Review

The Long Road to an Effective Vaccine for Meningococcus Group B (MenB)

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Article history

Received: 21 January 2013
Accepted: 15 April 2013
Available online: 15 June 2013

Provenance and Peer Review

Unsolicited and Editorial Review

Keywords

Evidence Based Medicine
Mass Media
Misrepresentation
Randomised Controlled Trials

Abstract

Neisseria meningitidis infection can cause life-threatening meningitis and meningococcal septicaemia. Over the past 40 years, vaccines against most of the main meningococcal serogroups have offered increasingly good protection from disease, with one major exception in the developed world: serogroup B meningococcus (MenB). In the United States, MenB accounts for about a quarter of cases of meningococcal meningitis, with the bulk of the rest caused by meningococcus serogroups C (MenC) and Y (MenY). In the UK, where a vaccine against MenC is widely used, MenB is now responsible for nearly 90% of cases of invasive meningococcal disease. Recent attempts to create a universal MenB vaccine have been thwarted by the variability of the surface proteins of MenB and by the similarity of the MenB capsule to human glycoproteins. This review discusses current meningococcal vaccine strategies and their limitations with regard to MenB, and examines a promising new strategy for the rational design of a MenB vaccine. Thanks to a fusion of a rational reverse genetics approach and a membrane vesicle approach, a MenB vaccine, 4CMenB (Bexsero®), has finally gained regulatory approval in Europe and could be in clinical use by the end of 2013.

Meningococcal meningitis and septicaemia are life-threatening *Neisseria meningitidis* infections. Most meningococcal disease in the developed world is caused by *N. meningitidis* serogroups B, C, and Y; most disease in the meningitis belt in Africa and elsewhere in the developing world is caused by serogroup A, as well as emergent serogroups X and W.[1,2] Vaccines for serogroups A, C, and Y have been in use since the 1970s, but there is still no universal vaccine on the market for meningococcus group B (MenB). Why has no MenB vaccine been developed? The simple reason is that the strategy used for the other meningococci doesn't work for MenB. Vaccines for meningococcus groups A, C, W, and Y induce an immune response against the polysaccharide capsule around the bacterium. The capsular polysaccharide of MenB however, is structurally similar to certain abundant human glycoproteins like NCAM. It is therefore not a suitable immune target due to the risk of autoimmune damage through molecular mimicry. The barrier to developing a MenB vaccine thus has two facets: the difficulty in developing vaccines in general, and the specific challenge of creating a vaccine against a pathogen that mimics host molecules. The requirements for the development of an effective vaccine for MenB will be examined in three parts: first, an overview of the general characteristics of an effective vaccine; second, a discussion of current meningococcal vaccine strategies and their limitations with regard to MenB; and third, an examination of a promising new strategy for inoculation against MenB.

Four criteria must be met if a vaccine is to be effective: the immune system must be able to generate an effective response; the response must cover all major strains; the vaccine must be produced cheaply and efficiently, and the side-effects must be small enough to be accepted by the public. The immune system can generate a protective response against MenB, as infection is normally protective.[3–5] Those who survive infection produce serum bactericidal antibodies (SBA) that lead to lysis of *N. meningitidis* in the presence of complement. Complement is important, as individuals with complement deficiencies typically get more *Neisserial* infections.[6] SBA activity is used as a correlate of protection, and has been validated as a marker of immunity with different vaccines.[3,5,7]

To provide universal protection, a MenB vaccine must contain antigens that are present in all strains in both time and in space; i.e. the antigen should not vary from one month to the next, or from one part of the country to another. This is problematic as there is wide sequence variation of the exposed antigens of *N. meningitidis*, particularly of the immunodominant surface protein PorA. There is also antigenic variation of the pili and extensive phase variation.[8] The many repetitive sequences in the genome allow for frequent recombination; DNA transformation is common, and some virulent strains also show hypermutability.[9,10] This increases the risk of selecting for vaccine escape variants. Meningococci tend to be found as relatively stable clonal complexes, but the prevalence can change rapidly. For example, clonal complex CC213 was not isolated in England before 1995, but accounted for 14% of cases of invasive MenB disease by 2008.[11]

A useful vaccine needs to be produced in sufficient quantity to inoculate a large section of the population at a reasonable cost. A simple and stable vaccine formulation reduces production and transport costs, making immunization a cost-effective public health strategy. A vaccine must also be palatable to the public. Meningococcal meningitis and septicaemia are very serious but relatively rare diseases. The annual incidence is about 2 per 100,000 population in the UK, 87% of this from MenB.[12] As even uncommon side-effects might be noticeable compared to the burden of disease, a

very safe vaccine is needed. A vaccine for Lyme disease was introduced in 1998 in the United States, but was withdrawn in 2002 after (unfounded) complaints that it caused autoimmunity.[13] Yet the incidence of Lyme disease is seven times that of meningococcal disease.[14] The higher annual incidence of meningococcal disease in infants (36 per 100,000),[12] and the fact that meningitis often strikes down otherwise healthy young adults might however encourage use of the vaccine.

Two types of vaccine are currently in use for meningococcus: vaccines using the capsular polysaccharide, and vaccines based on outer membrane vesicles (OMVs). The first vaccine against meningococcus was simply the capsular polysaccharides of Meningococcus groups A, C, W, and Y. More recent vaccines, Menactra and Menveo, are conjugates: polysaccharide fused to an carrier protein (a modified form of the diphtheria toxin that acts as an adjuvant to enhance immunogenicity and memory).[15,16] The best-established single-group vaccine is a conjugate for Meningococcus group C (MCC). It offers 97% protection in infants shortly after vaccination, dropping to 67% protection after a year. This vaccine brought about a striking drop in the incidence of invasive Meningococcus group C (MenC) disease in the UK from 1.85 per 100,000 in 1998–1999 to 0.02 per 100,000 in 2008–2009.[7] This is largely due to a herd-immunity effect, mediated by the unexpectedly large reduction in MenC carriage (the MCC vaccine is 75–80% effective against carriage).[17,18] Breakthrough cases do occur, however, with more than 10% of MenC cases in the UK in vaccinated individuals.[19] A MenA vaccine is also being rolled out in the meningitis belt, and early indications are positive.[20]

Current vaccines target the polysaccharide capsule, but the MenB capsule is composed of polymers of α(2-8)-linked N-acetylneuraminic acid, which is also found on the human neural cell adhesion molecule NCAM.[21,22] A vaccine directed at a host molecule might be expected either not to raise an immune response, or to cause autoimmunity. The MenB polysaccharide is not immunogenic in animal models or in humans.[23] This tolerance is expected, as T-cells and B-cells that recognise this self-antigen would either have been deleted as self-reactive in the thymus or bone-marrow, or inactivated by peripheral anergy. However, an immune response against α(2-8)-linked N-acetylneuraminic acid was obtained in mice when it was administered conjugated to a tetanus toxoid.[24] Furthermore, antibodies against α(2-8)-linked N-acetylneuraminic acid have been isolated from patients convalescing from MenB meningitis.[25] Immune tolerance to α(2-8)-linked N-acetylneuraminic acid can therefore be overridden. However, there is a concern that this could lead to autoimmune disease.

When grown in culture, *N. meningitidis* sheds spherical blebs of membrane containing outer membrane proteins.[26] These outer membrane vesicles (OMV) can be purified and used for immunisation, usually after processing to remove most of the lipo-oligosaccharide (LOS), an endotoxin. OMV vaccines were developed to combat MenB outbreaks in Cuba, Norway, and New Zealand.[27,28] They induce a protective immune response against the strain from which the OMVs were collected, principally directed against PorA. However, the sequence of PorA is extremely variable,[29,30] and mutation can make a daughter strain resistant to antibodies raised against the parent strain.[31] There is, therefore, little cross protection between MenB strains. Consequently, vaccines based on OMV are at the moment only useful in localised epidemics.[32]

There are three competing strategies to make a universal MenB vaccine: first, to immunize with the capsular polysaccharide regardless of the risk of autoimmunity; second, to "universalize" the OMV vaccine; and third, to rationally design a subunit vaccine based on genomic information.

Despite the risks of autoimmunity, it may be possible to use the capsular polysaccharide of MenB as an immunogen. There are no documented cases of autoimmunity in humans after MenB infection, or in animals vaccinated with α(2-8)-linked N-acetylneuraminic acid.[33] Moreover, survivors of MenB infection have the same sequelae as MenC survivors, with no increased autoimmunity.[34] Vaccination with the MenB capsular antigen has the added advantage of potential protection against other bacteria that use this polysaccharide, such as *E. coli* strain K, and *Klebsiella*. However, this remains a risky strategy. Natural infection might only induce a small rise in low-affinity antibodies, while vaccination would have to induce protective antibodies. This level of humoral response might be sufficiently high to lead to autoimmunity. Carriage or aborted infections might also boost initially tolerable antibody levels.

OMV vaccines are the only MenB vaccines that have been proven to be protective in a general population setting. As such, they are a reasonable platform on which to try to build a more universal vaccine. One possible solution to PorA variation is to generate OMVs with multiple different PorA subtypes, and thus protect against different MenB subtypes.[35] Another elegant strategy to attempt to address the problem of PorA variability is to generate OMVs without PorA.[36] OMVs from mutant bacteria lacking PorA can be used to induce immunity against less immunogenic but more conserved meningococcal surface proteins, with the promise of immunity against all strains of *N. meningitidis*. However, despite promising results in mice, these PorA-deficient OMVs were poorly immunogenic in human trials.[37] As antibodies against LOS appear to be protective, a genetically modified strain of *N. meningitidis* was used to produce OMVs containing mutant LOS that is less toxic, allowing OMVs to be generated with higher levels of LOS but without the associated endotoxin side-effects. These OMVs were found to be protective not only against several strains of MenB, but also against MenC, Menigococcus group W (MenW), and Menigococcus group Y (MenY).[38] Native outer membrane vesicles (NOMVs) can be isolated without chemical treatment, so the LOS and lipoproteins are in their native conformation, which should improve their immunogenicity.[39] A trivalent NOMV vaccine induces SBA in mice against MenB, MenC, MenY, MenW, and certain strains of MenA.[39,40]

Reverse vaccinology is a strategy for rational (or at least rigorous) vaccine design. It aims to test the vaccine potential of every predicted surface protein of a pathogen. The MenB genome was sequenced,[10] and 350 putative surface proteins were expressed and used to inoculate mice.[41] The antibodies were used to look for surface localisation of their cognate antigen, and tested for serum bactericidal activity. Candidate antigens were then screened to see if they were present and did not vary in different MenB strains. The reverse vaccinology strategy identified a panel of proteins that seem to be ideal antigens: accessible to the immune system, immunogenic, inducing a protective response, present in all strains, and with minimal sequence variation.[41] Five antigens were combined to make the multivalent 5-component vaccine against MenB (5CVMB) [42]. The constituents are the Neisserial adhesion protein (NadA),[43] Neisseria Heparin Binding Antigen (NHBA),[44,45] factor H binding protein (fHbp),[46,47] and two Genome-derived Neisserial Antigens (GNA) (GNA1030 and GNA2091) fused to NHBA and fHbp respectively. 5CVMB was effective against 94% of 85 different strains when formulated with an adjuvant (MF59) that is licensed in

humans.[42] 5CVMB has been tested in humans either alone or in formulation with the OMV used for vaccination in New Zealand.[48] Both were immunogenic, but the formulation with the OMV was more effective, particularly against certain strains expressing homologous PorA and for which only low SBA was achieved using 5CVMB alone. This formulation was renamed 4-component MenB (4CMenB), counting the NHBA-GNA1030 fusion and the fHbp-GNA2091 fusion as one component each, NadA as the third component and OMV as the fourth component. 4CMenB elicits serum bactericidal antibodies against MenB in infants,[49] adolescents,[50] and adults.[51]

There are two major concerns for 4CMenB: will it cover all strains and will it have important side-effects? The OMV component of 4CMenB only protects against certain PorA subtypes, and the vaccine only contains one of three fHbp variants. The fHbp component of 4CMenB is variant 1, and 5CVMB (without OMV) induced protective antibodies against 95% of fHbp variant 1 strains, but only against 56% of fHbp variant 2 or 3 strains.[52] In US hospital isolates, 35% were fHbp variants 2 or 3,[52] and only 36% of isolates had the NadA gene, another target of 4CMenB. In terms of side-effects, in a phase three trial, 4CMenB in conjunction with routine immunizations resulted in fever in 50–60% of infants.[49] Reductions in rates of fever by the use of prophylactic paracetamol are being investigated.[53] Rare but serious side-effects of vaccination are almost impossible to assess until large numbers of infants have been inoculated. A possible link with Kawasaki's disease has been suggested for 4CMenB,[49] but this remains unlikely.[54] Nonetheless, an apparently effective MenB vaccine, 4CMenB, has been developed. Marketed as Bexsero by Novartis, it has recently been recommended by the European Medicines Agency, and could be available in the UK by the end of 2013.[55] Careful post-implementation surveillance will be required to monitor side-effects and uptake, and to optimise vaccination schedules. The impact on carriage and herd immunity and any drift towards strains that can escape the vaccine should be examined,[56] and cross-protection for other meningococcal groups verified. This is particularly important for MenX, which can cause epidemics in the meningitis belt of Africa, and for which there is no vaccine.[57,58]

An alternative vaccine to 5CVMB, containing one fHbp from each family, is currently in clinical trials. However, MenB and MenC strains that do not express fHbp have been isolated from patients with disseminated meningococcal disease.[59] Although these strains are rare, it is possible that they would be selected for by a bivalent fHbp vaccine. Nonetheless, NOMV formulations using mutated fHbp designed not to bind to human fH show promise.[60] Other subcapsular antigens are also being investigated as vaccine targets.[61]

What will the future hold for MenB vaccines? The roll-out of 4CMenB (Bexsero) is highly anticipated. Beyond that, three populations could be specifically targeted by a next-generation vaccine: individuals with complement deficiencies, neonates, and asymptomatic carriers. First, individuals with a complement deficiency may not be able to mount a full immune response to MenB even with vaccination, as the vaccine is designed to elicit SBA that act at least in part through complement.[62] One vaccine antigen, GNA2091, does not induce SBA but is protective in a mouse model.[42] This type of antigen might provide better protection for those with complement deficiencies. Second, young infants are particularly vulnerable to MenB: 14% of MenB cases occur in infants less than six months old.[12] One solution is to vaccinate infants very young, as for MenC. Alternatively, vaccines can be offered to potential mothers to enhance the passive protection given to their children by transfer of IgG. Third, asymptomatic carriage of MenB could be directly targeted. About 17% of the population carry meningococci in the nasopharynx,[18] where it is likely to be more susceptible to IgA than to IgG. The 4CMenB vaccine aims to raise IgG, as this is effective at preventing disease and is the correlate of protection (and so mandated by the regulatory framework). A vaccine designed to produce IgA might however have a dramatic effect on carriage. This is similar to the difference between an injected (inactivated) polio vaccine, which leads to an IgG response, and the oral (attenuated) polio vaccine that also has an IgA response, protective in the gut.[63] Intranasal MenB vaccination by inhalation is immunogenic in humans, and might specifically induce a mucus-membrane based response.[64] Such a vaccine might even raise the prospect of MenB eradication.

Less than 15 years after the introduction of the vaccine for MenC, this serogroup causes almost no severe illness in the UK. With the advent of an effective vaccine against MenB, there is reason to be optimistic that invasive meningococcal disease will become a rarity in this country. Moreover, the new crop of MenB vaccines has the potential to be effective against most strains of *N. meningitidis*. Perhaps the goal of truly effective and universal protection against all meningococci is finally on the horizon, nearly half a century after the first meningococcal vaccines.

Ethical approval

No ethical approval required for this publication.

Conflicts of interest

No conflicts of interest have been declared by the author.

Author contributions

Single author manuscript.

Funding

No funding source declared by author.

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