

REVIEW ARTICLE

CURRENT CONCEPTS

Advances in the Development of Vaccines against *Neisseria meningitidis*

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ALTHOUGH TWO CENTURIES HAVE PASSED SINCE VIEUSSEUX DESCRIBED epidemic meningococcal disease,¹ *Neisseria meningitidis* remains a leading cause of meningitis and sepsis. Overwhelming meningococcal disease can develop rapidly and is associated with mortality rates exceeding 20%.² Thus, efforts to control the disease have focused on vaccination. In the past, vaccines against meningococcal disease have failed to provide immunogenicity and long-term protection in infants, who are at greatest risk. Although recent vaccines have improved coverage for this age group, there is still no broadly effective vaccine against *N. meningitidis* group B (NMB), now the predominant disease-causing isolate in industrialized countries.

Developments during the past decade have renewed hopes for solving this seemingly intractable problem. Knowledge of the meningococcal genome has led to the identification of novel antigens that have been incorporated into the NMB vaccines now being studied in clinical trials. However, it remains unclear whether these vaccines will provide sufficient immunogenicity in infants as well as wide-ranging coverage. This review highlights the evolution of meningococcal vaccines in general and discusses strategies being used to overcome the barriers to developing vaccines against NMB.

EPIDEMIOLOGY OF *N. MENINGITIDIS* INFECTION

Meningococcal disease is a global health problem. The World Health Organization estimates that there are 1.2 million cases of invasive meningococcal disease and 135,000 related deaths annually.³ Although the disease occurs sporadically in industrialized countries, with an incidence of 0.35 cases per 100,000 population in the United States and of 1.01 per 100,000 in Europe (ranging from 0.25 to 4.4 per 100,000 in Italy and Malta, respectively),⁴ the major disease burden is in the nonindustrialized countries. A recent epidemic in Nigeria resulted in 4164 cases and 171 deaths in 1 week alone.⁵

The meningococcus is pathogenic only in humans. It colonizes the nasopharynx asymptotically in up to 40% of the adult population but occasionally causes invasive disease. When the infection is classified according to the polysaccharide capsule surrounding the bacterium, only six capsular groups (A, B, C, W-135, X, and Y) are associated with invasive disease.⁶ The epidemiology of disease caused by these groups varies: group A is responsible for large epidemics in Africa, in which the incidence approaches 1000 cases per 100,000 population (and may involve environmental factors), whereas groups B and C cause disease predominantly in industrialized and newly industrialized countries.^{2,6} Recently, groups W-135 and X (predominantly in Africa) and group Y (in the United States and other countries) have emerged as important disease-causing isolates.

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HOST DEFENSES AGAINST *N. MENINGITIDIS*

Protection from meningococcal infection depends on innate immunity, in particular a functioning complement system; deficiencies of terminal complement components and alterations in complement regulators are both associated with an increased risk of infection.⁷ In addition, the humoral antibody response is essential for protection against the bacterium. The serum bactericidal antibody (SBA) assay measures killing of *N. meningitidis* in the presence of specific antibodies that bind to the bacteria and activate complement. Since the 1960s, when it was shown that persons with SBA titers of 4 or more (with the use of human complement against group C meningococcus) were protected against subsequent disease,⁸ the SBA assay has been the standard immunologic correlate of protection. Although the incidence of disease had been reported to be highest among infants 6 to 24 months of age who had the lowest SBA titers,⁸ recent U.S. data indicate that the incidence is actually highest among infants under 6 months of age, who have the lowest SBA titers because they lack meningococcal-specific maternal serum bactericidal antibody.⁹

EVASION OF COMPLEMENT

The outer surface of the meningococcus possesses several structures involved in complement evasion. The polysaccharide capsule, which contains sialic acid in all invasive meningococcal groups other than group A, provides protection against complement-mediated bacterial killing, opsonization, and phagocytosis.⁶ Meningococcal lipo-oligosaccharide and outer-membrane proteins are also involved in pathogenesis.⁶ During invasive disease, the bacterium releases outer-membrane vesicles that contain lipo-oligosaccharide and outer-membrane proteins into the bloodstream, potentially diverting the immune response.⁷ Furthermore, the meningococcus interacts specifically with complement regulators, thereby enhancing the evasion of complement. For example, the bacterium binds to the negative complement regulator factor H through an outer-membrane lipoprotein, factor H-binding protein,¹⁰ a component of two vaccines currently in clinical trials, and may bind to another complement regulator, C4BP through PorA, an immunogenic outer-membrane protein¹¹ (Fig. 1).

DEVELOPMENT OF VACCINES AGAINST *N. MENINGITIDIS***CAPSULAR POLYSACCHARIDE VACCINES**

In the 1960s, the first successful vaccines were developed against groups A and C and were based on capsular polysaccharide.¹² Subsequently, polysaccharide vaccines were introduced against groups W-135 and Y; a meningococcal quadrivalent A, C, W-135, and Y polysaccharide vaccine, which has been licensed in the United States since 1981 on the basis of its safety and immunogenicity, has over 85% efficacy against the A and C components in older children and adults.¹³ However, apart from the group A component, these vaccines are poorly immunogenic in children younger than 2 years of age.¹³ Furthermore, polysaccharides are T-cell-independent antigens that result in short-lived immunity with no memory response. Thus, dosing is required every 3 to 5 years, but this may cause a reduced antibody response (hyporesponsiveness) as compared with the response to initial vaccination, owing to a depleted memory B-cell pool.¹⁴

POLYSACCHARIDE-PROTEIN CONJUGATE VACCINES

To overcome the problem of short-lived protection against the meningococcus, covalent binding (conjugation) of polysaccharides to a protein carrier has been used, resulting in T-cell-dependent immunity and a memory response.¹³ In 1999, the United Kingdom became the first country to introduce the meningococcal group C polysaccharide-protein conjugate vaccine (MenC) into schedules for routine infant immunization, with an initial catch-up campaign for children and adolescents up to 18 years of age.¹⁵ After the introduction of this vaccine, there was a marked decline in group C carriage and disease.^{16,17} MenC provides significant herd immunity, with a decline in disease even among unvaccinated persons¹⁷; this effect is the result of reduced carriage among teenagers, who constitute the main reservoir for meningococcal transmission.¹⁷

MenC is safe,¹⁵ and surveillance in all age groups has suggested an effectiveness of 95% at 1 year, with significant waning over a period of 4 years.¹⁸ Although protection was maintained in the catch-up group (overall effectiveness, 90%), the immunization of infants at 2, 3, and 4 months of age resulted in an overall effectiveness of only 66%. Vaccine effectiveness was 93% for up to

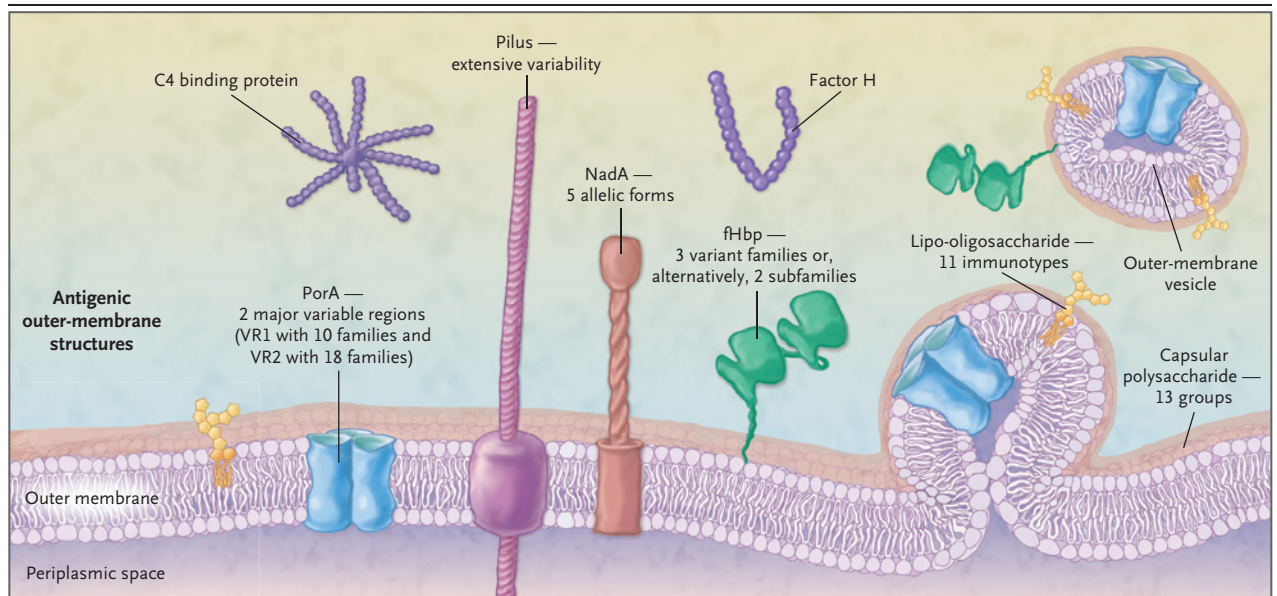


Figure 1. Structure of Meningococcal Outer Membrane, Showing Variability of Outer-Membrane Proteins and Capsule Used in Vaccines and Interaction with Complement.

Neisseria meningitidis is able to recruit the negative complement regulator factor H (fH) to its surface and thus escape complement-mediated killing. Binding to fH occurs by means of a lipoprotein named factor H-binding protein (fHBP) that is expressed on the surface of the organism. The meningococcus also binds the negative complement regulator C4 binding protein through the outer-membrane protein PorA; however, experiments have shown that this binding occurred predominantly in hypotonic (nonphysiologic) buffers,¹¹ so the impact on pathogenesis is not known. During invasive disease, outer-membrane vesicles are released by the bacterium into the bloodstream, potentially diverting the immune response away from the bacterium. Several structures on the bacterial outer surface are candidates (or are potential candidates) for use as antigens in several vaccines. They all demonstrate sequence variability, thus limiting their use. NadA denotes *Neisseria meningitidis* adhesin A.

1 year in this group, but there was no evidence of protection after this time, with an effectiveness of -81% and a wide confidence interval (-7340 to 71).¹⁸ Bacterial invasion can occur within hours, so the memory response that has been primed by conjugate vaccines cannot be initiated in time.¹⁹ Instead, protection requires circulating bactericidal antibodies, but their levels are not sustained after immunization in infancy,¹⁹ possibly owing to limited plasma-cell survival.²⁰ To maintain protective antibody levels, the United Kingdom changed the MenC immunization regimen to vaccinations at 3 and 4 months of age with a booster at 12 months. Other European countries, Canada, and Australia now include MenC in routine immunization schedules.

Meanwhile, owing to a relatively high incidence of group Y disease (accounting for 37% of all cases of meningococcal disease between 1997 and 2002¹³), the United States has licensed a quadrivalent (A, C, W135, and Y) vaccine conjugated to diphtheria toxoid for persons 2 to 55 years of age. Although this vaccine is recommended for

routine immunization of persons 11 to 18 years of age, its immunogenicity in infants — the most vulnerable age group — is poor. However, other multivalent vaccines are now being studied in clinical trials in infants, including an A, C, W-135, and Y vaccine conjugated to a mutant diphtheria toxoid (Menveo, Novartis).²¹ This vaccine has provided good seroprotection in all age groups and is likely to be licensed soon for persons 11 to 55 years of age, with licensure for younger children and infants pending further trial results. In addition, a combined *Haemophilus influenzae* type B and meningococcal C, Y vaccine conjugated to tetanus toxoid is undergoing clinical investigation.²²

On the basis of the success of MenC, a conjugate vaccine is being introduced against the formidable burden of group A disease in Africa, where currently only polysaccharide vaccines are widely available. The Meningitis Vaccine Project has developed an affordable group A conjugate vaccine (MenAfriVac, Serum Institute of India), which has been safe and immunogenic in phase 2 and 3 trials in Africa and India.²³ Ongoing

clinical trials will determine whether the vaccine provides long-lasting protection in infants.²³ Meanwhile, an ambitious campaign is being implemented to immunize 250 million people in 25 African countries with this vaccine during the period from 2010 through 2015.²⁴ However, one potential problem of using a monovalent group A vaccine is that no protection is provided against serogroups W-135 and X, which have emerged in this region.

DEVELOPMENT OF VACCINES AGAINST NMB

With declining group C disease, the development of multivalent conjugate vaccines for infants, and the promise that MenAfriVac holds in Africa, group B disease remains the major public health challenge. NMB vaccine development has been impeded by the group B capsule, which is composed of α 2-8-linked polysialic acid and is structurally identical to fetal brain-cell adhesion molecules.²⁵ Thus, immune tolerance renders the NMB capsule poorly immunogenic. Attempts to provide cross-reactive immune responses against group B capsular polysaccharide led to the development of a vaccine in which the *N*-acetyl group of polysialic acid was substituted for an *N*-propionyl group and conjugated to tetanus toxoid. Although this vaccine was safe and immunogenic in 17 healthy adult volunteers, serum samples obtained after vaccination showed no functional activity in bactericidal assays and other tests of protection.²⁶ One concern about using group B polysaccharide vaccines is the development of autoantibodies against human neural-cell adhesion molecules, as has been suggested by some *in vitro* findings.^{27,28} However, no autoantibodies developed during short-term follow-up of these vaccine recipients,²⁶ and a 31-year follow-up of persons with meningococcal disease showed no excess risk of autoimmune disease in those who had NMB as compared with the general population.²⁹ Nevertheless, anxiety about possible autoimmunity led to vaccine development with the use of noncapsular outer-membrane structures.

OUTER-MEMBRANE-VESICLE VACCINES

Outer-membrane vesicles contain a cocktail of immunogenic antigens, including lipo-oligosaccharide and outer-membrane proteins, and can be

prepared from cultures of meningococci. Lipo-oligosaccharide (also known as endotoxin) is potentially toxic but can be depleted from outer-membrane vesicles by using detergents, with retention of the outer-membrane-protein constituents, which can then be used in vaccines. This was the basis for several outer-membrane-vesicle vaccines against NMB that were used with varying efficacy in clinical trials in the 1980s and 1990s in Chile,³⁰ Cuba,³¹ Brazil,³² and Norway.³³ For example, the Cuban vaccine, which used outer-membrane vesicles from an epidemic-causing strain, was efficacious in the trials in Cuba but strikingly less efficacious in the Brazilian trials.^{31,32} More recently, MeNZB (Norwegian Institute of Public Health and Novartis), a tailor-made outer-membrane-vesicle vaccine, successfully controlled an epidemic in New Zealand³⁴ (Table 1). These outer-membrane-vesicle vaccines generate largely strain-specific immune responses against a protein, PorA, that is highly variable across NMB strains.³⁵ Although they are effective in NMB epidemics caused by a single PorA-expressing strain, outer-membrane-vesicle vaccines are ineffective against the diverse range of PorA proteins found across strains that cause endemic disease. For example, a vaccine containing 20 different PorA proteins would be required to cover 80% of the strains that cause endemic disease in the United States.³⁶ Clearly, this degree of PorA diversity would make it impractical to use unmodified outer-membrane-vesicle vaccines in many countries. Furthermore, the duration of vaccine protection is unclear; infants required four doses of MeNZB during the New Zealand vaccination campaign.³⁴

One potential solution to the limited coverage of single PorA-containing outer-membrane-vesicle vaccines is to engineer vaccines based on two or more outer-membrane vesicles, each containing multiple PorA proteins.³⁷ This approach resulted in a hexavalent vaccine (HexaMen, Netherlands Vaccine Institute), which was shown in phase 2 trials to be safe and immunogenic in infants³⁷ but required a fourth dose between 12 and 18 months of age to produce cross-reactive responses.³⁷ Adding a third outer-membrane vesicle led to a nonavalent vaccine (NonaMen, Netherlands Vaccine Institute), which is currently undergoing preclinical evaluation.³⁸

The Walter Reed Army Institute of Research has developed a multivalent vaccine based on native outer-membrane vesicles, as opposed to

Table 1. Summary of Studies of Outer-Membrane-Vesicle Vaccines against *Neisseria meningitidis*.

Location	Study Period	Vaccine Name and Serologic Classification*	Age Group	Disease Incidence before Vaccination	Study Design	No. of Doses	Control Vaccine or Placebo	No. of Persons Vaccinated	Vaccine Efficacy or Effectiveness†
Iquique, Chile (Walter Reed Army Institute of Research) ³⁰	1987–1989	B:15:P1.3	1–21 yr	20 <i>no. of cases/100,000 population</i>	Prospective, randomized, double-blind	2	A, C, Y, and W135 polysaccharide vaccine	40,811	51%
Cuba (Finlay Institute) ³¹	1987–1989	VA-MENCOG-BC B:4:P1.15	10–14 yr	14.4	Prospective, randomized, double-blind	2	Placebo	106,000	83
São Paulo, Brazil ³²	1989–1990	VA-MENCOG-BC B:4:P1.15	3 mo–6 yr	2.07 (1–6 yr)	Retrospective, case-control	2	Not applicable	2.4 million	47–74
Norway (Norwegian Institute of Public Health) ³³	1988–1991	MenBvac B:15:P1.7,16	13–21 yr	25 (13–21 yr)	Prospective, randomized, double-blind	2	Placebo	171,800	57.2
New Zealand (Novartis Vaccines and Norwegian Institute of Public Health) ³⁴	2004–2008	MenZB B:4:P1.7–2,4	6 mo–19 yr	17	Vaccination campaign‡	3 (4 in infants after 2006)	Not applicable	1,032,239	73‡

* The serologic classification of the *N. meningitidis* strain used in the vaccines includes the serogroup (capsular polysaccharide), the serotype (PorB outer-membrane protein), and the serosubtype (PorA outer-membrane protein).

† Vaccine efficacy is based on the ideal conditions that characterize clinical trials and compares the incidence of meningococcal disease in vaccinated persons with that in unvaccinated persons or in those given placebo. Vaccine effectiveness is based on the field conditions of vaccine-rollout programs and compares the percent reduction in attack rates among vaccinated persons as compared with those not vaccinated.

‡ There were no phase 3 trials of MenZB; instead, a vaccination campaign was launched on the basis of data on immunogenicity and safety from phase 1 and 2 trials and on data from studies of other, similar vaccines (mainly outer-membrane-vesicle vaccines). Thus, an estimate of vaccine effectiveness is provided instead of vaccine efficacy.

detergent-extracted antigens, from three strains genetically modified to express different native outer-membrane vesicles. In phase 1 trials, this vaccine was safe and broadly effective against a range of target strains in adults.³⁹ However, a potential problem of vaccines based on outer-membrane vesicles is the ability of meningococcal outer-membrane proteins to undergo antigenic shift or gene deletion, as seen with PorA,⁴⁰ thus rendering the vaccine ineffective.

REVERSE VACCINOLOGY AND rMENB

The need to find highly conserved antigens for a universal NMB vaccine has led to alternative strategies. First described in 2000, the technique of reverse vaccinology (Fig. 2) was used to identify 350 genes from the *N. meningitidis* genome encoding potential surface-exposed protein antigens, which were evaluated for their ability to elicit bactericidal antibodies.^{41,42} Five of the most promising genome-derived neisserial antigens (GNAs) — *N. meningitidis* adhesin A (NadA, or GNA1994), factor H-binding protein (GNA1870), GNA2091, GNA2132 (recently renamed neisserial heparin-binding antigen), and GNA1030 — were combined in a vaccine formulation named rMenB (Novartis). Serum from mice immunized with this vaccine was found to have bactericidal antibodies against 78% of selected NMB strains.⁴³

ROLE OF TWO VACCINE ANTIGENS IN MENINGOCOCCAL PATHOGENESIS

Since their inclusion in the rMenB vaccine, two antigens, NadA and factor H-binding protein, have been found to be involved in the pathogenesis of meningococcal disease. NadA is a surface-exposed protein found in only 50% of meningococcal strains isolated from patients with meningococcal infection and 5% of strains isolated from carriers.⁴⁴ This protein is involved in mucosal colonization and cell invasion; a hypervirulent meningococcal strain with an inactivated *NadA* gene was shown to have reduced ability to invade human epithelial cells.⁴⁵ NadA is also implicated in tissue and bloodstream invasion through interaction with macrophages and monocytes.⁴⁶

As previously discussed, factor H-binding protein binds to the complement regulator factor H, enhancing resistance against complement¹⁰; the

protein is classified into different variant families,^{47,48} all of which bind to factor H with its complement regulatory activity retained.⁴⁹ Hypervirulent strains express high levels of factor H-binding protein,⁴⁷ a finding that highlights its role in pathogenesis. A recent study has shown that the way in which this protein binds to factor H mimics host-molecule interactions — that is, factor H-binding protein binds to factor H through a mechanism similar to that involved in the binding of human sugar molecules to factor H⁵⁰ (Fig. 3).

Both factor H-binding protein, a genome-derived vaccine antigen, and PorA, an outer-membrane-vesicle vaccine antigen, interact with complement regulators (PorA under nonphysiologic conditions).^{10,11} The recruitment of complement regulators by these immunogenic bacterial proteins may help to moderate the immune response that these proteins elicit. Thus, the use of these antigens within vaccines may be advantageous, since they not only induce bactericidal antibodies but also may induce antibodies that block the attachment of complement regulators to the bacterial surface, thereby enhancing complement-mediated bacterial killing. Identifying other bacterial components that interact with complement may reveal additional vaccine candidates.

CURRENT CLINICAL TRIALS AND FUTURE PROSPECTS

In 2008, Novartis Vaccines initiated clinical trials of rMenB — both with and without an outer-membrane vesicle from the New Zealand vaccine strain — in adolescents and infants. In a phase 2 trial, 150 infants were vaccinated at 2, 4, and 6 months of age. Safety and immunogenicity were satisfactory, with SBA titers of 4 or higher against three reference strains in 89%, 96%, and 85% of subjects after the third dose; these values increased to 100%, 98%, and 93%, respectively, after a booster dose was administered at 12 months.⁵¹ The addition of an outer-membrane vesicle to rMenB leads to a dramatic increase in strain coverage because the PorA antigen is present within the outer-membrane vesicle.⁵² Furthermore, Wyeth independently identified factor H-binding protein⁴⁸ and developed a vaccine containing two protein variants (rLP2086). This vaccine was safe and immunogenic in 103 young adults in a phase 1 study,

with SBA responses to five of six reference strains occurring in 87.5% of the study participants.⁵³ Serum samples from the vaccinees were also able to kill a large proportion of invasive meningococcal isolates.⁵⁴

Both vaccines that contain factor H-binding protein (rMenB and rLP2086) are undergoing further evaluation to determine their safety and immunogenicity. Recruitment is under way for phase 2b and 3 trials of rMenB in infants, toddlers (with the use of either a booster dose after previous rMenB vaccination or a catch-up regimen), and adolescents. Meanwhile, rLP2086 is now being investigated in phase 1 and 2 trials in infants and is being further evaluated in adolescents and adults. Although supposedly shorter than conventional approaches to vaccine development,⁴² the reverse vaccinology that led to the development of rMenB was performed a decade ago, yet it remains to be proved whether this vaccine will be a success.

One potential problem with using factor H-binding protein is that the bactericidal activity of antibodies raised against the protein is variant-specific,⁴⁷ and invasive meningococcal strains with truncated factor H-binding protein have been observed⁵⁵; studies are under way to establish the coverage attained with these vaccines. Whereas rLP2086 contains two variants of factor H-binding protein, rMenB contains only one variant; this feature narrows coverage of the factor H-binding protein component of the vaccine but is counterbalanced by the presence of the other antigens in rMenB. One alternative is to construct a single chimeric protein with epitopes from the immunodominant regions of multiple variants of factor H-binding protein.⁵⁶ In addition, future vaccines may contain recombinant factor H-binding protein that is engineered not to bind to factor H. The high-affinity interaction between factor H-binding protein and factor H may hide important epitopes within the binding site on the protein; thus, abolishing this interaction may elicit a greater array of bactericidal antibodies.⁵⁰ Meanwhile, reverse vaccinology continues to identify potentially useful antigens,⁵⁷ and detoxification of lipooligosaccharide by genetic modification holds promise as a vaccine candidate.⁵⁸ The successful development of NMB vaccines may give rise to a universal vaccine against all meningococcal groups through the presence of NMB vaccine antigens in strains from other groups.

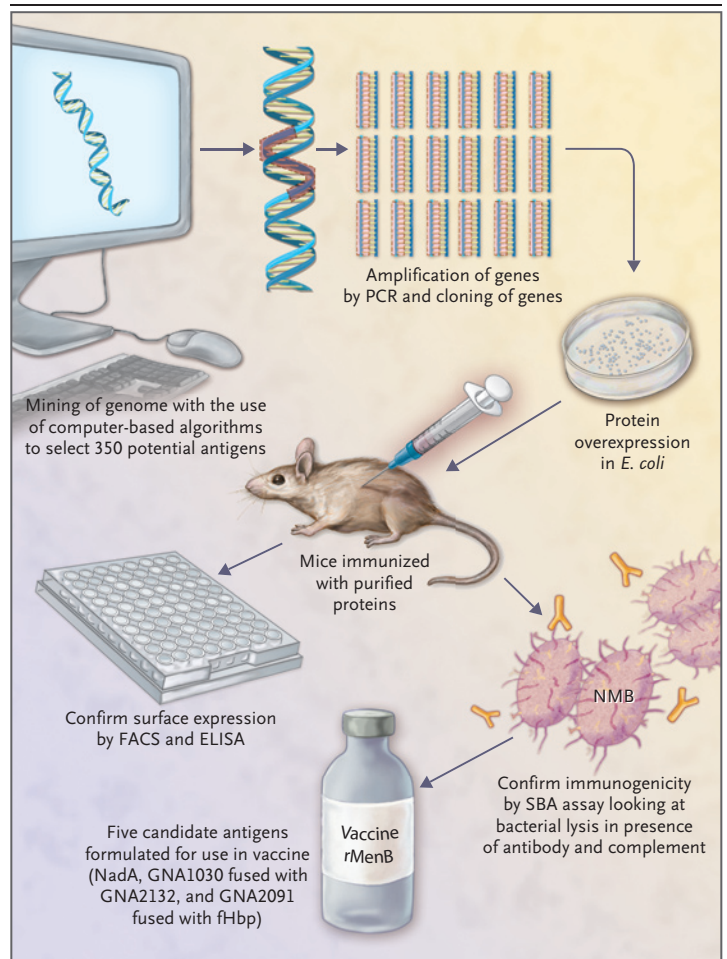


Figure 2. Application of Reverse Vaccinology in Development of a Vaccine for Group B *Neisseria meningitidis* Infection.

Reverse vaccinology has been so named because it depends on genome mining with the use of computer-based algorithms as the initial step rather than on the time-consuming conventional methods that involve culturing the live microorganism. Most of the antigens used in current vaccines (e.g., capsular polysaccharide or modified toxins) are also involved in pathogenesis. Reverse vaccinology involves the unbiased selection of vaccine candidates from the genome and includes those which would not be easily identified by conventional methods. Interestingly, *N. meningitidis* adhesin A (NadA) and factor H-binding protein (fHbp), which are also involved in meningococcal pathogenesis, were both identified by reverse vaccinology. ELISA denotes enzyme-linked immunosorbent assay, FACS fluorescence-activated cell sorting, NMB *N. meningitidis* group B, PCR polymerase-chain-reaction assay, and SBA serum bactericidal antibody.

CONCLUSIONS

Because of its devastating effects, meningococcal infection continues to be a global threat to human health. Although conjugate vaccines have been shown to be effective and safe, it is unclear whether recent advances in vaccine development

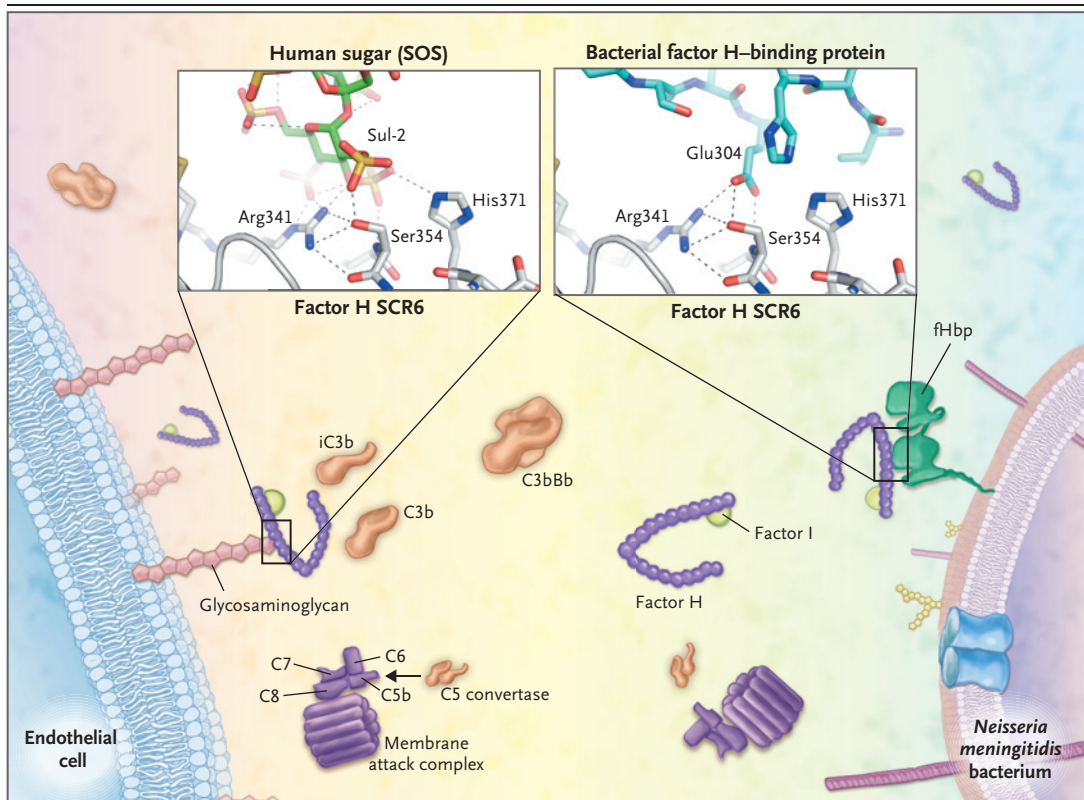


Figure 3. Interaction of Factor H with Factor H–Binding Protein.

Factor H comprises 20 repetitive short-consensus-repeat (SCR) or complement-control-protein domains, with complement regulatory activity and other functions being localized to specific SCRs. Factor H binds to charged glycosaminoglycan (GAG) sugars on host cells at several SCR domains, including SCR6 and SCR7. Factor H down-regulates complement and prevents complement-mediated damage to the host cell by inactivation of complement component C3b (iC3b) and through its action on the C3 convertase enzyme (C3bBb), which is critical in the generation of the C5 convertase enzyme and the membrane attack complex. The meningococcus binds to the same region of factor H as do the GAGs (at SCR6 and SCR7); however, it mimics the interaction by means of charged amino acids found within factor H–binding protein (fHbp) instead of charged sugars, as found in GAGs. Two amino acids in fHbp, at positions 283 and 304, and corresponding amino-acid binding partners in SCR6 and SCR7 of factor H have been shown to be critical for this interaction.⁵⁰ As shown in the inset, the amino acid glutamate-304 (Glu304) of fHbp binds to amino acids in factor H (right), mimicking the interaction between factor H and sucrose octasulfate (SOS), a highly sulfated analogue of human GAG sugars (left). (Insets reprinted from Schneider et al.,⁵⁰ with the permission of the publisher.)

will lead to a universal NMB vaccine in the foreseeable future. Several challenges remain: First, we must improve the immunogenicity of meningococcal vaccines in infants, since this age group is still the most vulnerable to meningococcal infection. This is especially true in the United States, where MenC does not provide adequate coverage; although multivalent conjugate vaccines are licensed for use, they currently do not provide protection for infants. Second, we must ensure that variations of any newly identified antigens do not limit future vaccine efficacy. Finally, we must select vaccines that induce herd immunity to provide the dramatic disease reduction seen with MenC. Only then will it be possible to provide the broad-

ranging vaccine against *N. meningitidis* group B that has so far remained elusive.

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