Meningococcal B vaccine – the Last Piece of the Puzzle?

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Meningococcal infection is a major cause of morbidity and mortality worldwide, and is most common in infants, young children, and adolescents. The large majority of invasive meningococcal disease (IMD) cases are caused by five main *Neisseria meningitidis* serogroups, A, B, C, W135 and Y. Following an increase in cases of meningococcal serogroup C dis-ease in the 1990's there was a rapid development and deployment of monovalent polysaccharide-conjugate serogroup C meningococcal conjugate vaccines (Men C).[1] The successful incorporation of these vaccines into routine childhood vaccination schedules since 1999, is estimated to have prevented over 9,000 cases and 1,000 deaths over the subsequent years **(Figure 1).**[2,3] This has been followed by the development of effective quadrivalent glycoconjugate vaccines against the four serogroups, A, C, W135 and Y, but the development of a broadly effective vaccine against serogroup B has been difficult.

Serogroup B has always been the predominant meningococcal serogroup in the UK in the modern era, accounting for approximately 60% of IMD cases before the introduction of the Men C vaccines, increas-ing to approximately 90% of cases as serogroup C inci-dence has declined to virtually zero **(Figure 1).** With the similar successes of glycoconjugate vaccines against *Haemophilus influenza* type b (Hib) and *Streptococcus pneumoniae* this leaves serogroup B as the most common cause of bacterial meningitis and septicaemia in the UK, associated with high mortality and morbidity, particularly affecting young infants and pre-school children **(Figure 2).** So protecting infants against serogroup B meningococcal disease remains a major public health need.

The successful monovalent vaccines against serogroups C, and the multivalent vaccines against serogroups A, C, W135 and Y are polysaccharide-pr-tein glycoconjugates, exploiting the antigenicity of the characteristic capsular polysaccharides that define these serogroups, chemically conjugated to carrier proteins (typically forms of diphtheria or tetanus toxoids) to enhance the immune response.[4] The serogroup B polysaccharide, however, is poorly anti-genic as it closely resembles some human neural poly-saccharides, so another approach to develop a serogroup B vaccine was necessary.[4,5]

For some strain specific regional outbreaks, notably in New Zealand, Norway and Cuba, prepara-tions of outer membrane vesicles (OMV) in which the main antigen is the PorA protein were used as the basis for MenB vaccines. However, while successful against the specific strains responsible for each out-break, and with the variability of the PorA proteins, such vaccines provide neither long-lasting nor broad responses against other strains.[5] In response, by applying the techniques of reverse vaccinology, Novartis Vaccines and Diagnostics took the novel approach of sequencing and analysing the meningococcal genome to identify and select surface-exposed proteins that would be present on a majority of serogroup B strains, and thus provide recombinant protein candidates for inclusion in a broadly effective vaccine.

This resulted in the multicomponent vaccine (4CMenB), which has recently received European approval as Bexsero®. This innovative vaccine con-tains three recombinant proteins: *Neisseria* heparin binding antigen (NHBA) and factor H binding antigen (fHbp)?both which are presented as fusion proteins with other recombinant proteins - and *Neisserial* adhesin A (NadA), in addition to the OMV from the New Zealand outbreak strain, NZ98/254, which has the PorA P1.4 variant. In the development of this vac-cine to licensure, it has been evaluated in large scale clinical trials involving over 6400 infants, children, adolescents and adults.

Immunogenicity

The relative rarity of meningococcal disease means vaccines cannot be assessed on the basis of their effi-cacy, but a surrogate of efficacy is applied, namely the ability of sera from vaccinees to kill *N. meningitidis* bacteria *in vitro* - the serum bactericidal activity (SBA).[6] An exogenous complement source must be included in this assay, and some meningococcal vaccines have been licensed on the basis of their ability to elicit SBA with baby rabbit complement (rSBA), but the gold standard is to use human complement (hSBA). The correlate applied to license MenC vaccines was a serum dilution of

1:4 in an hSBA assay (i.e., an hSBA titre of 4), which was considered to be protective, as indicated by data from recuperating IMD patients.[6] Subsequent experience with the large-scale use of MenC vaccines in the UK has supported this concept[2] and the same correlate has been accepted for the quadrivalent ACWY vaccines which followed, and the new MenB vaccine. Due to the multicomponent nature of Bexsero® immunogenicity of the vac-cine was tested as hSBA against several *N. meningitidis* target strains, each selected to be relatively specific for one of the four vaccine antigens, as not all MenB strains either have the genes or express each of the individual antigens. As with the glycoconjugates, an hSBA titre >4 was used as indicator of protection, although in some infant studies a titre >5 was applied as cut-off as this is considered to be protective with
95% confidence.

In these clinical studies Bexsero® has been shown to be immunogenic and generally well tolerated in all age groups from 2 month-old infants to adolescents and adults. In infants, three doses of Bexsero® at 2,4,6 or 2,3,4 months elicit high levels of protective titres, and a 4th dose at 12 months boosts all responses **(Figure 3).**[7,8] The vaccine has no clinically significant effect on responses to concomitantly administered routine vaccines (Infanrix™-Hexa and Prevenar™).[7,8] There were also high responses to two doses of Bexsero® in toddlers at 12-15 months, with the first dose given either concomitantly with or separately from measles, mumps, rubella and varicella (MMRV) vaccine.[9] Other studies have confirmed similar high immunogenicity to two doses in adolescents given 1, 2 or 6 months apart[10] and adults,[11] achieving the protective response in virtually 100% of subjects against at least two antigens.

Reactogenicity and safety

In the licensure studies, Bexsero® has been assessed in 4843 infants and children, and 1584 adolescents and adults and raised no safety concerns. When given alone, reactions to Bexsero® are similar to routine vaccines, but there is a small incremental increase in reactions when routine vaccines and Bexsero® are given concomitantly **(Figure 4).**[7,8] The increase in reports of fever when Bexsero® is given concomitantly with routine vaccines is principally associated with more fever on the day of vaccination and can be mitigated by prophylactic paracetamol, without compromising the responses to the vaccine components.[12]

The coverage and hence effectiveness of Bexsero® against circulating strains of serogroup B meningococci will depend upon the presence and expression of the vaccine antigens in those strains. As it is technically not feasible to test sera from Bexsero® vaccinees against all potential strains, especially when one considers the small volumes of sera obtained from infants, an automated technique has been developed to predict coverage. The Meningococcal Antigen Testing System (MATS) uses antigen-specific ELISAs to determine the cross-reactivity and quantity of the antigens expressed by individual meningococcal strains, and is predictive of the susceptibility of any particular strain to killing in the SBA by Bexsero® -induced antibodies.[13] MATS has been developed and validated in several national reference laboratories, where testing so far has revealed conservative estimates (as synergies and additional OMV antigens are not taken into account) of strain coverage from 69% to 87% in different European countries, with a coverage
of 73% (95% CI: 57-87%) in England and Wales.

Conclusions

Meningococcal serogroup B disease is a public health problem, particularly affecting infants and young children, and is now the major cause of meningitis and sepsis in UK children. Strategies to successfully develop glycoconjugate vaccines against other bacterial causes of meningitis and meningococcal serogroups cannot be applied to serogroup B, making the licensure of Bexsero® a milestone in paediatric vaccine development. In extensive clinical testing this innovative vaccine has been shown to be well tolerated and highly immunogenic in the primary target age groups of infants and young children, and immunogenicity has also been demonstrated in older children and adolescents who are likely to be included in any catch-up campaign when Bexsero® vaccination is implemented. Bexsero® can be administered concomitantly with cur-rent routine infant and toddler vaccines to facilitate inclusion in the immunisation schedule. The predicted strain coverage includes the majority of serogroup B strain isolates from the UK, so inclusion of Bexsero® with established vaccines will offer the first realistic opportunity of providing children with protection against all causes of bacterial meningitis.

Declaration
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Figure 1

Meningococcal disease rates over the decasde following introduction of routine meningococcal serogroup C vaccination in Emgland and Wales.From reference 2.

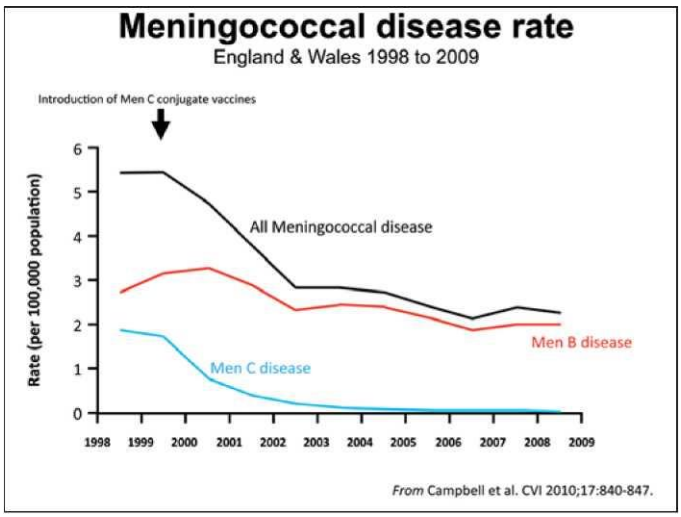


Figure 2

Laboratory-confirmed cases of meningococcal serogroup B infection in England and Wales per year and age group. Data from reference 3.

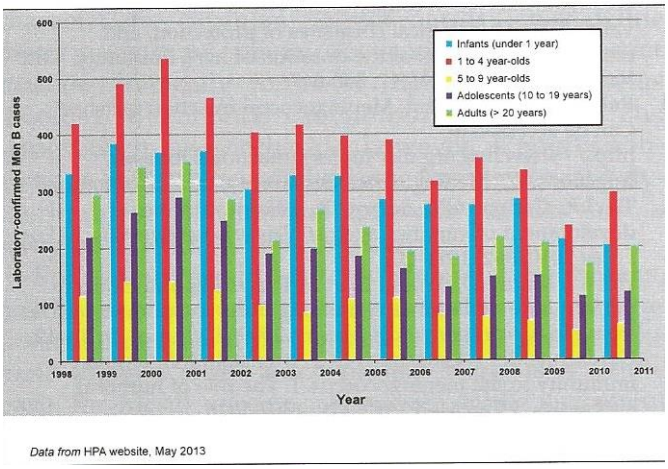


Figure 3

"Seroprotection rates" (hSBA titres >5) against the four indicator strains in infants and toddlers following four doses of 4CMenB at 2, 4, 6 and 12/13 months of age. Data from reference 8.

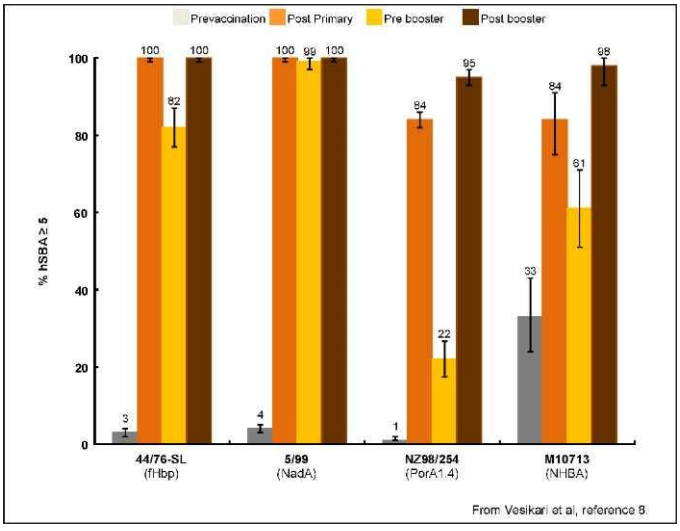
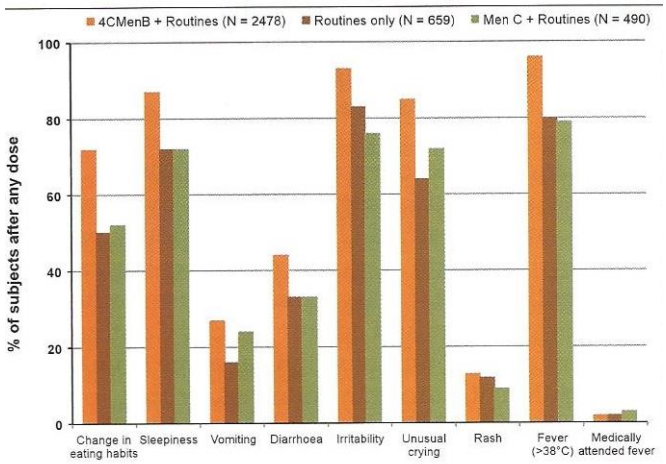


Figure 4

Systemic reaction incidence rates after any of the three doses in the infant schedule (2, 4, 6 months), when 4CMenB was administered concomitantly with routine (DTaP-HBV-IPV/Hib and PCV7) vaccines, compared with routine vaccines alone, or routine vaccines with MenC vaccine. Data from Reference 8.



From Vesikari et al. [