One disease, two vaccines: challenges in prevention of meningococcal disease

Gaps in availability of both meningococcal ACWY and B vaccines exist for high risk groups

Invasive meningococcal disease (IMD) is a serious disease and an emotive public health issue in Australia. In the early 2000s, IMD case numbers declined nationally by about 80%, from 688 in 2002 to 149 in 2013, due to a drop in serogroup C and B disease. The decline in serogroup C disease followed the comprehensive childhood meningococcal C vaccination program — free vaccination was available up to age 19 years — introduced in 2003. Simultaneously, but without clear cause in the absence of vaccination, meningococcal B (MenB) disease declined slowly from 1.49 cases per 100 000 population in 2003 to 0.47 in 2015 (293 and 112 cases respectively). Overall, the IMD incidence rose again after 2014, driven mainly by the emergence of serogroup W and, to a lesser extent, serogroup Y. Most serogroup W strains are close variants of the virulent ST-11 clone initially identified in the United Kingdom and South America in 2009, which was associated with more frequent atypical clinical presentations, greater severity and increased mortality. Although the emergence of serogroups W and Y was a game changer, serogroup B still accounted for about half of all IMD cases in Australia between 2016 and 2018. Compared with some other vaccine-preventable diseases, IMD is relatively rare, affecting about one in every 100 000 Australians, equating to an average of 250 cases per year between 2014 and 2018. However, the case fatality rate is high, and around 10–30% of survivors experience long term sequelae. Although IMD can occur at any age, it is more common in children aged less than 2 years (especially those aged < 12 months) and older adolescents (Box 1). Aboriginal and Torres Strait Islander (hereafter respectfully referred to as Indigenous) children aged up to 14 years are also disproportionately affected compared with non-Indigenous children (Box 2). For example, rates of serogroup W IMD in Indigenous children were more than 30-fold higher compared with non-Indigenous children of the same age during 2016–2018 (Box 2). People with certain medical conditions also have a high risk of IMD. These conditions include asplenia; complement deficiency, which in some types the risk is up to 10 000 times greater than in the general population; and use of eculizumab, which is a monoclonal antibody directed against complement and is used for treating paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome.

Increased use of quadrivalent meningococcal conjugate vaccines

Three brands of quadrivalent meningococcal conjugate (MenACWY) vaccines are available in Australia: Menactra (Sanofi), Menveo (GlaxoSmithKline) and Nimenrix (Pfizer). These quadrivalent vaccines include a capsular polysaccharide from each ACWY serogroup conjugated to a carrier protein, superseding the less immunogenic polysaccharide-only vaccines previously used. The rapid rise of serogroups W and Y disease prompted all states and territories to fund MenACW vaccination programs in 2017 and 2018 as an outbreak response. These programs varied but predominantly targeted adolescents aged 15–19 years, aiming to both directly prevent disease and to interrupt community transmission of meningococci through reduced acquisition of nasopharyngeal carriage, which is most prevalent in this age group. Some jurisdictions also implemented time-limited vaccination programs covering select age groups, from infancy up to older adolescence, to control serogroup W outbreaks. The most notable of these outbreaks began in September 2017 in the Northern Territory and spread to nearby communities in central Australia, including regions in Western Australia, Queensland and South Australia. Indigenous children aged less than 10 years living in remote communities were primarily affected, with 19 cases within a few months.

Meningococcal B vaccine use in Australia

The modes of transmission, pathogenesis and treatment of serogroup B IMD are the same as for IMD caused by other serogroups, although the case fatality rate appears lower for serogroup B (6.9%) than for serogroups W, C and Y (12.8%, 12.0% and 10.8% respectively). However, the development of a vaccine against serogroup B disease was problematic for decades because serogroup B capsular polysaccharide is cross-reactive with human tissues (an autoantigen) and thus poorly immunogenic. Two MenB vaccines, developed using novel recombinantly derived protein antigens common to many serogroup B strains, are now available in Australia: Bexsero (GlaxoSmithKline), since 2013, and Trumenba (Pfizer), since 2017. Trumenba is only registered for use from 10 years of age, whereas Bexsero can be used from 6 weeks of age.
Both MenB vaccines have a high cost (around $100 per dose) and require multiple doses. Bexsero also causes higher rates of fever in young children than other vaccines included in the National Immunisation Program (NIP), necessitating the use of prophylactic paracetamol around the time of immunisation.6

Data on the benefits of MenB vaccine use are gradually accumulating, predominantly from the UK, which is the only country to have formally evaluated an ongoing funded population-based program. Infants in the UK have been offered a three-dose course of Bexsero (scheduled at ages 2, 4 and 12 months) since 2015. New data from the UK over 3 years estimate vaccine effectiveness against serogroup B IMD to be 52.7% (95% CI, −33.5 to 83.2) for a two-dose primary schedule for infants, and 59.1% (95% CI, −31.1 to 87.2) for a two-dose primary schedule followed by a booster dose at one year.14 However, Bexsero does not appear to have an impact on nasopharyngeal carriage of serogroup B,7 which implies that herd immunity (indirect protection in unvaccinated individuals) would be limited or absent despite population-based vaccination.9 In addition, for both vaccines, protection against only around three-quarters of all circulating MenB strains is predicted, based on in vitro assays.15

To date, the use of MenB vaccines in Australia has been limited in the absence of NIP funding. In October 2018, in the context of higher serogroup B IMD incidence rates compared with other parts of Australia, the South Australian government introduced the only state-funded MenB vaccination program for young children, expanding to adolescents in February 2019.8 In 2020, a population-level study of adolescent MenB vaccination in the Northern Territory will commence to explore its impact on gonorrhoea — a high incidence sexually transmitted disease caused by the related organism Neisseria gonorrhoea — as well as on serogroup B IMD (Helen Marshall, Professor in Vaccinology and National Health and Medical Research Council Practitioner Fellow, Robinson Research Institute, University of Adelaide, Australia, personal communication, January 2020).
Assessment and introduction of meningococcal vaccines to Australia’s National Immunisation Program

Both equity and cost-effectiveness are important considerations when approaching decision making regarding vaccine incorporation into immunisation programs. To be added to the Australian NIP, vaccines require a comprehensive assessment and must be recommended as cost-effective by the Pharmaceutical Benefits Advisory Committee (PBAC); this is based on economic modelling, typically undertaken by the vaccine manufacturer. With a low IMD incidence (one per 100,000), relatively small numbers of deaths, and trends in serogroup incidence being difficult to predict, the accurate assessment of the cost-effectiveness of both types of meningococcal vaccines (MenACWY and MenB) has been challenging. Low incidence rates have meant reliance on immunologic correlates of protection to predict vaccine impact (randomised placebo-controlled efficacy studies are not feasible for such rare outcomes) and a limited number of post-market vaccine effectiveness estimates. Other key uncertainties include the duration of protection and the magnitude of any herd protection effect, particularly for MenB vaccines, for which evidence is showing that there is no effect on nasopharyngeal meningococcal carriage. These uncertainties, together with the high cost of the MenB vaccines in particular, provide challenges for the value for money assessment necessary to underpin vaccine introduction into long-term programs.

In 2018, the MenACWY vaccine Nimenrix replaced the meningococcal serogroup C vaccine on the NIP at 12 months of age, and was also added to the NIP for use in a single birth cohort of adolescents aged 14–16 years from early 2019, replacing jurisdictionally funded programs. This is expected to provide direct protection to vaccinated individuals as well as some indirect protection to unvaccinated people over time. The potential to fund the MenACWY vaccine for certain high risk groups with underlying medical conditions through the NIP has also been flagged in a recent positive PBAC recommendation, which is under active consideration by the Australian Government.

The Bexsero MenB vaccine was assessed by the PBAC on three occasions between 2013 and 2015, but was deemed as not being cost-effective at the manufacturer’s proposed price. In November 2019, following another manufacturer application, the PBAC recommended the NIP inclusion of Bexsero for Indigenous infants (with a catch-up to 2 years of age) and for anyone with certain medical conditions (asplenia, complement deficiency, and eculizumab treatment). However, once again, the use of the vaccine in a broader population-based program for infants and adolescents was not considered cost-effective. The implementation of these recommendations is under active consideration by the Australian Government.

Gaps in the prevention of meningococcal disease in Australia

The Australian immunisation handbook recommends that any person who wants to protect themselves against invasive meningococcal disease can receive MenACWY and MenB vaccines from as early as 6 weeks of age. Box 3 shows groups particularly recommended for vaccination based on their higher risk of disease, compared with current and anticipated funded meningococcal vaccine programs.

New proposed and existing funded programs are a substantial achievement and will provide protection to many individuals most at risk from vaccine-preventable meningococcal strains. However, some equity gaps remain. It will take time to accrue the benefits of reduced MenACWY disease incidence and disease transmission across the population when vaccinating only at ages one and 15 years, especially without including all infants in the NIP-funded program. It is possible that the disparity in IMD rates between Indigenous and non-Indigenous children may persist for years, particularly for serogroup B disease, in the absence of herd immunity and of an adolescent program funded by the NIP. Assessing program impact on disease, particularly in jurisdictions where wider populations did, or continue to, receive state-funded vaccines (against MenACWY or MenB disease), such as Western Australia, Tasmania and South Australia, is essential to evaluate evidence of benefit. The remaining access gaps are very challenging to address for high cost vaccines that are not offered at cost-effective prices by the manufacturer. Other initiatives, such as ensuring that health services fund vaccination of persons living with human immunodeficiency virus and of at-risk laboratory workers (two groups not included in the NIP), and addressing the social determinants of health that underpin high rates of meningococcal disease (and other vaccine-preventable diseases), are also important.

Conclusion

Australia has progressively implemented funded vaccination programs for various high risk groups using MenACWY and MenB vaccines over the past 5 years. The anticipated expansion of NIP funding to include medical at-risk groups for both vaccines and to include young Indigenous children for MenB vaccine, in addition to established MenACWY programs, should be effective over time to protect those most at risk of disease. Close monitoring of emerging data on the duration of vaccine protection from Australia and internationally is needed, particularly for individuals with underlying medical conditions whose risk is enduring. It remains challenging that for one disease, IMD, we must use two vaccines; while at least one pentavalent vaccine (MenABCWY) is under development, it is years away from use, and the assessment of cost-effectiveness is equally uncertain. This rare but deadly disease will continue to challenge; clinicians should remain aware and
discuss vaccination options against both MenB and MenACWY disease with their patients.

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