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Meningococcal B Conjugate Vaccine (4CMenB) Meets Expectations but Does Not Exceed Them

P. Gavin

CHI at Crumlin and Temple Street Hospitals, Dublin.

In December 2016, meningococcal B conjugate vaccine (4CMenB) was included in childhood immunisation in Ireland and offered to all infants in a three-dose schedule (primer at 2 and 4 months and booster at 12 months). While its introduction represented a major advance in the decades long effort to protect from invasive meningococcal disease (IMD), novel aspects of its development and licensure raised questions about its clinical efficacy to protect the individual directly and the population indirectly by inducing herd immunity. Articles by Ladhani et al. and Marshall et al. in the January 23rd, 2020 issue of the *New England Journal of Medicine* provide answers to these questions. [1, 2]

Neisseria meningitidis is a Gram-negative diplococcus adapted to colonise the human nasopharynx and a leading cause of bacterial meningitis and invasive disease worldwide. Case-fatality rates range from 10%-20%. Incidence rates of IMD are highest in infants and young children under one-year of age. Six serogroups A, B, C, W-135, X and Y, based on antigenically distinct polysaccharide capsular antigens, are responsible for all IMD. Polysaccharide antigens are poorly immunogenic in infants and young children under two-years of age, but conjugation (covalent linkage) to protein carriers improves immunogenicity by eliciting a T-cell dependent immune response and immunologic memory. Polysaccharide-protein conjugate vaccines are now widely used to protect against IMD caused by serogroups A, C and ACWY. [3] Vaccination of Irish infants with meningococcal C conjugate, in 2000, when IMD was hyperendemic (incidence rate, 14.7/100,000 was the highest in Europe) was associated with a 85% decrease in IMD caused by serogroup C (135 cases in 1999 to 20 cases in 2018; 1.6/100,000). [4] However, concern for autoimmunity because of structural homology between meningococcal B capsular polysaccharide and sugars on the surface of many human cells, especially dendritic cells, required a new approach to vaccine development. 4CMenB was developed using reverse vaccinology - whole genome sequencing to identify protein antigens with protective potential. [5] 4CMenB contains recombinant meningococcal outer membrane proteins shared by serogroup B and non–B meningococci but no B capsular polysaccharide component.

Much of the protective effect of conjugate vaccines is due to a combination of increased immunogenicity and a powerful herd immunity effect. [6] Vaccination of US infants with PCV7 was associated with a 90% reduction in disease caused by PCV7 serotypes of *S. pneumoniae* in all adult populations (not just those vaccinated). [7] Introduction of meningococcal C vaccine in the UK saw a 67% reduction in disease in the unvaccinated population; primarily resulting from immunisation of teenagers, the age group associated with high rates of meningococcal carriage and transmission. [8, 9] And introduction, in 2010, of meningococcal A conjugate vaccine in the sub-Saharan African meningitis belt, where a 1996-97 meningococcal epidemic caused >250,000 reported cases and 25,000 deaths, led to control and near elimination of serogroup A IMD. [10] However, dependence on antigenically variable protein antigens in 4CMenB rather than invariant polysaccharide antigens used in Men A, C and ACWY vaccines, meant 4CMenB would not protect the individual against all serogroup B strains and the ability to reduce asymptomatic carriage, prevent transmission and indirectly protect the population (herd immunity) was uncertain. While small observational studies of 4CMenB in outbreaks of serogroup B IMD in universities in the US showed no significant effect on carriage, it was hoped that shared protein antigens in 4CMenB might reduce carriage of serogroup B and non-serogroup B strains capable of causing IMD. [11, 12]

4CMenB (Bexsero) was licensed in Europe in 2013 as a four-dose schedule based on safety and in vitro serological data predicting protective potential rather than on clinical protection in large population vaccine efficacy trials. The rarity of IMD in Europe and North America (0.1/100,000) - incidence had been declining prior to the introduction of vaccine - and large numbers of subjects required to demonstrate a reduction in incidence of disease made classical vaccine efficacy trials unfeasible.

Ladhani et al. report on the effect of 4CMenB following its inclusion in the national immunisation program in England and its effectiveness in preventing serogroup B IMD in infants and children. [1] In the three-years following its introduction, there was a 75% reduction in incidence of serogroup B IMD (63 observed versus 253 expected cases) in age groups in which all children were eligible for vaccination. Estimated vaccine effectiveness of 59% against all serogroup B IMD among children who received three doses is at the lower end of predictions for the UK and Ireland. [13, 14] While somewhat disappointing, this likely underestimates true vaccine effectiveness because the analysis included all children with group B IMD in the vaccine-eligible cohorts, irrespective of vaccination status or strain coverage and 4CMenB should not protect against all group B strains.

Because carriers of serogroup B meningococcus are an important source of transmission, population meningococcal carriage must be reduced for a herd immunity effect. Marshall et al. provide more clarity on the ability of 4CMenB to eradicate carriage of IMD causing meningococci in teenagers and produce herd immunity. [2] From 2017 through 2018, as part of the “B Part of It” study, 24,269 15 to 18-year old secondary school students in South Australia were randomised according to school to receive 4CMenB. The primary outcome was prevalence of carriage of any disease-causing serogroup of *N. meningitidis* 12 months after vaccination.

Disappointingly, despite a moderate vaccine coverage rate of 62%, there was no discernible effect on carriage of disease-causing meningococci, including serogroup B, between the vaccination and control groups at 12 months. Whilst it is possible that unvaccinated students served as a source of ongoing transmission and that vaccine may have reduced carriage earlier, the effect did not last for 12 months. Receipt of 4CMenB did protect vaccinated individuals; there were no cases of serogroup B IMD in students during the trial and the following year, as compared with 12 cases among students in the preceding year.

These articles provide important information for clinicians on the benefits and limitations of 4CMenB. We now have real-world evidence that the reduced three-dose 4CMenB schedule adopted by the UK and Ireland protects infants and toddlers against serogroup B IMD for at least two years. We also have validation of vaccine licensure based on serological data rather than traditional clinical efficacy trials, which may expedite future vaccine development and licensure. Unfortunately, three doses of vaccine may not protect against IMD caused by close to 40% of serogroup B strains and one dose only provides about 25% protection. So, notwithstanding vaccination, many infants, particularly the very young, will remain susceptible to IMD. In addition, we have confirmation that 4CMenB has no effect on carriage of serogroup B or other disease-causing meningococci and does not protect the unvaccinated population by providing herd immunity. So 4CMenB will not eradicate serogroup B IMD. Individuals at high risk for serogroup B IMD need direct protection and, in the outbreak setting, antibiotics remain necessary to rapidly eliminate carriage. Introduction of 4CMenB undoubtedly represents a major success in the effort to prevent serogroup B IMD but the need for a better vaccine remains.

Corresponding Author:
Dr Patrick Gavin
CHI at Crumlin and Temple Street Hospitals, Dublin.
Email: gavinpa@tcd.ie

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