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Meningococcal serogroup B vaccines: will they live up to expectations?

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"Unlike other meningococcal serogroups, major cross-reactive antigens suitable for inclusion in human vaccines that convey broad protection have not been identified for meningococci expressing serogroup B capsules."

The prevention of invasive meningococcal disease caused by serogroup B meningococci (MenB) has been the subject of intensive investigation. The MenB polysaccharide capsule is poorly immunogenic and outer membrane proteins, as part of outer membrane vesicles (OMVs) or in combinations of subunit surface proteins, are being investigated, but the genetic and antigenic diversity of the meningococcus represents a major obstacle. Meningococcal populations comprise a large number of genetic lineages, and although only a subset cause most disease, invasive meningococci can express a wide diversity of subcapsular antigen variants. Vaccination approaches therefore have to identify conserved antigen variants, or include carefully assembled 'cocktails' of antigen variants to provide broad coverage. Of the noncapsular vaccine candidates, the most advanced are vaccines containing factor H-binding protein (fHbp; also known as GNA1870 or LP2086), currently included in formulations under investigation by Novartis (rMenB-OMV) and Pfizer (bivalent rLP2086), and a range of OMV vaccines modified in various ways to improve strain coverage. A particular challenge is the induction of cross-bactericidal antibodies in naive infants.

rMenB-OMV

The rMenB-OMV vaccine candidate is currently leading in the field and has recently been submitted for licensure by Novartis. This vaccine contains six antigenic components [1]: fHbp, Neisserial adhesin A protein (NadA), Neisserial heparin-binding antigen (NHBA; also known as GNA 2132), GNA 1030 (fused with NHBA), GNA 2091 (fused with fHbp), whose structure and function remains unknown, as well as the later added outer membrane porin protein PorA-containing OMV vaccine, NZ98/254 (P1.7-2,4, ST41/44 complex), used to control epidemic meningococcal disease in New Zealand between 2004 and 2008 [2].

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fHbp is likely to be the most immunologically active antigen in rMenB. It is thought to inhibit the alternative complement pathway and is expressed by most meningococcal isolates, but at least two antigenic subfamilies exist whose distribution varies geographically [3]. At the time of writing, 448 genetic alleles and 378 protein variants had been described for this antigen [101]. The level of immune cross-protection among fHbp variants in humans is not known, but available data suggest that the immune response is variant-specific in naive infants [4]. NadA is an adhesion protein and is expressed in approximately 50% of meningococcal strains that cause disease; NadA variants

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show geographical distribution limiting the expected coverage of this antigen. NHBA appears to be present in all meningococci revealing extensive sequence variability; it increases survival of *Neisseria meningitidis in vivo* by binding glycosaminoglycans. NadA and NHBA were selected for inclusion in rMenB-OMV on the basis of assumed broad protection and passive protection in animal models [1,5]. GNA 1030 and GNA 2091 were included as fusion proteins because they improved serum bactericidal antibody (SBA) responses. The New Zealand OMV contains P1.7,4 PorA and may also contribute an adjuvant effect.

Three doses of rMenB (without OMV) induced SBA responses against two selected strains homologous for fHbp and NadA, but failed to induce SBA against most heterologous strains [4,6]. Addition of OMV appeared to improve cross-reactivity in an initial study in 6–8-month-old infants [6]. However, these results were not sustained by a later pediatric study in the UK [4]: in a 2–4–6-month schedule, fHbp, NadA and OMV elicited SBA responses to homologous strains [4], but the percentage of rMenB-OMV-vaccinated subjects showing cross-protective SBA responses to three non-P1.7,4 UK-derived, wild-type strains was low. The OMV component contains the known protective PorA antigen, which is a strain-specific antigen and forms the basis of typing strains [7,8].

Clinical studies with the Pfizer rLP2086 vaccine (bivalent fHbp) in adults and older children have shown promising results, with evidence of cross-reactivity against strains of both fHbp subfamilies, but it is yet to be evaluated in infants [9].

OMV vaccines

Outer membrane vesicle vaccines remain a valid option for control of invasive disease due to MenB. OMVs containing multiple outer membrane antigens have been used in several countries, most recently in New Zealand for epidemic control [10,11]. Pediatric immune responses against OMV vaccines are primarily directed against PorA [12], an outer membrane porin protein earlier recognized by preclinical studies to be the main target for bactericidal antibodies after OMV immunization [13]. PorA induces SBA responses in humans but shows antigenic variability that is strain specific [12]. Geographic antigenic variation in PorA has been considered a limitation in its use in a global vaccine antigen, since antigenic changes between regions and over time would require periodic modification of the vaccine. As evidenced by the yearly re-evaluation and renewal of seasonal influenza vaccines that are modified to address antigenic drift that occurs at a much faster rate than changes in prevailing meningococcal clones, these issues are not insurmountable. A bivalent OMV based on the B:4:P1.7-2,4 (New Zealand) and B:4:P1.19,15 (Cuba) OMV vaccine strains showed good immunogenicity and cross-reactive potential against European MenB strains in a clinical study in young adults [14]. Broader bactericidal activity can be achieved by increasing the number of PorA variants, such as in a hexavalent PorA OMV, that could potentially deliver coverage against disease-causing MenB strains in Europe of between 60 and 80% [15,16]. Expanded coverage is also possible by the addition of other antigens such as the iron-limitation-inducible outer membrane protein (FrpB; also known as FetA) [16]. Like PorA, FrpB induces bactericidal antibodies in preclinical immunogenicity models [17]. Another approach to increasing the cross-reactive potential of OMV vaccines is the use of native OMVs from strains with genetically detoxified lipooligosaccharide and enhanced expression of key outer membrane proteins. Native OMVs obtained without exposure to detergent may be less reactogenic and retain more of the membrane-associated lipoproteins and lipooligosaccharides as well as insuring native conformation of integral membrane proteins [18–20].

Conclusion

Unlike other meningococcal serogroups, major cross-reactive antigens suitable for inclusion in human vaccines that convey broad protection have not been identified for meningococci expressing serogroup B capsules. Vaccine development is therefore currently dominated by two main approaches. The first relies on the inclusion of multiple conserved 'minor' (i.e., expressed at low levels) antigens to achieve immunogenicity across a broad range of strains, and to reduce the risk of emerging strains with novel antigenic combinations [1,21]. To date, the type and number of antigens needed to achieve either goal is not known.

The main alternative is the use of multivalent PorA-based OMV vaccines. Similar questions about the number of valencies needed to achieve broad coverage and prevent emergent strains need to be answered, and periodic modifications to adjust to changing MenB epidemiology may be required. Multivalent PorA-based vaccines can be further improved by additional components such as FrpB (FetA) and/or fHbp.

The leading candidate rMenB-OMV vaccine will probably offer a reasonable level of protection in older children/adolescents but, although capable of inducing bactericidal antibodies in infants, the available data do not convincingly demonstrate that the vaccine will be broadly protective in the very young, and the role of each component in terms of immunogenic and protective potential is undefined. The addition of P1.7,4 OMV has increased coverage of the poorly immunogenic subunit proteins in pediatric populations. The bivalent fHbp (LP2086) vaccine still needs to be evaluated in a pediatric study. To achieve high coverage, a subunit MenB vaccine appears to need a high valency of minor subunit proteins. OMV technology has been available for 20 years and OMV vaccines have proved efficacious in preventing MenB disease in regions where a single strain predominates. Efforts to increase the coverage offered by OMVs via multivalent approaches or combining subunit antigens with less reactogenic, modified OMVs appears an alternative pathway towards a MenB vaccine, although these vaccines could need some adaptation of composition over time. Group B meningococci remain a cause of devastating disease and research should continue to offer public health vaccines.

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References

1 Giuliani MM, Adu-Bobie J, Comanducci M *et al.* A universal vaccine for serogroup B meningococcus. *Proc. Natl Acad. Sci. USA* 103, 10834–10839 (2006).

2 Wong SH, Lennon DR, Jackson CM *et al.* Immunogenicity and tolerability in infants of a New Zealand epidemic strain meningococcal B outer membrane vesicle vaccine. *Pediatr. Infect. Dis. J.* 28, 385–390 (2009).

3 Pajon R, Beernink PT, Harrison LH, Granoff DM. Frequency of factor H-binding protein modular groups and susceptibility to cross-reactive bactericidal activity in invasive meningococcal isolates. *Vaccine* 28, 2122–2129 (2010).

4 Findlow J, Borrow R, Snape MD *et al.* Multicenter, open-label, randomized Phase II controlled trial of an investigational recombinant meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. *Clin. Infect. Dis.* 51, 1127–1137 (2010).

5 Bambini S, Muzzi A, Olcen P, Rappuoli R, Pizza M, Comanducci M. Distribution and genetic variability of three vaccine components in a panel of strains representative of the diversity of serogroup B meningococcus. *Vaccine* 27, 2794–2803 (2009).

6 Snape MD, Dawson T, Oster P *et al.* Immunogenicity of two investigational serogroup B meningococcal vaccines in the first year of life: a randomized comparative trial. *Pediatr. Infect. Dis. J.* 29, e71–e79 (2010).

7 Frasch CE, Zollinger WD, Poolman JT. Serotype antigens of *Neisseria meningitidis* and a proposed scheme for designation of serotypes. *Rev. Infect. Dis.* 7, 504–510 (1985).

8 Jolley KA, Brehony C, Maiden MCJ. Molecular typing of meningococci: recommendations for target choice and nomenclature. *FEMS Microbiol. Rev.* 31, 89–96 (2007).

9 Bai X, Borrow R. Genetic shifts of *Neisseria meningitidis* serogroup B antigens and the quest for a broadly cross-protective vaccine. *Expert Rev. Vaccines* 9, 1203–1217 (2010).

10 Bjune G, Høiby EA, Grønnesby JK *et al.* Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. *Lancet* 338, 1093–1096 (1991).

11 Sierra GV, Campa HC, Varcacel NM *et al.* Vaccine against group B *Neisseria meningitidis*: protection trial and mass vaccination results in Cuba. *NIPH Ann.* 14, 195–207; discussion 208–210 (1991).

12 Tappero JW, Lagos R, Ballesteros AM *et al.* Immunogenicity of 2 serogroup B outer-membrane protein meningococcal vaccines: a randomized controlled trial in Chile. *JAMA* 281, 1520–1527 (1999).

13 Saukkonen K, Leinonen M, Abdillahi H, Poolman JT. Comparative evaluation of potential components for group B meningococcal vaccine by passive protection in the infant rat and *in vitro* bactericidal assay. *Vaccine* 7, 325–328 (1989).

14 Boutriau D, Poolman J, Borrow R, F *et al.* Immunogenicity and safety of three doses of a bivalent (B:4:p1.19,15 and B:4:p1.7–2,4) meningococcal outer membrane vesicle vaccine in healthy adolescents. *Clin. Vaccine Immunol.* 14, 65–73 (2007).

15 Cartwright K, Morris R, Rümke H *et al.* Immunogenicity and reactogenicity in UK infants of a novel meningococcal vesicle vaccine containing multiple class 1 (PorA) outer membrane proteins. *Vaccine* 17, 2612–2619 (1999).

16 Urwin R, Russell JE, Thompson EAL, Holmes EC, Feavers IM, Maiden MCJ. Distribution of surface protein variants among hyperinvasive meningococci: implications for vaccine design. *Infect. Immun.* 72, 5955–5962 (2004).

17 Pettersson A, Kuipers B, Pelzer M *et al.* Monoclonal antibodies against the 70-kilodalton iron-regulated protein of *Neisseria meningitidis* are bactericidal and strain specific. *Infect. Immun.* 58, 3036–3041 (1990).

18 Koeberling O, Giuntini S, Seubert A, Granoff DM. Meningococcal outer membrane vesicle vaccines derived from mutant strains engineered to express factor H binding proteins from antigenic variant groups 1 and 2. *Clin. Vaccine Immunol.* 16, 156–162 (2009).

19 Keiser PB, Biggs-Cicatelli S, Moran EE *et al.* A Phase 1 study of a meningococcal native outer membrane vesicle vaccine made from a group B strain with deleted *lpxL1* and *synX*, over-expressed factor H binding protein, two PorAs and stabilized OpcA expression. *Vaccine* 29, 1413–1420 (2011).

20 van de Waterbeemd B, Streefland M, van der Ley P *et al.* Improved OMV vaccine against *Neisseria meningitidis* using genetically engineered strains and a detergent-free purification process. *Vaccine* 28, 4810–4816 (2010).

21 Weynants VE, Feron CM, Goraj KK *et al.* Additive and synergistic bactericidal activity of antibodies directed against minor outer membrane proteins of *Neisseria meningitidis*. *Infect. Immun.* 75, 5434–5442 (2007).

Website

101 Neisseria factor H binding protein sequence typing http://pubmlst.org/neisseria/fHbp/