First statewide meningococcal B vaccine program in infants, children and adolescents: evidence for implementation in South Australia

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Summary

- Invasive meningococcal disease (IMD) is an uncommon but life-threatening infection caused by *Neisseria meningitidis*. Serogroups B, C, W and Y cause most IMD cases in Australia. The highest incidence occurs in children under 5 years of age. A second peak occurs in adolescents and young adults, which is also the age of highest carriage prevalence of *N. meningitidis*.
- Meningococcal serogroup B (MenB) disease predominated nationally before 2016 and has remained the predominant cause of IMD in South Australia with 82% of cases, compared with 35% in New South Wales, 35% in Queensland, 9% in Victoria, 29% in Western Australia and 36% nationally in 2016.
- MenB vaccination is recommended by the Australian Technical Advisory Group on Immunisation for infants up to 2 years of age and adolescents aged 15–19 years (age 15–24 years for at-risk groups, such as people living in close quarters or smokers), laboratory workers with exposure to *N. meningitidis*, and Aboriginal and Torres Strait Islander children from age 2 months to 19 years.
- Due to the epidemiology and disease burden from MenB, a meningococcal B vaccine program has been implemented in South Australia for individuals with age-specific incidence rates higher than the mean rate of 2.8/100 000 population in South Australia in the period 2000–2017, including infants, young children (< 4 years) and adolescents (15–20 years).
- Program evaluation of vaccine effectiveness against IMD is important. As observational evidence also suggests 4CMenB may have an impact on *Neisseria gonorrhoeae* with genetic homology between bacterial species, the vaccine impact on gonorrhoea will also be assessed.

Invasive meningococcal disease (IMD) is an uncommon but life-threatening infection that occurs worldwide and is caused by *Neisseria meningitidis*. An estimated 0.5–1.2 million cases of meningococcal disease occur every year, causing 50 000–135 000 deaths globally.[1,2] There are 13 known serogroups,[1] of which serogroups A, B, C, W, X and Y cause most IMD cases. In Australia and other high income countries, such as the United States, the United Kingdom and countries in the European Union, most IMD cases are due to serogroups B, C, W and Y, but recent cases due to serogroup E have been reported in Australia.[3] The highest incidence of IMD occurs in children aged less than 5 years (particularly those under 12 months), with a second peak during age 15–19 years, although cases occur throughout life.[4] The fatality rate for IMD ranges from 6.9% for serogroup B, to 12.8% for serogroup W, and is highest in infants and older people.[5] There is significant morbidity in IMD survivors, with 20–40% of patients developing sequelae, which include necrosis of the skin and gangrene of the limbs requiring extensive skin grafting and amputation, and other patients having permanent neurological deficits.[6]

Around 10–20% of the population carries *N. meningitidis* in the posterior pharynx, with higher carriage rates in adolescents and young adults.[7] In South Australia, the carriage rate in first year university students is about 6.2% (95% CI, 4.2–8.9%).[8] Only a very small proportion of carriers develop IMD,[2] with the mechanism of invasion poorly understood.

In 2018, in Australia, 281 IMD cases were notified nationally, with a notification rate of 1.1/100 000 population.[9] In children aged less than 5 years and adolescents aged 15–19 years, the notification rate was 4.6/100 000 and 2.6/100 000 respectively. National notification rates of IMD for Aboriginal and Torres Strait Islander people were over seven times (9.3/100 000 *v* 1.3/100 000) and four times (2.0/100 000 *v* 0.5/100 000), respectively, the rate for non-Aboriginal people.[10]

Historically, from 1997 until 2015 and again in 2018, MenB has predominated in Australia.[11] In 2016 and 2017, meningococcal serogroup W (MenW) disease became the most common serogroup nationally, and more recently, there has been an increase in meningococcal serogroup Y (MenY) disease.[3] In 2016, 97 of 105 MenW IMD cases in Australia were due to the hypervirulent MenW strain (ST-11: PorA P1.5,2).[4] This same strain has also caused disease outbreaks in the UK and South America (eg, Chile and Argentina), where meningococcal ACWY (MenACWY) vaccination programs have subsequently been introduced.[12] This increase in disease due to the hypervirulent MenW has resulted in the introduction of a Commonwealth-funded MenACWY vaccination program in Australia for infants at 12 months of age (replacing the meningococcal C vaccine) and adolescents aged 14–19 years.

In the UK, where MenB is the predominant serogroup causing disease,[13] an infant program of a multicomponent MenB vaccine (Bexsero [4CMenB]; GSK) was introduced for infants in a three-dose schedule — at 2 and 4 months of age (primary doses) and at 12 months of age (booster dose).[13] In the US, about one-third of cases are due to each of serogroups B, C and Y. Although the incidence of IMD in the US (average annual incidence 2006–2015, 0.26/100 000 population)[14] is lower than in the UK and Australia, several recent MenB outbreaks in universities have required implementation of MenB vaccine programs for university students to control outbreak disease.[15–17]

Meningococcal B vaccines

Two MenB vaccines to protect against capsular MenB disease (although lacking the capsular polysaccharide that defines this group) have been developed to offer protection against endemic and epidemic disease and are now licensed and available in Australia and many other countries, including the US and the UK.[18] Bexsero (4CMenB) and Trumenba (MenB-fHbp) (Pfizer), were licensed in Australia in 2013 and 2017 respectively.

MenB vaccine development has required new technologies, compared with the development of MenACWY vaccines, because

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the serogroup B capsular polysaccharide is identical to sugars in human fetal neural cell adhesion molecules and therefore considered a human self-antigen.[18]

The 4CMenB vaccine is a multicomponent recombinant vaccine consisting of outer membrane proteins, which have been identified as important bacterial virulence factors and targets for functional bacterial antibodies. These proteins include factor H binding protein (fHbp), neisserial adhesion A, and neisserial heparin binding antigen, which were formulated with the New Zealand epidemic strain meningococcal B outer membrane vesicle (MeNZB) vaccine to produce 4CMenB. This vaccine was initially registered for use from 2 months of age (recommended from 6 weeks of age by the Australian Technical Advisory Group on Immunisation [ATAGI]), in a four-dose schedule, at 6 weeks and at 4 and 6 months of age (primary doses) and at 12 months of age (booster dose).[19] More recently, an alternative three-dose schedule — at 6 weeks and at 4 months of age (primary doses) and at 12 months of age (booster dose; at least 6 months after the previous dose) — in infants has been approved by the Therapeutic Goods Administration, consistent with effectiveness and safety data from the three-dose infant program in the UK.[20] A two-dose schedule of 4CMenB, 8 weeks apart, is recommended for adolescents and young adults.[19] As the vaccine is reactogenic, with increased fever when administered concomitantly with other routine immunisations, paracetamol is recommended in children aged less than 2 years 30 minutes before vaccination, and two further doses can be given with 6 hourly intervals.[19] Using paracetamol prophylactically in infants reduces by about half the likelihood of high grade fever after any vaccine dose.[21] Administration of paracetamol has no overall impact on the immune responses to either Bexsero or other vaccines given at the same time.[21]

The MenB-fHbp vaccine includes the outer membrane protein fHbp (subfamily A and subfamily B). Although 4CMenB also contains this important outer membrane protein, it only contains fHbp from one subfamily.[22] MenB-fHbp is registered for use in individuals from 10 years of age, in a two-dose schedule 6 months apart or three doses in children at increased risk of IMD in Australia,[19] the UK and the European Union. Ongoing clinical trials are assessing its use in younger children.[23]

ATAGI recommends MenB vaccination for infants from 6 weeks of age up to 2 years of age and adolescents aged 15–19 years (15–24 years for certain at-risk groups, such as people living in close quarters or smokers), for laboratory workers with exposure to *N. meningitidis*, and for Aboriginal and Torres Strait Islander children aged from 2 months to 19 years.[19] However, no funded program has been implemented nationally. This is due to the Pharmaceutical Benefits Advisory Committee's assessment of unfavourable cost-effectiveness, with multiple uncertainties in relation to the clinical effectiveness of the 4CMenB vaccine against the disease when delivered in a vaccination program, optimistic assumptions about the extent and duration of effectiveness and herd immunity, and the unacceptably high and uncertain incremental cost-effectiveness ratio presented in two resubmissions.[24] In Australia, MenB vaccine is available for private purchase with a medical practitioner's script. However, individuals most at risk from MenB disease, including Aboriginal children and children from crowded households — often associated with lower socio-economic status — are less likely to be able to access this vaccine.

In light of ATAGI's recommendations, and the epidemiology and disease burden from MenB disease in SA, including four deaths in children over the past 5 years, the South Australian government has implemented a funded MenB vaccine program for young children and adolescents.

Evidence for a meningococcal B vaccine program in South Australia

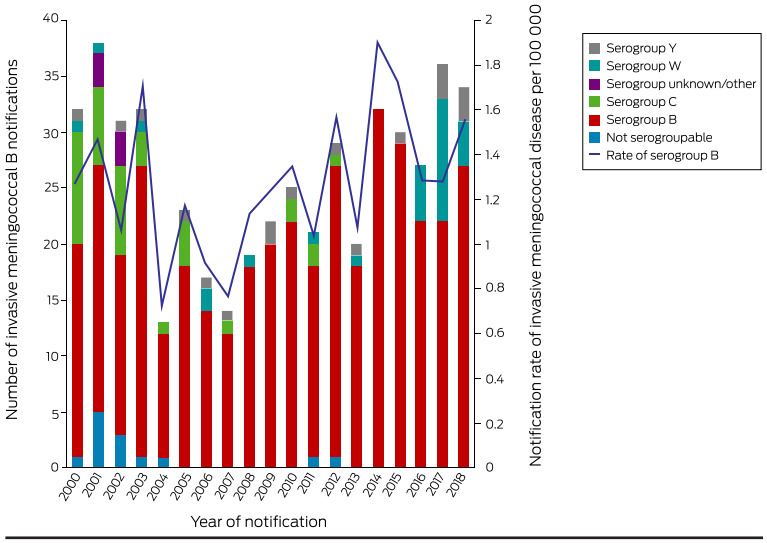
The literature review supporting the evidence for a MenB vaccine program in South Australia was performed searching the PubMed online database, including articles published between 2000 and 2019, with relevant conference abstracts included from international infectious diseases conferences.

Epidemiology and meningococcal B disease burden

The IMD notification rate in SA in 2017 was 2.1/100 000 population.[9] MenB has remained the predominant cause of IMD in SA,[3] with serogroup B causing 79% of all IMD cases from 2000 to 2018 (Box 1).[25] This is contrary to the national trend of a reduction in both the number and proportion of cases due to serogroup B from 2008 to 2016. In 2016, the proportion of IMD cases due to MenB was highest in SA, with 82% of cases, compared with 35% in New South Wales and Queensland, 9% in Victoria, 29% in Western Australia and 36% nationally.[25,26] In SA, from 2000 to 2017, the mean annual incidence for all individuals aged 0–25 years for MenB disease was 2.8/100 000.[25] During 2017, there were 36 IMD cases (22 MenB, 11 MenW and three MenY) in SA. Of these 36 cases, 13 were in children aged less than 5 years (eight MenB, four MenW, one MenY), one of whom died (MenB); there was one case in 5–9-year-olds, and one case in 10–14-year-olds (two MenW), four cases in adolescents aged 15–19 years (four MenB), three cases in 20–24-year-olds (two MenB, one MenW) and 14 cases (eight MenB, four MenW, two MenY) and two deaths (one MenB, one MenW) in adults aged 25–78 years. There have been 13 deaths from MenB in SA over the past decade, with a case fatality rate of 5.5% (unpublished data; Communicable Disease Control Branch, SA Health).

Most IMD cases in SA are caused by the New Zealand epidemic strain (clonal complex [CC]41/45: PorA 1.7,2.4).[25] Through the

1 Notifications of invasive meningococcal disease in South Australia by serogroup, 2000–2018



Source: Communicable Disease Control Branch, SA Health.

meningococcal antigen typing system,[27] it is predicted that, in SA, 4CMenB should be 90% effective against invasive group B disease. This compares to a predicted effectiveness of 71% in NSW, 84% in Queensland and 76% overall in Australia against invasive isolates (data collected from 2007 to 2011).[28]

Adolescents in SA have higher disease rates than in other states, with almost a third of adolescent MenB cases nationally in 2016 occurring in SA.[25] It is unclear why MenB rates are higher in SA, why adolescents have a greater disease burden and why the New Zealand strain dominates compared with other states. Host, pathogen and/or environmental factors are likely to contribute and may relate to specific virulence factors of the predominating genotype or population elements such as a dry dusty climate,[26,29] lower interstate mobility[30] and proportionately lower international visitors than many other states.[31]

Selection of meningococcal B vaccine for the South Australian Immunisation Program

A number of factors were considered in determining the vaccine schedule and vaccine choice for the SA MenB vaccine program, in addition to financial considerations. The safety profile of 4CMenB vaccine is acceptable for infants and adolescents, with ongoing safety surveillance in place in countries using the vaccine to detect any rare unexpected adverse events. The safety of 4CMenB has been extensively demonstrated in infants in the UK at a population level,[32] and at a state level in 35 000 adolescents enrolled in the SA MenB herd immunity study, from 2017 to 2018.[33] Over 17 million doses of 4CMenB have been delivered globally, with 3 million doses administered to infants in the UK showing no safety signals or concerns.[32] An increase in visits to emergency departments for fever in the UK was reported following implementation of the program.[34]

The safety of MenB-fHbp has been assessed in children and adolescents from 10 years of age, with over 2 million doses now distributed, mostly in the US, showing no safety concerns.[35] Clinical trials are ongoing to assess safety of MenB-fHbp in toddlers. Although only two doses of MenB-fHbp vaccine given 6 months apart are required for adolescents in general, a third dose of MenB-fHbp is recommended for adolescents at increased risk of IMD, compared with two doses of 4CMenB vaccine 2 months apart for adolescents.[19]

As 4CMenB is licensed from 2 months and recommended from 6 weeks, this vaccine would cover all age groups considered for vaccination, with the lowest number of vaccinations required for the age groups included in the SA MenB program.[19] The use of 4CMenB only eliminates the risk of administration errors such as the potential for MenB-fHbp being administered to children aged less than 10 years, for which it is not licensed. However, limiting the program to one manufacturer may have implications in terms of ensuring supply.

Meningococcal B immunisation schedule

In infants, the immunisation schedule chosen for the SA MenB program is the three-dose schedule recently approved by the Therapeutic Goods Administration, based on evidence of effectiveness and safety.[19] UK data show vaccine effectiveness estimated at 83% against all MenB cases after the two-dose primary series, and 94% against matched circulating strains with a three-dose schedule.[20] Adolescents receive a two-dose vaccine schedule of 4CMenB a minimum of 2 months apart (Box 2). There are limited safety and effectiveness data on adolescent 4CMenB vaccination population programs. SA is the first place globally to implement such an extensive program and already has the largest cohort of adolescents vaccinated with 4CMenB through the SA MenB vaccine herd immunity study.[36] Over 56 000 doses of 4CMenB were administered to adolescents from 2017 to 2018, with no safety signals identified.[33]

Vaccine program options

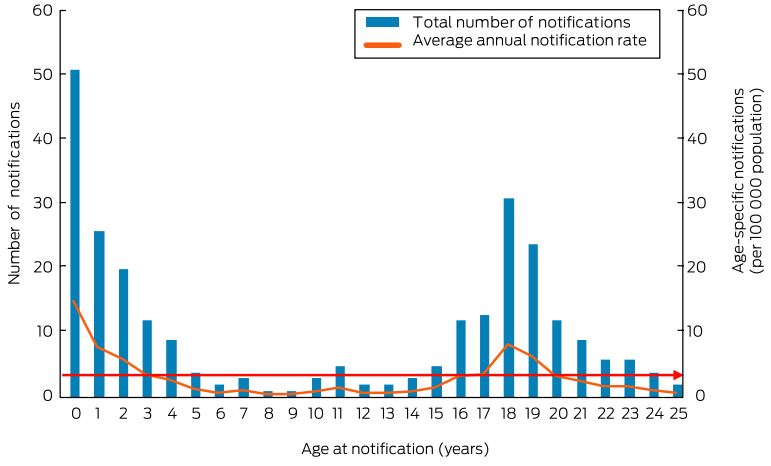
Several options for a MenB vaccine program for SA were considered. Given the disease burden and clustering of cases in infant and adolescent cohorts, those with age-specific incidence rates for MenB disease higher than the mean age-specific incidence rate of 2.8/100 000 for individuals aged 0–25 years in the SA population 2000–2017 were identified as the priority and focus of the program. Rates were calculated using the Australian Bureau of Statistic's data on estimated resident population for SA. Infants and children from birth to 3 years of age experience higher rates of disease, ranging from 14.9/100 000 in infants less than one year of age to 3.5/100 000 in 3-year-olds. In adolescents, notification rates ranged from 3.2/100 000 in 16-year-olds to 8.2/100 000 in 18-year-olds and 3.1/100 000 in 20-year-olds (Box 3).

2 South Australian Meningococcal B Immunisation Program

Program	Age	Program implementation	Program availability	Vaccine schedule
Childhood Immunisation Program	6 weeks to 12 months	Community*	1 October 2018 (ongoing)	2 months (or 6 weeks) and 4 months (primary doses); 12 months (booster dose)
Catch-up Childhood Immunisation Program	> 12 months to < 4 years	Community*	1 October 2018 to 31 December 2019	2 doses 8 weeks apart
Year 10 School Immunisation Program	15–16 years	School Immunisation Program	1 February 2019 (ongoing)	2 doses 8 weeks apart
Year 11 Catch-up School Immunisation Program	16–17 years	School Immunisation Program	1 February to 31 December 2019	2 doses 8 weeks apart
Young Adult Catch-up Immunisation Program	17 to < 21 years	Community*	1 February 2019 to 29 February 2020	2 doses 8 weeks apart

* Community includes general practice, local government clinics, Aboriginal Health Services, Child and Family Health Services, Country Health, SA Local Health Networks, and the Women's and Children's Health Network. ◆

3 Invasive meningococcal disease serogroup B notifications and notification rates in people aged 0–25 years in South Australia, 2000–2017



Source: Communicable Disease Control Branch, SA Health.

The cohorts for MenB vaccination include:

- children from 6 weeks to less than one year of age (ongoing), with a catch-up program for those less than 4 years of age (2018–2019); and
- year 10 student program (ongoing), with a catch-up program for year 11 students and adolescents and young adults up to 20 years of age (2019) (Box 2).

While year 10 students had an incidence rate of 1.4/100 000, they were included to provide protective immunity before the peak risk adolescent years. This program considered only direct protection against MenB disease, as evidence for a significant herd immunity impact for 4CMenB is lacking.[37] This extensive program is expected to prevent 12 cases of IMD per year and about one death every 2 years.

Discussion

Given the relative significance and precedence of this program in both the Australian and global context, measurement and evaluation of the program is central to demonstrating not only the program's effectiveness but, more importantly, its safety as a public health intervention. Program evaluation including cost-effectiveness will be instrumental in informing other potential state, national or international programs to provide population data in the field, which are not possible to obtain through clinical trials.

There are several questions remaining in relation to the safety and effectiveness of MenB vaccines, which a program evaluation will assist in answering.

Meningococcal antigen typing system testing suggests a possible effect of MenB vaccine on disease caused by other serogroups, as the outer membrane proteins in the vaccine are expressed by other serogroups in addition to serogroup B.[28] Recent evidence from New Zealand[38] and Canada[39] suggests 4CMenB vaccine may have an impact on *N. gonorrhoeae*, as there is 80–90% genetic homology between the two bacterial species. The SA program will assist in confirming whether there is a clinically significant impact of 4CMenB on gonorrhoea, with young adults aged 20–24 years having the highest rates of disease in SA. Any impact on gonorrhoea may result in a significant reduction in gonorrhoea incidence in groups with the highest rates. Notification rates of gonorrhoea are 22-fold higher in Aboriginal compared with non-Aboriginal youth, with the highest rates in 15–19-year-old Aboriginal adolescents.[40] Finally, the duration of protection and whether a booster vaccination is required in adolescents who received MenB vaccine as infants remain unclear. Continued surveillance for any breakthrough disease over the next decade will assist in determining booster vaccination requirements.

Vaccine safety will be monitored through the South Australian Vaccine Safety Surveillance system — an enhanced passive surveillance system used for timely detection of signals suggestive of an increase in adverse events following immunisation.

Vaccine coverage for adolescents will be assessed through the SA Immunisation Records and Inventory System and the Australian Immunisation Register. Vaccine coverage of 4CMenB vaccine and all vaccines covered under the National Immunisation Program will be reported. SA is the only state to provide vaccination against all common invasive meningococcal serogroups for infants and adolescents.

Vaccine impact will be measured using published methods for the evaluation of the UK MenB vaccine program.[20] Likely complete case ascertainment occurs in SA by surveillance of *N. meningitidis* through medical and laboratory reporting, as IMD is a notifiable disease. IMD attack rates will be reported by serogroup and fine typing of any isolates (identifying antigens based on whole genome sequencing results). Whole genome sequencing will also provide evidence of matching between the invasive disease isolates and the vaccine antigens and will assist in the determination of any true vaccine failures or evidence of waning immunity.

Vaccine effectiveness for vaccine-eligible age groups will be estimated using published methods.[20] Similar methods will be applied to measure any impact of 4CMenB on *N. gonorrhoeae*.

In SA, the addition of 4CMenB to the vaccination schedule means that, at 12 months of age, it is recommended all healthy infants receive four injections, but medically at risk Aboriginal children may be recommended to receive up to seven injections. Communication strategies to assist immunisation providers have been developed to provide guidance on the recommended limbs for vaccine administration and to ensure paracetamol is administered before vaccination to reduce the risk of fever. Paediatric emergency physicians are also being reminded of the importance of taking an immunisation history in considering the differential diagnosis in infants presenting with fever, particularly in relation to administration of 4CMenB within 48 hours of presentation, to avoid any unnecessary invasive tests. Targeted communication to parents, adolescents and young adults on the opportunity to be protected against this life-threatening infection will be essential, along with ensuring equitable access to the vaccine for our most disadvantaged children who bear the brunt of this severe disease.

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