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Emerging clinical experience with vaccines against group B meningococcal disease

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ABSTRACT

The prevention of paediatric bacterial meningitis and septicaemia has recently entered a new era with the availability of two vaccines against capsular group B meningococcus (MenB). Both of these vaccines are based on sub-capsular proteins of the meningococcus, an approach that overcomes the challenges set by the poorly immunogenic MenB polysaccharide capsule but adds complexity to predicting and measuring the impact of their use.

This review describes the development and use of MenB vaccines to date, from the use of outer membrane vesicle (OMV) vaccines in MenB outbreaks around the world, to emerging evidence on the effectiveness of the newly available vaccines. While recent data from the United Kingdom supports the potential for protein-based vaccines to provide direct protection against MenB disease in immunised children, further research is required to understand the breadth and duration of this protection. A more detailed understanding of the impact of immunisation with these vaccines on nasopharyngeal carriage of the meningococcus is also required, to inform both their potential to induce herd immunity and to preferentially select for carriage of strains not susceptible to vaccine-induced antibodies.

Although a full understanding of the potential impact of these vaccines will only be possible with this additional information, the availability of new tools to prevent the devastating effect of invasive MenB disease is a significant breakthrough in the fight against childhood sepsis and meningitis.

1. Introduction

Neisseria meningitidis is responsible for severe and often fatal cases of invasive bacterial disease. Of the 6 capsular groups (A, B, C, W, X, Y) responsible for severe meningitis and septicaemia, capsular group B meningococcus (MenB) is now the leading cause of invasive meningococcal disease (IMD) in many high-income settings. Although there is a trend for a reduction in annual cases of MenB per 100,000 population in some countries, the case fatality ratios are significant, with an average of 3 - 10% globally [1].

The immunological cross-reactivity between the MenB polysaccharide capsule and human polysialyted neuronal cell adhesion molecule (PSA-NCAM) gives rise to a poorly immunogenic capsule that risks inducing autoimmune disease if used as a vaccine antigen,leading to significant challenges in the development of an effective vaccine. To overcome this limitation, vaccines using outer membrane proteins as target antigens have been developed, presented either in outer membrane vesicles or as recombinant proteins. One of the vaccines (Bexsero®, 4CMenB; GSK) is now used in the routine immunisation schedules for infants in the United Kingdom (UK) and Ireland, while another (Trumenba®, Bivalent rLP2086; Pfizer) has been licensed in adolescents in the United States (US) and Europe. This article will review the development of these MenB vaccines, their current use and highlight areas requiring further research.

2. Outer membrane vesicle vaccines

Outer membrane vesicle (OMV) vaccines against MenB disease have been developed for use in humans since the 1970s [2–4]. The immunodominant protein in these OMVs is Porin A (PorA), resulting in induction of antibodies which are most effective in targeting MenB strains bearing homologous PorA variants. Due to this specificity, these vaccines are most suitable for use in clonal outbreaks, where a vaccine can be developed to target a specific strain.

OMV MenB vaccines have been used across Cuba, New Zealand, Brazil, Chile and France to combat epidemic MenB outbreaks. Efficacy results of the first OMV vaccines used (in Cuba, Norway and

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France) – were over 80% for 2 dose schedules [5–7]. However, when longer follow up periods were assessed including an OMV vaccine studied over 20 months in Chile, the efficacy decreased to 50%, indicating poor longevity of response [6,8,9]. The OMV vaccines developed in Cuba and Chile demonstrated reduced efficacy and effectiveness (respectively) in children aged < 4 years old when compared to older children and adolescents [8,10,11]. There was particularly poor protection against MenB vaccine strains bearing heterologous PorA in this age group [5,12].

A national campaign using an OMV MenB vaccine (MeNZB) was conducted in New Zealand in 2004–2008 in response to an outbreak due to meningococcal clonal complex (cc) 41/44, harbouring PorA variable region (VR) P1.4. The effectiveness of a 3 dose schedule was estimated at as high as 77% for those aged 0-19 years old over a 3 year period [13]. An observational comparison of fully immunised and non-immunised New Zealanders aged less than 20 years suggested that immunisation with 4CMenB may have had more than 50% effectiveness against non-epidemic strain meningococci (both MenB and non-group B) [13]. However, there were wide confidence intervals for these estimates and the possibility of confounding factors contributing to these results is highlighted by the authors.

3. 4CMenB (Bexsero®)

The need for a MenB vaccine with the potential to protect against multiple endemic strains led to the development of a multicomponent MenB vaccine (4CMenB), incorporating novel proteins identified from the genome of a representative MenB strain through a process of 'reverse vaccinology'. 4CMenB combines the OMV component of the New Zealand vaccine (derived from strain NZ 98/254), in which PorA is the immunodominant protein, with the recombinant sub-capsular proteins factor H binding protein (fHbp), Neisserial adhesin A (NadA) and Neisserial Heparin Binding Antigen (NHBA).

3.1. Immunogenicity

4CMenB was licensed in Europe in 2013 for children ≥ 2 months of age, followed by other parts of the world including Canada and Australia for children ≥ 2 months of age, and in the US for individuals aged 10–25 years (see table 1 for the current licensed dosing schedules) [14–17]. In the absence of efficacy data, licensure was based on immunogenicity as determined in clinical trials, measured using serum bactericidal antibody (SBA) assays with human complement, the known correlate of protection. When tested against MenB strains expressing closely matched antigens to those included in the vaccine, these licensed schedules of 4CMenB are able to induce levels of bactericidal antibodies above the correlate of protection in the vast majority of recipients [14].

Vaccine induced SBA titres are known to wane following immunisation in infancy, such that by 12 months of age fewer than 20% of children had SBA titres ≥1:5 titres for two out of the four strains [18], with further waning by 24 months of age [19]. In both Phase 2 and 3 infant studies, following a booster dose at 12 months, the proportion of children reaching these titres against all strains increased to 93–100% [18,20], supporting the licensed recommendation for a booster dose in the second year of life. Despite this booster dose, by four years of age, SBA titres were consistently higher than controls only for 1 out of 4 reference MenB strains, regardless of whether the booster dose was administered at 12, 18 or 24 months of age [21]. A further booster dose at 4 years of age increased SBA titres to levels similar to, but no higher than, those observed after the toddler dose.

Recent immunogenicity data from a Phase IIIb multi-centre international study has demonstrated comparable immunogenicity in infants receiving a 2 dose (3.5 and 5 month) and 3 dose (2.5, 3.5 and 5 month) priming immunisation schedule [22], providing support for the reduced dose infant immunisation schedule adopted by the UK.

3.2. Predicted coverage

Given 4CMenB is based on antigens that vary in the meningococcus, it is not expected that immunisation with this vaccine would protect against 100% of MenB bacteria. Due to antigenic variability and differing levels of protein expression on a given MenB strain, in addition to uncertainty surrounding the degree of cross reactivity of antibodies against heterologous MenB strain antigens, the predicted coverage offered by 4CMenB vaccine is difficult to estimate. Coverage of 4CMenB has been assessed using several methods including the meningococcal antigen typing system (MATS), Bexsero Antigen Sequence Types (BAST) and using pooled sera from immunised children for testing against representative panels of hSBA strains.

MATS used a modified enzyme-linked immunosorbent assay (ELISA) to provide a strain-specific assessment of both the level of expression of target antigens (fHBP, NadA and NHBA), and their likely cross reactivity with antibodies induced by immunisation with 4CMenB. This, in combination with genotyping of PorA, ascertains whether the strain is 'covered' by 4CMenB [23]. Over 1000 meningococcal strains isolated across Europe were tested using

Table 1
Licensed dosing schedule for 4CMenB (based on European Medicine Agency licensure, comments regarding international licensing differences) [14–17].

Age group	Primary immunisation	Intervals between primary doses	Booster	Comment
Infants 2 months to 5 months	Three doses each of 0.5ml, with first dose given at 2 months of age	Not less than 1 month	Yes, one dose between 12 and 15 months	
Unvaccinated infants 6 months to 11 months	Two doses each of 0.5ml	Not less than 2 months	Yes, one dose in the second year of life with an interval of at least 2 months between the primary series and booster dose	
Unvaccinated children 12 months to 23 months	Two doses each of 0.5ml	Not less than 2 months	Yes, one dose with an interval of 12 months to 23 months between the primary series and booster dose	Need for a booster in this age group remains uncertain. Australian and Canadian guidelines do not recommend booster
Children 2 years to 10 years	Two doses each of 0.5ml	Not less than 2 months	Need not established	
Adolescents (from 11 years of age) and adults	Two doses each of 0.5ml	Not less than 1 month	Need not established	No data on the use of 4CMenB in individuals aged over 50 years

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