Opinion

How important is the meningococcal B vaccine?

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Neisseria meningitidis (NM) is the most important cause of meningitis and septicemia in previously healthy children. Even when diagnosed early and with appropriate treatment, case fatality is estimated at 5–10%. Approximately 30% of survivors suffer severe sequelae, with deficits in physical, cognitive and psychological functioning [1]. In its early stages, invasive meningococcal disease (IMD) often presents with nonspecific symptoms and is therefore difficult to diagnose. If untreated, the disease can progress rapidly with the patient dying within 24–48 h.

Young children and adolescents are the age groups that suffer the greatest disease burden. The highest incidence of disease is seen in children less than 5 years of age, particularly those <1 year [2].

Neisseria meningitidis is carried in the oropharynx of approximately 10% of the population; the highest rate of carriage is in adolescents. Transmission is through close contact as the bacteria do not survive outside of the human body for more than a few hours [3]. There are 13 different serogroups of *N. meningitidis*, six of which cause the majority of invasive disease (serogroups A, B, C, W135, X and Y). These strains differ in their geographical distribution, and somewhat in disease presentation.

Serogroup B *N. meningitidis* (MenB) causes greater than 50% of cases in the USA and as many as 90% of cases in Europe since the successful introduction of conjugated MenC vaccine, which has all but eliminated MenC disease in countries that have a routine immunization programme against MenC [4,5].

In 2011, there were 3769 reported cases of IMD in 29 European countries, of which 1036 were from the UK [6]. Of these >80% were caused by serogroup B. It is assumed that the number of laboratory confirmed cases is an under-representation of true disease prevalence.

MenB in contrast to the other serogroups, has a poorly immunogenic capsule, hence why progress in developing an effective vaccine has been hindered [7]. The polysaccharide capsule of MenB is composed of polysialic acid (α2–8 *N*-acetylneuraminic acid), which is present in glycoproteins found in fetal brain tissue. Consequently, there is immune tolerance to this polysaccharide and theoretical concerns regarding the effect of modifying the sugar structure to make it immunogenic, in case of induction of autoimmunity. Therefore, MenB vaccine development has required a different approach from that used for the preparation of conjugate vaccines for the other serogroups.

Vaccines for serogroup B meningococcal infection

Because of these difficulties, the development of MenB vaccines has focused on use of subcapsular antigens. For example, *N. meningitidis* sheds outer membrane blebs containing proteins and lipopolysaccharide. These outer membrane vesicles (OMVs) can initiate complement activation and may redirect complement activation away from whole meningococci in the circulation, hindering the bactericidal effects of complement [8]. OMVs have been shown to

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contain outer membrane proteins (OMPs) and other periplasmic and cytoplasmic proteins [7].

N. meningitidis produces a surface protein that binds human complement factor H (factor H binding protein, fHbp). Factor H regulates the alternative complement pathway, and its binding to the surface of meningococci may inhibit complement-mediated bacterial lysis. Consequently, this is protective for the bacteria, thus promoting their survival.

Several candidate OMV vaccines have been developed and tested in large-scale efficacy studies in Norway, Cuba, Brazil, Chile and New Zealand, with variable results. A Norwegian double-blind, placebo-controlled, efficacy trial in 171,800 secondary school students demonstrated protection of 57.2% [9]. Although the vaccine conferred protection against MenB disease, these findings suggested that the effect was insufficient to justify a public vaccination program.

By contrast, a Cuban OMV vaccine study in 106,000 10–14-year-olds estimated efficacy at 83% [10]. These results coupled with the fact that no severe or long-lasting reactions to the vaccine were observed prompted the Cuban Ministry of Public Health to vaccinate all children aged between 3 months and 6 years in the most severely affected provinces. The efficacy of vaccination varied from 83 to 94%. Following a 3-year, widespread program, no severe reactions occurred and one of the most severe epidemics was practically eradicated.

These results were only partially confirmed in epidemics in Brazil and Chile. Since these vaccines are based on OMVs from a single meningococcal isolate, they only provide partial protection against heterologous meningococci; a degree of protection appears to be related to age. This is particularly pertinent in countries where MenB disease is of a multiclonal nature, e.g. The Netherlands and the UK.

It is clear that these OMV vaccines may be useful in curtailing localized epidemics through the administration of a specific 'tailor-made' vaccine, as the New Zealand experience subsequently demonstrated [11]. Since 1991, epidemic MenB infection has afflicted New Zealand, causing more than 4700 cases and >200 deaths [12]. The overall incidence peaked in 2001 at 17.4 cases per 100 000 people. In 2002, Maori and Pacific Island children under the age of 1 year displayed incidence rates of 286 and 368 per 100,000, respectively.

A new strain-specific MenB vaccine was developed by preparing a protein-based OMV vaccine from a wild-type strain typical of the one responsible for the epidemic, referred to as 'MeNZB'. A nationwide vaccination campaign began in July 2004. Fully vaccinated children <5 years of age were up to six-times less likely to contract epidemic strain meningococcal disease in the 24 months post-vaccination, corresponding to an estimated vaccine effectiveness of 80% [13]. OMV vaccines are useful for control of epidemics because they are directed against specific surface proteins that are antigenically variable, as a result, they can be tailored to a predominant strain during an epidemic. However, they do not confer crossprotective immunity against other MenB strains and, therefore, are only effective where a single clone predominates.

Development of a licensed MenB vaccine

It was noted that bactericidal antibodies that develop after MenB disease and carriage are directed against subcapsular antigens including OMPs, suggesting that incorporating OMPs into a vaccine may be protective. These antigens are found in OMVs.

There are approximately 600 meningococcal OMP variants identified to date, therefore to increase the breadth of strains protection offered by a broadly effective vaccine, other antigens must be incorporated into the vaccine [14]. To identify such antigens, a technique called 'reverse vaccinology' was used. The *N. meningitidis* genome sequence was decoded, and hundreds of potential target proteins bioinformatically identified. Based on their function, immunogenicity and conservation between different strains, eventually four targets were chosen for evaluation and incorporated into the final formulation of Bexsero®. These targets are: factor H binding protein (fHbp), Neisserial adhesin A (NadA) and Neisseria heparin binding antigen (NHBA), which were incorporated in a vaccine together with the New Zealand OMV [15]. In January 2013 the EMA licensed Bexsero, a four component protein-based MenB vaccine manufactured by Novartis [16].

Bexsero has undergone several immunogenicity and safety studies, enrolling over 8000 children and adolescents.

A Phase III study with 3630 infants confirmed the immunogenicity of three doses of Bexsero alongside routine immunization, and an anamnestic response to a fourth dose administered at 12 months of age [17].

This and other studies have demonstrated Bexsero's immunogenic and safety profile, with the main side effects being local reactions, pain at the injection site and fever [18]. These findings are supported by extensive post-marketing surveillance in New Zealand of over 3 million doses of their MenB OMV vaccine [19]. However, it is worth emphasizing that rare severe adverse events may only become apparent following widespread introduction.

Testing immunogenicity of Bexsero has proven challenging. Hundreds of different subserotypes of MenB cause disease; it is impractical to test serum from immunized individuals against each of them. A surrogate of serum bactericidal antibody (SBA) testing, the Meningococcal Antigen Typing System (MATS) was developed to predict strain coverage by Bexsero. MATS predicted that Bexsero will cover 73% of MenB strains circulating in England and Wales [20]. When this presumption was further tested using SBA against 40 different strains, it was noted that 88% of strains were killed, suggesting that MATS was conservative in its estimates [21]. In fact, the antigens included in Bexsero are also commonly found in other, non-group B meningococci, and theoretically provides coverage against other meningococcal serogroups. It has recently been shown *in vitro* that Bexsero strain coverage could reach 22% for serogroup Y, 80% for serogroup C and 83% for group serogroup W-135 [22]. This has also been demonstrated with Meningococcus X, which is an increasingly common cause of meningitis in parts of Africa [23].

Other potential vaccines

Clinical trials for other vaccines against MenB that contain recombinant fHbp, along with other components of the bacterial outer membrane or cell wall, are currently underway. Pfizer have independently identified fHbp as an important immunogenic antigen and developed a vaccine that contains two fHbp variants. A vaccine containing antigenic components from subfamilies A and B of meningococcal fHbp has undergone Phase II studies that demonstrate bactericidal activity against subfamily A and B strains in a high proportion of children, adolescents and adults, with no significant safety concerns [24,25]. Further evaluation of this vaccine is ongoing.

Despite these promising findings, important questions remain: vaccine effectiveness on the different geographical distribution of pathogenic strains, impact on carriers; and the timing of the appearance of escape mutants once herd immunity has been achieved.

One of the most important issues to be determined is impact on nasopharyngeal carriage. Asymptomatic carriage of *N. meningitidis* is common (found in 5–35% of individuals). The prevalence of carriage is low in infancy, peaks in adolescents and young adults, after which it declines [26].

The only way to properly assess the effects of these vaccines on herd immunity is to carry out enhanced surveillance following vaccine introduction. It is of course possible that these novel MenB vaccines will have no impact at all on nasopharyngeal carriage, in which case there would be no clear strategy to induce herd immunity.

If there is an impact on carriage, strategies targeting carriers such as immunization of adolescents or adults may be appropriate.

A further possible benefit of these MenB vaccines is their potential to induce crossprotection against other meningococcal serogroups. The FHbp gene was present in all MenC isolates from patients with MenC disease in the USA, suggesting an FHbp-based vaccine may also be effective in protecting against a diverse range of meningococcal serogroups that cause disease [27]. Thus, raising the possibility of a universal meningococcal vaccine, potentially leading to complete eradication of meningococcal disease.

Conclusion

Development and implementation of effective MenB vaccines will confer significant health benefits, preventing deaths and long-term disabling sequelae following meningitis and septicemia.

Clinicians, parents, children and society have been desperately waiting for an effective MenB vaccine. By recommending introduction of Bexsero into the UK infant schedule, the message the Joint Committee on Vaccination and Immunisation has sent out is that the UK remains an innovative power in healthcare and prevention, and leads the rest of the developed world in this field. It is likely that other countries will now follow the UK's example in approving Bexsero for widespread introduction [28].

Future perspective

With advances in genomics and proteomics, other vaccine candidates for MenB disease will become available, with potential for broader coverage and better immunogenicity. It is unclear at present what the effects of the licensed vaccine will be on circulating serosubtypes of meningococci, nasopharyngeal carriage (and thus herd immunity) and duration of immunity will be. The vaccine schedule will evolve as it has with other vaccines introduced into the schedule.

The prospects for a single vaccine against all serogroups of meningococci are clear, and thus the potential eradication of this dreadful disease.

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