adolescents and young adults (aged 20–24 years) who live in close quarters (e.g. new military recruits and students living in residential accommodation) are recommended to receive:
    a) a single dose of MenACWY vaccine.
    b) two doses of MenB vaccine.
6. Adolescents and young adults (aged 20–24 years) who are current smokers are recommended to receive:
    a) a single dose of MenACWY vaccine.
    b) two doses of MenB vaccine.
7. All Aboriginal and/or Torres Strait Islander persons aged 2 months to 19 years are recommended to receive:
    a. MenACWY vaccine (according to an age-based dose schedule as shown in Table 1).
    b. MenB vaccine (according to an age-based dose schedule as shown in Table 2).
8. Infants with specified medical conditions associated with an increased risk of meningococcal disease (refer to List 1 below) who are aged 6–11 months old are recommended to receive 3 doses of MenACWY vaccine (instead of 2 doses) (refer to Table 1).

C ATAGI proposes that the 4th dose of *Hib* vaccine is now recommended at 18 months of age (rather than age 12 months).

Detailed overview of ATAGI recommendations

List 1 shows the specified medical conditions that are associated with increased risk of meningococcal disease. People with these conditions are recommended to receive additional vaccine doses.

Tables 1 and 2 show the proposed ATAGI recommended dosing schedule for the three available conjugate MenACWY vaccines and the two available MenB vaccines, respectively, and according to the new recommendations described above. The number of doses required depends on the age when vaccination is started, the vaccine brand used and whether the person receiving the vaccine has a specified medical condition associated with increased risk of meningococcal disease.

List 1: Specified medical conditions associated with increased risk of meningococcal disease

- 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

Note: This list is unchanged from the conditions specified in the current online chapter of *The Australian Immunisation Handbook*

Table 1: ATAGI recommendations for immunisation using MenACWY vaccines, by age and vaccine brand, showing the number of doses required and minimum intervals

Age at commencement of vaccine course	MenACWY vaccine brand*	Without any medical conditions (associated with increased risk of meningococcal disease on List 1)	With specified medical conditions (associated with increased risk of meningococcal disease on List 1)	Eligibility for funding through national or state-based immunisation programs[#]
6 weeks–5 months	Menveo or Nimenrix[†]	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)	4 doses (8 weeks between doses; 4th dose at 12 months of age or 8 weeks after 3rd dose, whichever is later)	Infant schedule not funded Note: 1 dose of Nimenrix funded at age 12 months under the NIP from July 2018
6–8 months	Menveo or Nimenrix[†]	2 doses (2nd dose at 12 months of age or 8 weeks after 1st dose, whichever is later)	3 doses (8 weeks between 1st and 2nd doses; 3rd dose at 12 months of age or 8 weeks after 3rd dose, whichever is later)	Infant schedule not funded Note: 1 dose of Nimenrix funded at age 12 months under the NIP from July 2018
9–11 months	Menveo or Nimenrix[†] or Menactra[§]	2 doses (2nd dose at 12 months of age or 8 weeks after 1st dose, whichever is later)	3 doses (8 weeks between 1st and 2nd doses; 3rd dose at least 8 weeks after 2nd dose)	Infant schedule not funded Note: 1 dose of Nimenrix funded at age 12 months under the NIP from July 2018
12–23 months	Menveo	2 doses (8 weeks between doses)	2 doses[‡] (8 weeks between doses)	1 dose of Nimenrix funded at age 12 months under the NIP from July 2018 2nd dose for Nimenrix for individuals with a medical condition in List 1 not funded Doses of Menveo or Menactra are NOT funded under any program.
	Nimenrix	1 dose		
	Menactra[†]	2 doses (8 weeks between doses)		
2–14 years	Any brand	1 dose	2 doses (8 weeks between doses)	Not funded
15–19 years	Any brand	1 dose	2 doses (8 weeks between doses)	State-funded MenACWY vaccination programs (using differing brands) in all states except SA and NT
20–24 years	Any brand	1 dose	2 doses (8 weeks between doses)	Not funded
≥25 years**	Any brand	1 dose	2 doses (8 weeks between doses)	Not funded
Booster doses for all ages	Any brand	Not required	For those with ongoing increased risk for IMD who completed age-specific primary vaccination at:	Not funded

Age at commencement of vaccine course	MenACWY vaccine brand*	Without any medical conditions (associated with increased risk of meningococcal disease on List 1)	With specified medical conditions (associated with increased risk of meningococcal disease on List 1)	Eligibility for funding through national or state-based immunisation programs#
			a) **≤6 years of age:** Give a booster dose at 3 years after completion of primary immunisation schedule, then every 5 years thereafter b) ≥7 years of age: Give a booster dose every 5 years after completion of the primary immunisation schedule	

Abbreviations: NT – Northern Territory; QLD – Queensland; SA – South Australia; WA – Western Australia

* Wherever possible, Nimenrix or Menveo should be used in preference to Menactra.

\# Information current as of 17 May 2018.

† Use of Nimenrix in this age group is considered a variation to the Product Information, as it is registered for use from 12 months of age as of May 2018. ATAGI's recommendation to use Nimenrix in this age group is based on data from clinical trials.

§ Do not co-administer Menactra with 13vPCV (Prevenar 13). If Menactra is used, there should be a minimum interval of 4 weeks between the dose of 13vPCV and Menactra. Other MenACWY vaccines (Menveo or Nimenrix) may be co-administered with 13vPCV.

‡ For those with specified medical conditions aged 12–23 months, 2 doses of either Menveo, Menactra or Nimenrix are required.

** There is no registered upper age limit for use of Menveo. Although both Menactra and Nimenrix are registered for use up to 55 years of age only, either of these brands can be given to people over 55 years of age, as per *The Australian Immunisation Handbook.*

Table 2: ATAGI recommendations for immunisation using MenB vaccines, by age and vaccine brand, showing the number of doses required and minimum intervals

Age at commencement of vaccine course	MenB vaccine brand	Without any medical conditions associated with increased risk of meningococcal disease on List 1	With any specified medical conditions associated with increased meningococcal disease on List 1
6 weeks–5 months	Bexsero	4 doses (8 weeks between doses; 4th dose at 12 months)	4 doses (8 weeks between doses; 4th dose at 12 months 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 or 8 weeks after 2nd dose, whichever is later)	3 doses (8 weeks between 1st and 2nd doses; 3rd dose at 12 months or 8 weeks after 2nd dose, whichever is later)
12 months–9 years	Bexsero	2 doses (8 weeks between doses)	2 doses (8 weeks between doses)
≥10 years*	Bexsero	2 doses (8 weeks between doses)	2 doses (8 weeks between doses)
	Trumenba	2 doses (6 months between doses)	3 doses (At least 4 weeks between 1st and 2nd doses; 3rd dose at least 4 months after 2nd dose and at least 6 months after 1st dose)

* Bexsero and Trumenba are not interchangeable. The same vaccine should be used to complete the primary vaccination course.

Research evidence

Recommendations A and B 1-4

A ATAGI proposes that the current recommendation in *The Australian Immunisation Handbook* regarding the use of MenC and *Hib* vaccination in children aged 12 months is revoked. Existing recommendations regarding meningococcal vaccination using MenB and MenACWY vaccines, respectively, are retained as shown in Attachment 2.

New and expanded recommendations for meningococcal vaccines are summarised in Recommendation B and for the *Hib* vaccine in Recommendation C below.

B ATAGI proposes the following NEW expanded recommendations for the use of meningococcal vaccines in Australia.

1. Anyone who wants to protect themselves against meningococcal disease can be vaccinated with MenB and MenACWY vaccines.

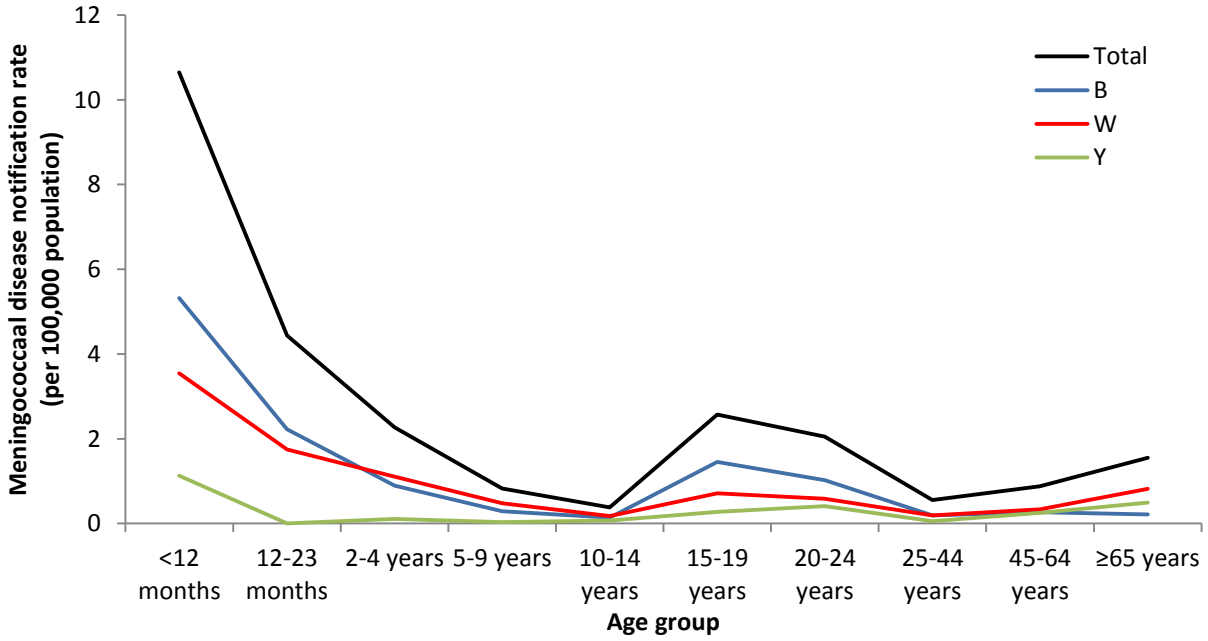
The meningococcal serogroups that cause meningococcal disease have been changing in the last few years. Since 2013, the occurrence of meningococcal W disease has been increasing rapidly. Many meningococcal W cases are caused by a strain (sequence type ST 11) associated with severe disease and a higher risk of death.[1] A smaller yet steady rise in the occurrence of meningococcal Y disease has also been seen since 2016.

Meningococcal B has historically caused the majority of meningococcal disease in Australia and it continues to cause around half of all reported cases of meningococcal disease. In the 17-year period between 1999 and 2015, serogroup B was the most common serogroup causing meningococcal disease.[2]

Data from recent years show that young children aged <2 years have the highest rates of new cases reported, particularly for disease caused by serogroup W. Among these young children, meningococcal disease due to serogroup W occurs most often in infants between 3 and 5 months of age. Serogroup B has historically affected the youngest people in the population, and has been most common in infants and children <2 years.[2] This trend has continued in recent years (Figure 1). Vaccination with MenB and MenACWY vaccines can prevent disease in this higher risk age group. A high number of meningococcal disease cases also occur among adolescents aged 15–19 years (Figure 1).

People can carry the meningococcal bacteria in their throat and/or nose (i.e. ‘carriage’), with studies showing that adolescents and young adults have the highest carriage rates of meningococcal bacteria.[3] Vaccinating populations with high carriage rates is critical to achieve protection of the community more broadly (community or herd immunity).

Figure 1: Age-specific rates of meningococcal disease by serogroup and age group, Australia, 2016–2017*



*Data is for cases with a diagnosis date from 1 January 2016 onwards, as of 14 December 2017. Rates for 2017 have not been annualised. Unpublished data from analysis of National Notifiable Diseases Surveillance System core data by NCIRS.

B ATAGI proposes the following NEW expanded recommendations for the use of meningococcal vaccines in Australia.

2. All children aged 2–23 months (<2 years) are recommended to receive MenACWY vaccines (according to an age-based dose schedule as shown in Table 1).
    - Children who have received MenACWY vaccination before 12 months of age should also receive at least one dose of MenACWY vaccine at 12 months of age (refer to Table 1).
3. Adolescents aged 15–19 years are recommended to receive a single dose of MenACWY vaccine.
4. Three MenACWY vaccines are available and recommended for use for protection against serogroups A, C, W and Y (Nimenrix, Menveo and Menactra). However, among people ≥2 years, if more than one MenACWY vaccine brand is available, a single dose of Nimenrix or Menveo is preferred to a single dose of Menactra.

Safety of MenACWY vaccines

MenACWY vaccine safety has been shown in multiple clinical trials and large population studies (conducted in countries after the vaccines have become available) in people of different ages, from infants to adults.[4-19] The vast majority of reactions after vaccination are mild and resolve on their own. MenACWY vaccines are safe for use in patients with human immunodeficiency virus (HIV) infection.[20,21]

MenACWY vaccines can be safely administered at the same time as other routine vaccines provided to young children through the National Immunisation Program. Clinical trials in young children have included giving MenACWY vaccines with:

- diphtheria-tetanus-acellular pertussis (DTPa) combination vaccines (which included hepatitis B vaccine, inactivated polio vaccine [IPV] and/or *Hib* vaccine),
- 7-valent pneumococcal conjugate vaccine (7vPCV) and 13-valent PCV (13vPCV),

- rotavirus vaccine,
- hepatitis A vaccine,
- measles-mumps-rubella (MMR) vaccine,
- measles-mumps-rubella-varicella (MMRV) vaccine.[6,12-15,22-25]

In adolescents, clinical trials have included giving MenACWY vaccines with:

- 4-valent and 9-valent human papillomavirus (HPV) vaccine,
- diphtheria-tetanus-acellular pertussis (dTpa) vaccine,
- combined hepatitis A and B vaccine and seasonal influenza vaccine.[26-31]

In most studies, the frequencies of reactions following vaccination were similar regardless of whether the vaccines were given together or separately. In some studies, slight increases in mild reactions were observed when vaccines were given together.

Immune responses to MenACWY vaccines and their dose schedules

Invasive meningococcal disease is rare; studies assessing the effectiveness of vaccination in preventing IMD are difficult to conduct due to the requirement to vaccinate very large numbers of people and follow them for long periods of time to demonstrate a benefit. As an alternative, studies with meningococcal vaccines measure and report the immune response to the vaccines. This information is used to indicate how effective the vaccine is likely to be and support registration of the vaccines. An immune response is considered to have occurred if antibodies are detected above a standard threshold that is likely to be protective against the disease. The proportion of vaccinated people who develop antibodies above this threshold is taken into account when making vaccine recommendations.

The number and spacing of meningococcal vaccine doses vary by brand and the age the vaccination commences. There is currently no recommendation for additional or booster doses among healthy individuals in any age group (other than those who are travelling to a country where there is a high risk of getting meningococcal disease, or who have an occupational risk) once the age-appropriate primary course of either Nimenrix, Menveo or Menactra is completed.

i) Children aged <2 years at commencement of vaccination

ATAGI proposes the following vaccination schedules in children aged <2 years (refer to Table 1 in Recommendations section above). The number of doses required is different depending on how old the child is when they receive their first dose, as shown in Table 1.

As the highest rates of meningococcal disease occur very early in life, it is highly desirable to start vaccination as early as possible so that infants can develop an immune response early. Clinical trials have shown that Menveo and Nimenrix are safe to use in children from 2 months of age.[11-14,32] When given in a 3-dose schedule at 2, 4 and 12 months of age, more than 99% of children in clinical trials of Menveo or Nimenrix developed protection against meningococcal W and Y after the completion of the course.[14,32]

For children who commence vaccination at age 6 to <12 months, a 2-dose schedule with Menveo produces a good immune response. In one large study with over 1,600 participants, more than 96% of children given 2 doses of Menveo at age 7–9 months and 12 months developed protection against meningococcal C, W and Y.[15] Another smaller study showed that 100% of children who received Menveo at 6 and 12 months of age produced an immune response against meningococcal C, W and Y after the second dose.[17] In both studies, the response to meningococcal A was slightly lower (87-88%).

Although Menveo is currently registered in a 2-dose schedule from 7 months onwards, data from these clinical trials showed that the immune response in children starting vaccination at 6 months of age was similar. The 6-months schedule point is well-established and accepted in Australia, with consistently high vaccine coverage.[33]

Regarding Nimenrix, a study showed that among those given Nimenrix at 6 and 15–18 months of age, 94% developed an immune response against all four meningococcal serogroups after the first dose at 6 months, with all but 1 out of 139 vaccinated subjects having a protective response to all four serogroups after the booster dose in the second year of life.[34] In another study, a 2-dose schedule of Nimenrix given at age 9 and 12 months produced immune responses against all four serogroups in 98% of vaccinated infants after the first dose and in all children after the second dose.[35]

A 2-dose schedule with Menactra produces a good immune response in infants and children 9 months of age and older after the second dose. In a small study of infants aged 9 months who were given 1 dose of Menactra, the proportion of infants who had an immune response was low, especially against serogroups W and Y (20–27% of children). However, after a second dose was given at either 12 or 15 months of age, more than 92% of children had an immune response against serogroups C, W and Y and 89% against serogroup A.[36] A larger study showed similar results, although the proportion of children who had an immune response against serogroup W was slightly lower (between 81–88%).[25]

All three MenACWY vaccines (Nimenrix, Menveo and Menactra) are registered for use in children aged 12–23 months of age. Because of differences in some of the vaccine components, there are differences in the level of immune response produced. However, the vaccines have been shown to produce immune responses in the vast majority of children 1 month after vaccination when given in the appropriate schedule. Data from clinical studies have shown that 1 dose of Nimenrix produces an immune response against all four meningococcal serogroups (A, C, W and Y) in over 97% of children in this age group.[6,7,23,24] With Menveo, 97% of children developed a protective immune response to all four meningococcal serogroups after 2 doses.[11] Two doses of Menactra given at 12 and 18 months of age resulted in more than 96% of children developing a protective immune response against all four meningococcal serogroups.[37]

ii) Children aged ≥2 years, adolescents and adults at commencement of vaccination

ATAGI proposes that children aged ≥2 years, adolescents and adults receive a single dose of MenACWY vaccine for protection against meningococcal disease caused by serogroups A, C, W and Y. Of note, in this population of people aged ≥2 years, the highest rates of meningococcal disease occur in adolescents aged 15–19 years. Therefore, vaccination for adolescents aged 15–19 years is particularly recommended.

There are three registered MenACWY vaccines available for people aged ≥2 years: Nimenrix, Menveo and Menactra. Each of these produces an immune response against the four meningococcal serogroups included in the vaccine when given as a single dose.[8,10,26,27,38-40]

In studies with adolescents, 67–100% of recipients of a MenACWY vaccine developed an immune response.[4,10,26,27,38,39,41] Population data collected in the United States showed that Menactra was 79% effective in preventing clinical infection in a population during the first year after vaccination.[42]

iii) Choice of MenACWY vaccine brand

Because of differences in the components of the vaccines, there are differences in the level of immune response produced by the three vaccines. It is not certain that these differences will have an

impact on a person's protection against meningococcal disease; however, as population-level data on the effectiveness of all three vaccines are lacking, data on immune responses of subjects in clinical trials have been taken into account in the following proposed recommendations.

Choice of MenACWY vaccine brand among people ≥2 years old

ATAGI proposes that either Nimenrix or Menveo be given in preference to Menactra among people aged ≥2 years. If Nimenrix or Menveo are unavailable, Menactra can be given at an appropriate age as it will still provide adequate protection against meningococcal disease caused by serogroups A, C, W and Y, and is highly preferred to no vaccination.

The differences in immune responses between Nimenrix and Menveo are very minor, based on studies in young children (see below) and adolescents.[43] Either vaccine may be given as a single dose in those aged ≥2 years.

Data from some clinical trials in adolescents and adults indicate that the immune responses produced after a single dose of Nimenrix or Menveo are better than after a dose of Menactra. This is especially true for the immune response against meningococcal serogroups W and Y which are the most common of the four vaccine serogroups in Australia. Both the proportion of subjects who had an immune response above the standard threshold and the level of antibodies produced against serogroups W and Y were better following vaccination with Nimenrix or Menveo than with Menactra.[8,19,38,40] Another study comparing Menactra with Menveo in children aged 2–10 years found results similar to the adolescent studies, i.e. that immune responses against serogroups W and Y were higher with Menveo than with Menactra.[44]

Data from vaccinated adolescents in the United States has shown that the effectiveness of Menactra declines over time (from 79% in the first year after vaccination to 69% between 1 and 3 years after vaccination, and to 61% between 3 and 8 years after vaccination). During this follow-up time, cases of meningococcal disease occurred in people who had received the vaccine.[42] Although there is no population use data on effectiveness of Nimenrix or Menveo, some evidence from clinical trials shows that antibody levels were lower several years after vaccination with Menactra than with Nimenrix or Menveo.[8,40,45]

Choice of MenACWY vaccine brand among infants and toddlers <2 years old

ATAGI proposes that any one of the three available MenACWY vaccines can be given to infants and toddlers aged <2 years, in their respective age-appropriate schedules,.

A study[i] of 1 dose of either Nimenrix or Menveo in toddlers aged 12–15 months found that a similar proportion of children developed a protective immune response immediately after vaccination.[16] However, 6 months after vaccination, the proportion of children with protective antibody levels was lower with Menveo than with Nimenrix. Of note, this study used a single dose schedule of Menveo, whereas a 2-dose schedule in this age group is recommended and is expected to have similar protection to 1 dose of Nimenrix. Therefore, the recommended schedules for toddlers aged 12–23 months for Nimenrix (single dose) and Menveo (2 doses) are considered to be equivalent.

There are no clinical trials directly comparing Menactra with either Nimenrix or Menveo in infants and toddlers aged <2 years. Clinical trials of Menactra indicated that immune responses after 1 dose were inadequate for protection, but that 2 doses resulted in protective immune responses in more than 92% of vaccinated children.[36,37] Results of comparative clinical trials in adolescents cannot be generalised to infants and toddlers <2 years as those studies compared a single dose of Menactra with a single dose of either Nimenrix or Menveo, whereas a 2 dose schedule of Menactra is recommended in infants and toddlers <2 years.

[i] Includes review of published data and unpublished data provided in-confidence by the vaccine manufacturer

As there is no evidence that any of the MenACWY vaccines provides better protection than the others when given in the age-appropriate schedules, any MenACWY vaccine can be used for infants and toddlers <2 years, according to their respective age-appropriate schedules.

However, there are possible concerns regarding concurrent administration of Menactra with some other vaccines routinely given to infants and toddlers. Specifically, a study has shown that co-administration with a pneumococcal conjugate vaccine can lead to lower immune responses to certain pneumococcal serotypes,[25] which could potentially reduce the protective benefit against pneumococcal disease expected from the vaccine. Therefore, as a precautionary measure, Menactra should not be co-administered with 13-valent pneumococcal vaccine (13vPCV). Recently, the NIP schedule was amended to give the final dose of 13vPCV at the age 12-month schedule point and is expected to be implemented in the latter half of 2018.

Additionally, some studies in young children (aged 4–6 years) and adolescents have shown that receiving Menactra one month after diphtheria-tetanus-acellular pertussis combination vaccines can lead to lower immune responses against the meningococcal serotypes.[46,47] Clinical guidance will be provided for infants and toddlers <2 years who may require catch-up of meningococcal vaccination close to the 18-month NIP schedule point (when DTPa is administered).

Recommendation B5

B ATAGI proposes the following NEW expanded recommendations for the use of meningococcal vaccines in Australia.

5. Adolescents and young adults (aged 20–24 years) who live in close quarters (e.g. new military recruits and students living in residential accommodation) are recommended to receive:
    a) a single dose of MenACWY vaccine.
    b) two doses of MenB vaccine.

Adolescents and young adults have the highest rates of meningococcal carriage (i.e. presence of meningococcal bacteria in the upper respiratory tract without any signs or symptoms of infection) and are thought to play an important role in how the bacteria are transmitted in a community.[3] Living in close or prolonged contact with a person who is carrying meningococcal bacteria can increase a person's chances of acquiring the bacteria.[48-50]

A clinical study of vaccination with Menveo in 18-24 year-old university students showed that there were reductions in meningococcal carriage among those who were vaccinated.[51] This reduction of the chances of transmission of the meningococcal bacteria is thought to reduce the risk of meningococcal disease occurring.

As Australian data show that the risk of meningococcal disease caused by serogroup B is also high among adolescents and young adults aged 20–24 years (compared with other age groups) (refer to Figure 1 above), ATAGI is proposing that the existing recommendation for MenB vaccination (currently for ages 15–19 years as per *The Australian Immunisation Handbook*) be extended to also include those aged 20–24 years.

Recommendation B6

B ATAGI proposes the following NEW expanded recommendations for the use of meningococcal vaccines in Australia.

6. Adolescents and young adults (aged 20–24 years) who are current smokers are recommended to receive:
    a) a single dose of MenACWY vaccine.
    b) two doses of MenB vaccine.

Smoking tobacco is known to increase the risk of carrying the meningococcal bacteria in the upper respiratory tract and of passing the bacteria to close contacts. Active smokers are at greater risk of meningococcal disease as they have high meningococcal carriage rates, which are approximately 1.5–2 times higher than those found in non-smokers.[52]

In a study of 14,000 teenagers aged 15–19 years, twice as many active smokers were carrying meningococcal bacteria compared with non-smokers, even after accounting for other risk factors known to impact carriage.[53] A study of meningococcal disease cases in Queensland found that regular smoking or passive exposure to tobacco smoke were risk factors for developing IMD at any age.[54] The risk of meningococcal carriage increases with heavier smoking[55] and studies have also shown adolescents in close contact to smokers are more likely to develop meningococcal disease.[53,54,56,57]

Vaccinating smokers can, therefore, reduce both the risk of meningococcal disease as well as carriage of the meningococcal bacteria in a person. By preventing carriage, transmission of the bacteria to others in the population can be reduced. As adolescents and young adults aged 15–24 years have the highest rates of meningococcal carriage,[3] the greatest possible individual-level and population-wide benefits are likely to be attained by vaccinating smokers aged 15–24 years. As 15–19 year olds are already recommended to receive MenACWY vaccine (as per recommendation B3), ATAGI proposes extending the recommendation for MenACWY vaccine to also include smokers aged 20–24 years.

Recommendation B7

B ATAGI proposes the following NEW expanded recommendations for the use of meningococcal vaccines in Australia.

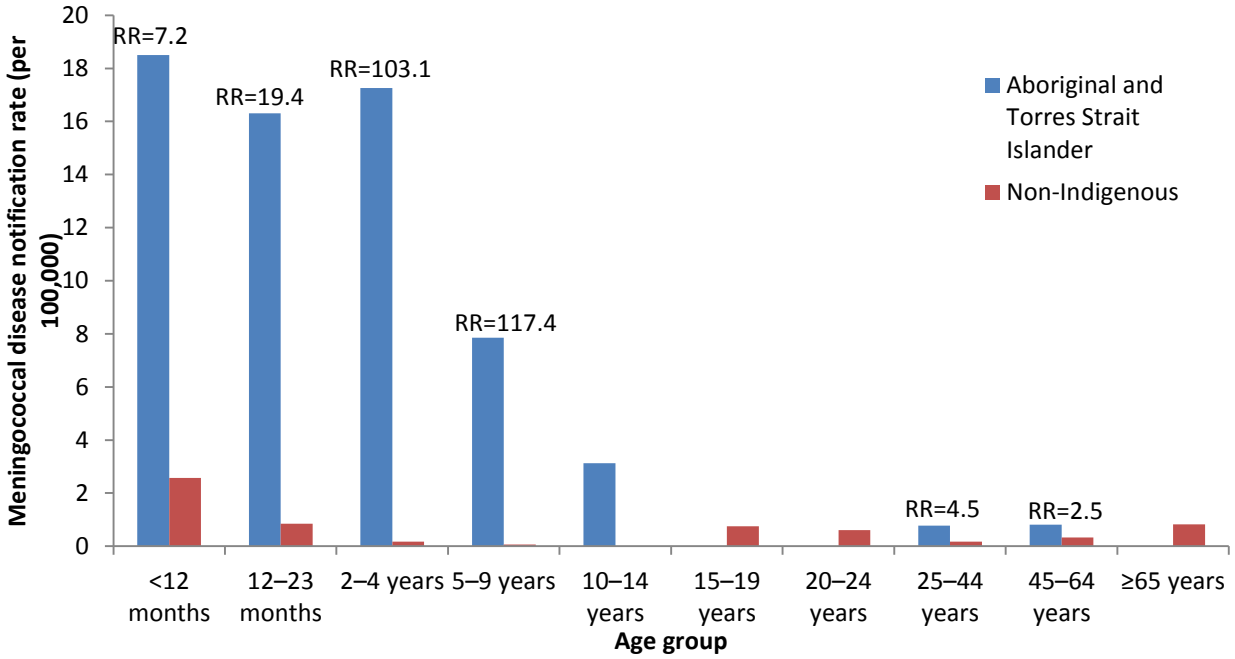
7. All Aboriginal and/or Torres Strait Islander persons aged 2 months to 19 years are recommended to receive:
    a. MenACWY vaccine (according to an age-based dose schedule as shown in Table 1).
    b. MenB vaccine (according to an age-based dose schedule as shown in Table 2).

Aboriginal and Torres Strait Islander Australians have much higher incidence rates of meningococcal disease compared to non-Indigenous Australians. This is particularly observed among children aged <15 years for the two most common meningococcal serogroups B and W.

During 2012–2017, the incidence rate of meningococcal disease caused by serogroup W was higher in Aboriginal and Torres Strait Islander children aged <5 years (3.10 versus 0.34 per 100,000; rate ratio=9.1).

More recently in 2016–2017, this disparity was even more striking, with meningococcal disease rates among Aboriginal and Torres Strait Islanders being greater than 100 times those observed among non-Indigenous Australians in certain age groups (refer to Figure 2). This has been partly due to the outbreak of serogroup W disease in Central Australia which particularly affected young Aboriginal and Torres Strait Islander people in remote communities.

Figure 2: Notification rates for meningococcal disease caused by serogroup W and rate ratio for Aboriginal and Torres Strait Islanders compared with non-Indigenous people, by age group, 2016–2017*

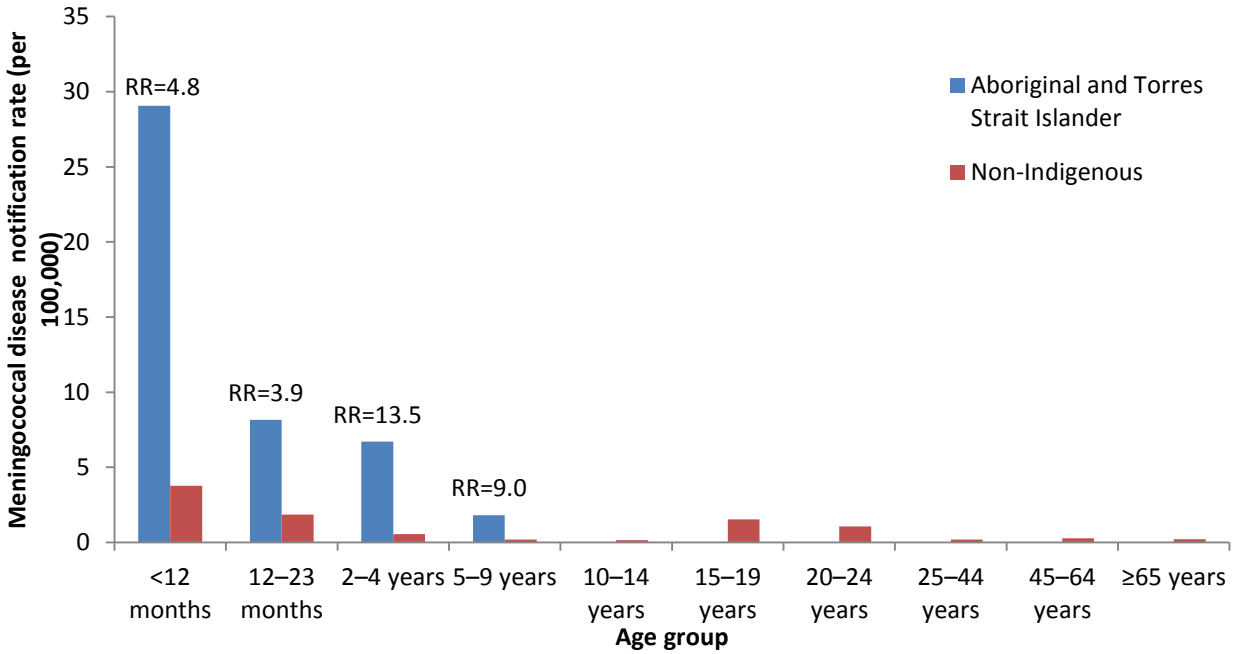


RR=rate ratio (Aboriginal and Torres Strait Islanders/non-Indigenous Australians). RR was not calculated where there were zero cases in one of the two population groups.
*Data shown is for notifications from 1 January 2016 to 14 December 2017. Rates for 2017 are not annualised.
Source: Unpublished data from analysis of National Notifiable Diseases Surveillance System core data by NCIRS.

In 2016–17, there was a substantial disparity in the reported cases of meningococcal disease caused by serogroup B between Aboriginal and Torres Strait Islander people compared with non-Indigenous Australians, particularly among children aged <10 years old (refer to Figure 3).

This trend is longstanding. Between 2006 and 2015, rates of meningococcal disease caused by serogroup B disease were reported as being 3.4 times and 3.8 times higher among Aboriginal and Torres Strait Islander infants aged <12 months and children aged 1–4 years, respectively, compared with non-Indigenous infants and children of the same age.[2] Rates of serogroup B disease among older children up to and including age 14 years are also elevated in Aboriginal and Torres Strait Islander children compared with non-Indigenous children, occurring 6.3 times and 2.5 times among Aboriginal and Torres Strait Islander children aged 5–9 years and 10–14 years, respectively, compared with non-Indigenous children of the same age.[2]

Figure 3: Notification rates for meningococcal disease caused by serogroup B and rate ratio for Aboriginal and Torres Strait Islanders compared with non-Indigenous people, by age group, 2016–2017*



RR=rate ratio (Aboriginal and Torres Strait Islanders/non-Indigenous Australians). RR was not calculated where there were zero cases in one of the two population groups.
*Data shown is for notifications from 1 January 2016 to 14 December 2017. Rates for 2017 are not annualised. Source: Unpublished data from analysis of National Notifiable Diseases Surveillance System core data by NCIRS.

Recommendation B8

B ATAGI proposes the following NEW expanded recommendations for the use of meningococcal vaccines in Australia.

8. Infants with specified medical conditions associated with an increased risk of meningococcal disease (refer to List 1 below) who are aged 6–11 months old are recommended to receive 3 doses of MenACWY vaccine (instead of 2 doses) (refer to Table 1).

Clinical trials of Menveo and Menactra in infants aged 6–11 months and 9–11 months, respectively, have only examined immune responses after 1 or 2 doses of the vaccine. No studies have examined immune response after 3 doses and no studies have been conducted in infants or young children with the specified medical conditions in List 1.

However, clinical studies of Menveo in young healthy infants starting vaccination at age 2 months show that immune responses were better after a third dose (given 6 months of age) compared with immune responses after a second dose (given at 4 months of age).[14] There are no studies of 3-dose primary schedules with Menactra; however there is some concern that immune responses to Menactra may be slightly lower than the other MenACWY vaccines (see Recommendation B4 above). Therefore, an additional dose of Menactra is recommended for infants with these specified medical conditions if Menactra is to be used (from age 9 months). This is consistent with the same principle used for the dosing schedule of the other MenACWY vaccines.

While the differences in immunity are minor and likely to be unimportant in a healthy infant, ATAGI considers the higher risk of disease in an infant with a specified medical condition justifies

the extra dose of vaccine. Studies with Menactra in older children and adolescents with HIV infection have shown that 2 doses, rather than 1, are required for an adequate immune response.[20,58]

Studies with meningococcal C vaccines have also shown that people with immunocompromising medical conditions have a lower immune response to vaccination and require additional doses.[59-63]

Extrapolating from these research findings, ATAGI considers a 3-dose course of Menveo or Menactra (refer to Table 1 for dosing schedule) to be appropriate for infants commencing vaccination at age 6–11 months or 9–11 months, respectively, with a specified medical condition. The extra dose given to infants, compared with infants without specified medical conditions, is similar to the schedule for older age groups, for whom an additional dose is currently recommended.

Recommendation C

C ATAGI proposes that the 4th dose of *Hib* vaccine is now recommended at 18 months of age (rather than age 12 months)

A 4th dose of *Hib* vaccine in the second year of life (in addition to the 3 doses given at 2, 4 and 6 months of age) is required to ensure long-term protection against *Hib* disease. A review of *Hib* cases from 1996 to 2013 found that more than half were either unimmunised or partially vaccinated.[64]

Currently, a 4th *Hib* vaccine dose is given at 12 months of age using the combination vaccine brand, Menitorix, which includes both *Hib* and meningococcal C.

In January 2018, the Pharmaceutical Benefits Advisory Committee recommended the listing of Nimenrix on the NIP for infants 12 months of age.

The introduction of a MenACWY vaccine at 12 months of age means the meningococcal C component of Menitorix will no longer be required and the 4th dose of *Hib* can be given in a monovalent formulation (i.e. containing only *Hib*).

In addition, the Chief Executive Officer of the National Health and Medical Research Council agreed to amend a pneumococcal recommendation in the Australian Immunisation Handbook, proposed by ATAGI in late 2017, to move the 3rd dose of the infant pneumococcal vaccine from 6 months to 12 months.

ATAGI has reviewed the epidemiology of all of the diseases with a vaccine scheduled at 12 months and proposes that the 4th dose of *Hib* be moved to the 18-month schedule point to reduce the number of vaccines given at 12 months of age.

Analysis of data on *Hib* disease in Australia found that between 1993 and 2016, only 17 cases of invasive *Hib* disease occurred in partially vaccinated children aged 6–23 months, with the majority (n=15/17) not having completed the initial 3-dose infant course (usually given at 2, 4 and 6 months of age).

In the United States, deferring the *Hib* booster dose by 18 months in response to a vaccine supply shortage did not cause an increase in the incidence of invasive *Hib* disease.[65]

On the basis of this information, ATAGI believes that moving the schedule point for the *Hib* booster dose from age 12 months to 18 months is unlikely to result in more cases of *Hib* in Australia.

Additional information to be included in *The Australian Immunisation Handbook*

Information on Trumenba, a newly registered MenB vaccine

Trumenba is a newly available alternative vaccine that provides protection against meningococcal disease caused by meningococcal serogroup B and is registered and suitable for use in people aged ≥10 years. Trumenba was licensed for use in Australia in September 2017 and has been supplied since early 2018. Clinical trials have shown that Trumenba is a safe and effective vaccine for use in adolescents and young adults.

Trumenba can be used in a 2-dose or a 3-dose schedule depending on the patient's risk of meningococcal disease[ii].[66,67] Among people aged 11–18 years, immune responses above the predefined protective threshold were produced in 82–83% of participants after 3 doses of Trumenba given at 0, 1 and 6 months or 0, 2 and 6 months, and in 73.5% of participants after 2 doses given at 0 and 6 months.[66] Several clinical trials in people aged 10–25 years have also shown that both 3-dose and 2-dose schedules are safe and can be administered with other vaccines.[66-70]

The recommended dosing schedule (3 doses or 2 doses) depends on the patient's level of risk of meningococcal disease. ATAGI proposes that adolescents without specific medical conditions, who have a lower risk of meningococcal disease, receive 2 doses of Trumenba. However, it is preferable that adolescents with a specified medical condition (refer to List 1), who have a higher risk of meningococcal disease, get the greatest protection as early as possible. The 3-dose schedule provides more rapid protection within the first 2 months of commencing vaccination, and the 3rd dose at 6 months ensures long term effectiveness. This is particularly important for these at-risk individuals, in whom responses to the 2-dose schedule may be suboptimal. Therefore, the 3-dose schedule of Trumenba is recommended for people with medical conditions listed in List 1.

There is no preference for the use of Trumenba or Bexsero for the prevention of meningococcal B disease. However, the vaccines should not be used interchangeably, that is, a person who has a first dose of one brand of meningococcal B vaccine should complete the course with the same brand.

Benefits/Harms

There are five key benefits from these proposed changes to the use of meningococcal vaccines:

1. Vaccination with MenACWY vaccine will provide protection to those age and population groups with the highest reported incidence rates of meningococcal disease; this is particularly true for disease caused by serogroups W and Y, the two serogroups that have emerged and contributed significantly to the total number of meningococcal disease cases in the past 2 years.
2. High uptake of MenACWY vaccine among adolescents has the potential to stop transmission of meningococcal bacteria in the community and provide community (herd) protection to other members of the population even if they are not vaccinated.
3. Vaccination of additional age groups (specifically 2–14 year olds) among Aboriginal or Torres Strait Islander Australians with MenACWY and MenB vaccines can address the large gap in the meningococcal disease burden compared with non-Indigenous Australians.
4. Additional vaccination recommendations to protect adolescents and young adults living in close quarters and those who are smokers can provide protection against the meningococcal serogroups that cause the majority of meningococcal disease in these high-risk individuals, and also reduce transmission.
5. An additional dose of MenACWY vaccine given to infants aged 6–11 months with specified medical conditions diagnosed in infancy, who are most vulnerable to meningococcal disease, will provide them with additional protection against meningococcal disease

[ii] [ii] Includes review of published data and unpublished data provided in-confidence by the vaccine manufacturer

compared with the dosing recommendations for healthy infants, especially disease caused by serogroups W and Y.

There are potential concerns that may arise from the proposed changes to the use of meningococcal vaccines:

1. *Potential concern of 'schedule crowding'*

   ATAGI has a strong preference for avoiding adding new National Immunisation Program vaccination schedule points and multiple visits for vaccinations scheduled at the same point. Vaccination with MenACWY vaccine from infancy and shifting the 4th dose of *Hib* vaccine will increase the number of vaccines administered at the 18-month schedule point. Non-Indigenous children without specified medical conditions will receive a maximum of 3 injections at both the 12- and 18-month schedule points. However, with the proposed changes, Aboriginal and Torres Strait Islander children living in four jurisdictions (Western Australia, South Australia, Northern Territory and North Queensland) will receive at least 4 injections at both the 12- and 18-month schedule points (because of the additional hepatitis A vaccine doses). In addition, children with various medical conditions (including but not limited to those in List 1) may require additional doses of other vaccines. This may impact acceptability for these population groups and may require additional visit(s) to receive all the recommended vaccines, which can affect compliance with the recommended schedule.

2. *Potential increased frequency and/or severity of adverse events due to a greater number of vaccinations being co-administered*

   Clinical trials have documented the general safety of MenACWY vaccines when given together with multiple routinely administered vaccines in both children aged <2 years and adolescents. In most studies, rates of adverse events when MenACWY and other vaccines were given together were similar to those when vaccines were given separately. In some studies, slight increases in mild reactions were observed when vaccines were given together.

3. *Potential for increased number of Hib cases occurring prior to the booster dose scheduled at 18 months of age.*

   Based on available Australian data and on the experience from a comparable situation in the United States, the postponement of the Hib dose from 12 months to 18 months is unlikely to lead to an increased number of Hib disease cases among children aged 12–18 months. In Australia, there has been a low number of Hib vaccine failures in the past two decades and a high population Hib vaccination coverage and community immunity. While an increase in Hib disease cases occurring among children aged 12–18 months who have received 3 primary doses of Hib-containing vaccine in infancy is not expected, there will be ongoing surveillance to detect any changes in the number of Hib cases in relation with age and vaccine-doses received.

Preference and values

The proposed changes to the use of meningococcal vaccines are in line with the best available clinical advice and with the ages for which the vaccines are currently registered. It is anticipated that use of the available meningococcal vaccines will result in additional protection for people most at risk and the wider community (including those who are not vaccinated) against meningococcal disease. This is considered consistent with societal expectations of the best use of vaccines in Australia, including vaccination use in the National Immunisation Program. Also, there has been substantial media interest in meningococcal vaccines following cases of meningococcal disease in young children and adolescents, and feedback from clinicians indicates a growing demand among parents for use of these vaccines especially for their young children. In 2017–2018, most states and territories initiated adolescent vaccination programs with MenACWY vaccine which were well-received, showing the importance of these vaccines in preventing this rare but serious condition.

Resources and other considerations

Product Information for Nimenrix is available at:

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02123-1

Product Information for Menveo is available at:

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-02475-3

Product Information for Menactra is available at:

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01448-1

Product Information for Bexsero is available at:

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02131-1

Product Information for Trumenba is available at:

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-02674-1

Product Information for Hiberix is available at:

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-05633-3

Practical information

Communication to providers will need to be made clear in *The Australian Immunisation Handbook* and other guidance to minimise confusion and ensure smooth implementation of these proposed changes in recommendations. In particular, the availability of three MenACWY vaccines and two MenB vaccines, all registered in different schedules for different age groups, may cause confusion among immunisation providers. The shift in the schedule point for the 4th dose of *Hib* from 12 to 18 months of age may cause further confusion in the initial stages of implementation of the revised vaccination schedule. Clear clinical advice, including fact sheets with answers to frequently asked questions, will need to be available for immunisation providers.

Glossary

Adverse event	An unwanted reaction usually following administration of a vaccine, which may or may not be caused by the vaccine. Adverse events may be at the site of injection or may be a general illness or a general allergic reaction.
Antibodies	A special protein produced by immune cells in response to antigens (foreign substances, bacteria, viruses or other microorganisms). Antibodies bind with antigens on microorganisms as one of the initial steps of the body's immune response against infection.
Carriage, or meningococcal carriage	The continual presence of bacteria (meningococci) in the upper respiratory tract, particularly the throat and/or nose, without causing disease to the host.
Carrier	A person who has carriage of bacteria, which are not currently causing disease or symptoms in that person, but which have the potential to be transmitted to others or to invade and cause disease in the individual.
Co-administration of	When two or more vaccines are administered at the same time (usually

vaccines	at different sites).
Conjugate vaccines	These are vaccines in which the vaccine antigen (the polysaccharides from the bacterial wall of meningococcal bacteria) has been joined or conjugated to a carrier protein to improve the immune response and immunological memory to the vaccine.
Herd protection	Herd protection, or herd immunity, is the protection of unvaccinated people indirectly, through a high vaccination rate in the rest of the population. The high level of vaccination and immunity in the population limits the number of people susceptible to infection and the ability for the infection to circulate.
Incidence or incidence rate	The number of, or rate of, new cases of a particular disease within a given period of time.
Immune response	The body's defence against a foreign object or infection, as shown in the case of a vaccine, by a rise in the level of antibodies above a threshold, or by an amount that is considered to provide protection against a particular disease.
Immunocompromising medical condition	A medical condition associated with a weakened immune system, either due to the condition or its treatment, which means that it is less able to fight off infection. People with these conditions are more vulnerable to infection and may have more severe disease than a healthy person.
Interchangeability of vaccines	This refers to the ability to use a different brand of vaccine against the same disease to complete a course of vaccination when more than one dose of vaccine is required.
Invasive disease (meningococcal or *Hib*)	Disease that results when bacteria (e.g. meningococcal or *Hib*), which are usually harmlessly carried by the body, invade and cause clinical infection. The bacteria may infect the blood, spinal fluid or another part of the body that would normally be sterile (or germ-free). Invasive meningococcal disease most commonly causes meningitis and/or septicaemia (i.e. infection of the blood).
Monovalent vaccine	A vaccine against only one bacterium/virus that causes a disease or one variant serogroup of that bacterium/virus.
National Immunisation Program (NIP)	The National Immunisation Program was set up by the Commonwealth and state and territory governments to increase national immunisation coverage of important vaccines in Australia. The NIP provides free vaccines to eligible people to reduce the occurrence of diseases that can be prevented by vaccination.
Quadrivalent vaccine	A vaccine that targets four variant serogroups of a virus or bacterium that causes a disease.
Routinely administered vaccines	These are vaccines that are already included in the current NIP schedule and are to be given at specified schedule points.
Schedule point	These are time points or age milestones (e.g. 12 months of age) throughout a person's lifetime when a vaccine is scheduled to be given.

	The schedule points for vaccines have been selected to provide the best possible protection against diseases preventable by vaccination.
Serogroups	Serogroups are classifications of certain bacteria distinguished by the presence of a common antigen. In the case of meningococcal bacteria, these antigens are the 'sugars' on their outer coating. The most common meningococcal serogroups that cause serious disease are A, B, C, W and Y.
Therapeutic Goods Administration (TGA) registration	Vaccines, like all medicines, are regulated by the TGA. They must be approved and registered for use by the TGA before they are available to the public in Australia. Before they are made available for use they are rigorously tested in human clinical trials to confirm that they are safe and that they stimulate protective immune responses. For a vaccine to be registered, the TGA reviews these data to ensure that the vaccine (or other medicine) works as it should and is safe to use.

References

1. Australian Government Department of Health. Invasive Meningococcal Disease National Surveillance Report 31 October 2017.2017. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/5FEABC4B495BDEC1CA25807D001327FA/$File/31-Oct-2017-IMD-Surveillance-report.pdf (Accessed 29 January 2018).
2. Archer BN, Chiu CK, Jayasinghe SH, et al. Epidemiology of invasive meningococcal B disease in Australia, 1999-2015: priority populations for vaccination. *Medical Journal of Australia* 2017;207:382-7.
3. Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta analysis. *The Lancet Infectious Diseases* 2010;10:853-61.
4. Keyserling H, Papa T, Koranyi K, et al. Safety, immunogenicity and immune memory of a novel meningococcal (groups A, C, Y and W-135) polisaccharide diphtheria toxoid conjugate vaccine (MCV-4) in health adolescents. *Archives of Pediatrics and Adolescent Medicine* 2005;159:907-13.
5. Keyserling H, Pollard A, Detora L, Gilmet G. Experience with MCV-4 a meningococcal diphtheria toxoid conjugate vaccine against serogroups A, C, Y and W-135. *Expert Review of Vaccines* 2006;5:445-59.
6. Vesikari T, Karvonen A, Bianco V, Van der Wielen M, Miller J. Tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine is well tolerated and immunogenic when co-administered with measles-mumps-rubella-varicella vaccine during the second year of life: An open, randomized controlled trial. *Vaccine* 2011;29:4274-84.
7. Vesikari T, Forsten A, Boutriau D, et al. Randomized trial to assess the immunogenicity, safety and antibody persistence up to three years after a single dose of a tetravalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine in toddlers. *Human Vaccines and Immunotherapeutics* 2012;8:1892-903.
8. Baxter R, Baine Y, Ensor K, et al. Immunogenicity and safety of an investigational quadrivalent meningococcal ACWY tetanus toxoid conjugate vaccine in healthy adolescents and young adults 10 to 25 years of age. *Pediatric Infectious Disease Journal* 2011;30:e41-8.
9. Perrett KP, Snape MD, Ford KJ, et al. Immunogenicity and immune memory of a nonadjuvanted quadrivalent meningococcal glycoconjugate vaccine in infants. *Pediatric Infectious Disease Journal* 2009;28:186-93.

10. Bermal N, Huang LM, Dubey AP, et al. Safety and immunogenicity of a tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine in adolescents and adults. *Human Vaccines* 2011;7:239-47.
11. Tregnaghi M, Lopez P, Stamboulian D, et al. Immunogenicity and safety of a quadrivalent meningococcal polysaccharide CRM conjugate vaccine in infants and toddlers. *International Journal of Infectious Diseases* 2014;26:22-30.
12. Klein NP, Reisinger KS, Johnston W, et al. Safety and immunogenicity of a novel quadrivalent meningococcal CRM-conjugate vaccine given concomitantly with routine vaccinations in infants. *Pediatric Infectious Disease Journal* 2012;31:64-71.
13. Nolan TM, Nissen MD, Naz A, et al. Immunogenicity and safety of a CRM-conjugated meningococcal ACWY vaccine administered concomitantly with routine vaccines starting at 2 months of age. *Human Vaccines and Immunotherapeutics* 2014;10:280-9.
14. Block SL, Shepard J, Garfield H, et al. Immunogenicity and Safety of a 3- and 4-dose Vaccination Series of a Meningococcal ACWY Conjugate Vaccine in Infants: Results of a Phase 3b, Randomized, Open-label Trial. *Pediatric Infectious Disease Journal* 2016;35:e48-59.
15. Klein NP, Shepard J, Bedell L, Odrljin T, Dull P. Immunogenicity and safety of a quadrivalent meningococcal conjugate vaccine administered concomitantly with measles, mumps, rubella, varicella vaccine in healthy toddlers. *Vaccine* 2012;30:3929-36.
16. Bona G, Castiglia P, Zoppi G, et al. Safety and immunogenicity of a CRM or TT conjugated meningococcal vaccine in healthy toddlers. *Vaccine* 2016;34:3363-70.
17. Halperin SA, Diaz-Mitoma F, Dull P, Anemona A, Ceddia F. Safety and immunogenicity of an investigational quadrivalent meningococcal conjugate vaccine after one or two doses given to infants and toddlers. *European Journal of Clinical Microbiology and Infectious Diseases* 2010;29:259-67.
18. Tseng HF, Sy LS, Ackerson BK, et al. Safety of quadrivalent meningococcal conjugate vaccine in 11- to 21-year-olds. *Pediatrics* 2017;139.
19. Reisinger KS, Baxter R, Block SL, et al. Quadrivalent meningococcal vaccination of adults: phase III comparison of an investigational conjugate vaccine, MenACWY-CRM, with the licensed vaccine, Menactra. *Clinical and Vaccine Immunology* 2009;16:1810-5.
20. Siberry GK, Warshaw MG, Williams PL, et al. Safety and immunogenicity of quadrivalent meningococcal conjugate vaccine in 2- to 10-year-old human immunodeficiency virus-infected children. *Pediatric Infectious Disease Journal* 2012;31:47-52.
21. Siberry GK, Williams PL, Lujan-Zilbermann J, et al. Phase I/II, open-label trial of safety and immunogenicity of meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine in human immunodeficiency virus-infected adolescents. *Pediatric Infectious Disease Journal* 2010;29:391-6.
22. Blanchard-Rohner G, Snape MD, Kelly DF, et al. The B-cell response to a primary and booster course of MenACWY-CRM197 vaccine administered at 2, 4 and 12 months of age. *Vaccine* 2013;31:2441-8.
23. Knuf M, Pantazi-Chatzikonstantinou A, Pfletschinger U, et al. An investigational tetravalent meningococcal serogroups A, C, W-135 and Y-tetanus toxoid conjugate vaccine co-administered with Infanrix hexa is immunogenic, with an acceptable safety profile in 12-23-month-old children. *Vaccine* 2011;29:4264-73.
24. Ruiz-Palacios GM, Huang LM, Lin TY, et al. Immunogenicity and safety of a booster dose of the 10-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine coadministered with the tetravalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine in toddlers: a randomized trial. *Pediatric Infectious Disease Journal* 2013;32:62-71.
25. Pina LM, Bassily E, Machmer A, Hou V, Reinhardt A. Safety and immunogenicity of a quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine in infants and toddlers: three multicenter phase III studies. *Pediatric Infectious Disease Journal* 2012;31:1173-83.

26. Arguedas A, Soley C, Loaiza C, et al. Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines. *Vaccine* 2010;28:3171-9.
27. Ostergaard L, Silfverdal SA, Berglund J, et al. A tetravalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine is immunogenic and well-tolerated when co-administered with Twinrix in subjects aged 11-17 years: an open, randomised, controlled trial. *Vaccine* 2012;30:774-83.
28. Aplasca-De Los Reyes MR, Dimaano E, Macalalad N, et al. The investigational meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (ACWY-TT) and the seasonal influenza virus vaccine are immunogenic and well-tolerated when co-administered in adults. *Human Vaccines and Immunotherapeutics* 2012;8:881-7.
29. Schilling A, Parra MM, Gutierrez M, et al. Coadministration of a 9-valent human papillomavirus vaccine with meningococcal and Tdap vaccines. *Pediatrics* 2015;136:e563-72.
30. Reisinger KS, Block SL, Collins-Ogle M, et al. Safety, tolerability, and immunogenicity of Gardasil given concomitantly with Menactra and Adacel. *Pediatrics* 2010;125:1142-51.
31. Weston WM, Friedland LR, Wu X, Howe B. Immunogenicity and reactogenicity of co-administered tetanus-diphtheria-acellular pertussis (Tdap) and tetravalent meningococcal conjugate (MCV4) vaccines compared to their separate administration. *Vaccine* 2011;29:1017-22.
32. Merino Arribas JM, Carmona Martinez A, Horn M, et al. Safety and immunogenicity of the quadrivalent meningococcal serogroups A, C, W and Y tetanus toxoid conjugate vaccine coadministered with routine childhood vaccines in European infants: an open, randomized trial. *Pediatric Infectious Disease Journal* 2017;36:e98-e107.
33. National Centre for Immunisation Research and Surveillance. Annual Immunisation Coverage Report 2015. Available from: http://www.ncirs.edu.au/assets/surveillance/coverage/Annual-Immunisation-Coverage-Report-2015.pdf (Accessed 28 August 2017).
34. GlaxoSmithKline. MenACWY-TT-087: Immunogenicity and safety study of GSK Biologicals' meningococcal conjugate vaccine (GSK 134612) when co-administered with routine vaccines in healthy infants and toddlers. 2017. Available from: https://www.gsk-clinicalstudyregister.com/files2/114858%20-Clinical-Study-Result-Summary.pdf (Accessed 17 May 2018).
35. Klein NP, Baine Y, Bianco V, et al. One or two doses of quadrivalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine is immunogenic in 9- to 12-month-old children. *Pediatric Infectious Disease Journal* 2013;32:760-7.
36. Sanofi Pasteur. Study of a tetravalent meningococcal diphtheria toxoid conjugate vaccine in toddlers 9 to 18 months of age (MTA26). Available from: https://clinicaltrials.gov/ct2/show/NCT00643916 (Accessed 9 May 2018).
37. Noya F, McCormack D, Reynolds DL, Neame D, Oster P. Safety and immunogenicity of two doses of quadrivalent meningococcal conjugate vaccine or one dose of meningococcal group C conjugate vaccine, both administered concomitantly with routine immunization to 12- to 18-month-old children. *The Canadian Journal of Infectious Diseases and Medical Microbiology* 2014;25:211-6.
38. Jackson LA, Baxter R, Reisinger K, et al. Phase III comparison of an investigational quadrivalent meningococcal conjugate vaccine with the licensed meningococcal ACWY conjugate vaccine in adolescents. *Clinical Infectious Diseases* 2009;49:e1-10.
39. Borja-Tabora C, Montalban C, Memish ZA, et al. Immune response, antibody persistence, and safety of a single dose of the quadrivalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine in adolescents and adults: results of an open, randomised, controlled study. *BMC Infect Dis* 2013;13:116.

40. Baxter R, Baine Y, Kolhe D, et al. Five-year antibody persistence and booster response to a single dose of meningococcal A, C, W and Y tetanus toxoid conjugate vaccine in adolescents and young adults: an open, randomized trial. *Pediatric Infectious Disease Journal* 2015;34:1236-43.
41. Jackson LA, Jacobson RM, Reisinger KS, et al. A randomized trial to determine the tolerability and immunogenicity of a quadrivalent meningococcal glycoconjugate vaccine in healthy adolescents. *Pediatric Infectious Disease Journal* 2009;28:86-91.
42. Cohn AC, MacNeil JR, Harrison LH, et al. Effectiveness and duration of protection of one dose of a meningococcal conjugate vaccine. *Pediatrics* 2017;139:pii:e20162193.
43. Ishola DA, Andrews N, Waight P, et al. Randomized Trial to Compare the Immunogenicity and Safety of a CRM or TT Conjugated Quadrivalent Meningococcal Vaccine in Teenagers who Received a CRM or TT Conjugated Serogroup C Vaccine at Preschool Age. *Pediatric Infectious Disease Journal* 2015;34:865-74.
44. Halperin SA, Gupta A, Jeanfreau R, et al. Comparison of the safety and immunogenicity of an investigational and a licensed quadrivalent meningococcal conjugate vaccine in children 2-10 years of age. *Vaccine* 2010;28:7865-72.
45. Baxter R, Reisinger K, Block SL, et al. Antibody persistence and booster response of a quadrivalent meningococcal conjugate vaccine in adolescents. *Journal of Pediatrics* 2014;164:1409-15.
46. Sanofi Pasteur. Study of Menactra® in US adolescents when administered concomitantly with Tdap vaccine (MTA21). 2014. Available from: https://clinicaltrials.gov/ct2/show/NCT00777257 (Accessed 18 May 2018).
47. Sanofi-Aventis Australia Pty Ltd. Australian Product Information: Menactra® (Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine. 2018. Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01448-1&d=20180507161146224 83&d=20180517161146224 83.
48. Bruce MG, Rosenstein NE, Capparella JM, et al. Risk factors for meningococcal disease in college students. *JAMA* 2001;286:688-93.
49. Bergman BP, Hayton JC, Green AD. Effectiveness of the meningococcal vaccination programme for British Armed Forces recruits. *Communicable Disease and Public Health* 2000;3:298-9.
50. Harrison LH, Dwyer DM, Maples CT, Billmann L. Risk of meningococcal infection in college students. *JAMA* 1999;281:1906-10.
51. Read RC, Chadwick DR, Faust SN, et al. Effect of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: an observer-blind, phase 3 randomised clinical trial. *The Lancet* 2014;13:2121-31.
52. Soeters HM, Whaley M, Alexander-Scott N, et al. Meningococcal carriage evaluation in response to a serogroup B meningococcal disease outbreak and mass vaccination campaign at a college-Rhode Island, 2015–2016. *Clinical Infectious Diseases* 2017;64:1115-22.
53. MacLennan J, Kafatos G, Neal K, et al. Social behavior and meningococcal carriage in British teenagers. *Emerging Infectious Diseases* 2006;12:950-7.
54. McCall BJ, Neill AS, Young MM. Risk factors for invasive meningococcal disease in southern Queensland, 2000–2001. *Internal Medicine Journal* 2004;34:464-8.
55. Stuart JM, Cartwright KA, Robinson PM, Noah ND. Effect of smoking on meningococcal carriage. *The Lancet* 1989;2:723-5.
56. Fischer M, Hedberg K, Cardosi P, et al. Tobacco smoke as a risk factor for meningococcal disease. *Pediatric Infectious Disease Journal* 1997;16:979-83.
57. Coen PG, Tully J, Stuart JM, et al. Is it exposure to cigarette smoke or to smokers which increases the risk of meningococcal disease in teenagers? *International Journal of Epidemiology* 2006;35:330-6.

58. Lujan-Zilbermann J, Warshaw MG, Williams PL, et al. Immunogenicity and safety of 1 vs 2 doses of quadrivalent meningococcal conjugate vaccine in youth infected with human immunodeficiency virus. *Journal of Pediatrics* 2012;161:676-81 e2.
59. Frota AC, Milagres LG, Harrison LH, et al. Immunogenicity and safety of meningococcal C conjugate vaccine in children and adolescents infected and uninfected with HIV in Rio de Janeiro, Brazil. *Pediatric Infectious Diseases Journal* 2015;34:e113-8.
60. Frota ACC, Harrison LH, Ferreira B, et al. Antibody persistence following meningococcal C conjugate vaccination in children and adolescents infected with human immunodeficiency virus. *Jornal de Pediatria* 2017;93:532-7.
61. Rezaei N, Aghamohammadi A, Siadat SD, et al. Serum bactericidal antibody response to serogroup C polysaccharide meningococcal vaccination in children with primary antibody deficiencies. *Vaccine* 2007;25:5308-14.
62. Bertolini DV, Costa LS, van der Heijden IM, Sato HK, Marques HH. Immunogenicity of a meningococcal serogroup C conjugate vaccine in HIV-infected children, adolescents, and young adults. *Vaccine* 2012;30:5482-6.
63. Balmer P, Falconer M, McDonald P, et al. Immune response to meningococcal serogroup C conjugate vaccine in asplenic individuals. *Infection and Immunity* 2004;72:332-7.
64. Menzies RI, Bremner KM, Wang H, Beard FH, McIntyre PB. Long-term trends in invasive Haemophilus influenzae type B disease among indigenous Australian children following use of PRP-OMP and PRP-T vaccines. *Pediatric Infectious Disease Journal* 2015;34:621-6.
65. Briere EC, Jackson M, Shah SG, et al. Haemophilus influenzae type b disease and vaccine booster dose deferral, United States, 1998-2009. *Pediatrics* 2012;130:414-20.
66. Vesikari T, Ostergaard L, Diez-Domingo J, et al. Meningococcal serogroup B bivalent rLP2086 vaccine elicits broad and robust serum bactericidal responses in healthy adolescents. *Journal of Pediatric Infectious Diseases Society* 2016;5:152-60.
67. Ostergaard L, Vesikari T, Absalon J, et al. A bivalent meningococcal B vaccine in adolescents and young adults. *New England Journal of Medicine* 2017;377:2349-62.
68. MacNeil JR, Rubin L, Folaranmi T, et al. Use of serogroup B meningococcal vaccines in adolescents and young adults: recommendations of the Advisory Committee on Immunization Practices, 2015. *Morbidity and Mortality Weekly Report* 2015;64:1171-6.
69. Patton ME, Stephens D, Moore K, MacNeil JR. Updated recommendations for use of MenB-FHbp serogroup B meningococcal vaccine – Advisory Committee on Immunization Practices, 2016. *Morbidity and Mortality Weekly Report* 2017;66:509-13.
70. Folaranmi T, Rubin L, Martin SW, Patel M, MacNeil JR. Use of serogroup B meningococcal vaccines in persons aged ≥10 years at increased risk for serogroup B meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, 2015. *Morbidity and Mortality Weekly Report* 2015;64:608-12.

Attachment 1: Meningococcal vaccine formulations and brands available for use in Australia and number of doses recommended by ATAGI for healthy individuals by age*

Vaccine	Formulation	Provides protection against serogroup	Currently registered age for its use	Number of doses recommended by ATAGI, according to age group*
Quadrivalent meningococcal conjugate vaccines (4vMenCV)				
Menveo	Quadrivalent CRM_{197} conjugate	A, C, W, Y	From 2 months†‡	2 to 5 months: • 2 primary doses and a booster 6 to 11 months: • 1 primary dose and a booster 12 to 23 months: • 2 primary doses From ≥2 years: • 1 primary dose
Nimenrix	Quadrivalent tetanus toxoid conjugate	A, C, W, Y	From 2 months# to 55 years‡	2 to 5 months: • 2 primary doses and a booster 6 to 11 months: • 1 primary dose and a booster From ≥12 months • 1 primary dose
Menactra	Quadrivalent diphtheria toxoid conjugate	A, C, W, Y	9 months to 55 years‡	9 to 23 months: • 2 primary doses From ≥2 years: • 1 primary dose
Multicomponent meningococcal B vaccines (MenBV)				
Bexsero	Recombinant multicomponent MenB	B	From 6 weeks§	6 weeks to 5 months: • 3 primary doses and a booster 6 months to 11 months: • 2 primary doses and a booster From 12 months: • 2 primary doses
Trumenba	Recombinant bivalent fHBP MenB	B	From 10 years§	• 2 primary doses
Meningococcal C conjugate vaccines (MenCCV)**				
Menitorix	Hib–MenC conjugate combination	C	From 6 weeks	Currently 1 dose at age 12 months. ATAGI recommends this dose to be replaced by a dose of meningococcal ACWY vaccine at 12 months and a dose of monovalent Hib vaccine at 18 months
NeisVac-C	Monovalent MenC conjugate	C	From 8 weeks	Currently ATAGI recommends 1 dose of meningococcal C vaccine at age 12 months, but monovalent meningococcal C vaccine is not currently used on the National Immunisation Program, as this dose is given in a combination vaccine with the Hib vaccine as Menitorix (refer to above)

* Dosing schedules are based upon ATAGI recommendations and may differ from the respective Product Information.

† The first dose of Menveo can be administered as early as 6 weeks of age.

The use of Nimenrix in infants aged 6 weeks to 11 months is a variation from the Product Information, and is based on data from clinical trials supporting its use in this age group.

‡There is no registered upper age limit for use of Menveo. Although both Menactra and Nimenrix are registered for use up to 55 years of age, either of these brands can be given to persons >55 years of age, as per *The Australian Immunisation Handbook.*

§ Bexsero and Trumenba are not interchangeable. The same vaccine should be used to complete the vaccination course.

** Currently in the National Immunisation Program a dose of meningococcal C vaccine is given at age 12 months; this is different from the youngest age at which this vaccine can be given as stated in the Product Information.

Attachment 2: Existing recommendations for the use of meningococcal ACWY conjugate vaccines and meningococcal B vaccines by age group in the current *Australian Immunisation* Handbook that are to be retained

Age group	Healthy people		Special risk groups*	Travellers#
	Aboriginal or Torres Strait Islanders	Non-Indigenous		
2†–23 months	MenB	MenB	MenB MenACWY	MenACWY
2–4 years	–	–	MenB MenACWY	MenACWY
5–14 years	–	–	MenB MenACWY	MenACWY
15–19 years	MenB	MenB	MenB§ MenACWY	MenACWY
≥20 years	–	–	MenB MenACWY	MenACWY

* Includes those with a specified medical condition associated with increased risk of meningococcal disease (refer to List 1), laboratory personnel who are at occupational risk of exposure to *Neisseria meningitides*# People (age ≥2 months) who are planning overseas travel to regions with an increased risk of exposure to meningococcal serogroups A, C, W, or Y disease.

† First dose can be administered as early as 6 weeks of age.

§ Young adults living in close quarters (such as new military recruits and students living in residential accommodation) are recommended to receive MenB vaccine