REVIEW

Meningococcal vaccine evolution*

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Key words

Meningococcal disease • *Neisseria meningitidis* • Meningococcal conjugate vaccines

Summary

Neisseria meningitidis is a leading cause of bacterial sepsis and meningitis worldwide. Invasive meningococcal disease (IMD) can develop rapidly and is associated with high mortality and morbidity. Case fatality in developed countries averages 10% and higher rates are reported in less prosperous regions. The incidence of invasive disease due to Neisseria meningitidis *is highly variable according to geographical area and serogroup distribution. The major disease burden is in developing countries; in industrialized countries meningococcal disease occurs sporadically and most IMD is caused by serogroups B and C. In the US serogroup Y is a major cause of meningococcal disease, accounting for more than one third of cases.*

Polysaccharide vaccines against serogroups A, C, W-135, and Y were developed but they were not so effective in protecting infants, who are at particularly high risk from invasive meningococcal infections. Conjugation of bacterial capsular polysaccharide to a carrier protein generates a T cell dependent immune response and immunological memory from infancy. After the introduction of serogroup C meningococcal conjugate vaccines since 1999, the incidence of serogroup C disease fell dramatically in countries in which they have been used. The first quadrivalent meningococcal conjugate vaccine (MenACWY-D) was licensed in the US in 2005. More recently, another tetravalent meningococcal conjugate vaccine (MenACWY-CRM, Menveo®) was licensed in Europe and the US. Although polysaccharide and glycoconjugate vaccines have been developed for serogroups A, C, Y and W-135, currently there are no broadly effective vaccines available for the prevention of meningococcal B disease.

Introduction

Neisseria meningitidis is a major cause of invasive bacterial infections worldwide and it is associated with high mortality and morbidity. The bacteria, a Gram-negative diplococcus and an obligate human pathogen, colonizes the nasopharinx and spreads through direct contact with respiratory secretions. In most countries, meningococcal disease is endemic, with incidence rates ranging from 0.2 to 5 per 100,000 persons, although this may increase to nearly 1% during major epidemics [1, 2].

Mortality rates in developed countries average 10% (higher rates are reported in less prosperous regions) and up to 20% of survivors suffer from permanent long-term sequelae (deafness, cognitive deficits, seizures, amputation, endocrinopathy, and neuropsychiatric disorders) [3-6].

The incidence of invasive meningococcal disease (IMD) is highest among infants, adolescents and the elderly with over half of all cases occurring in children less than 5 years. In all countries, the highest rates of meningococcal disease occur in infants less than one year of age.

Meningococcal carriage has a population prevalence of about 10%, which varies with age and in different settings. Carriage is rather low in young children, increases through childhood to a peak in 19-year-olds, who have a carriage rate of 20%, and declines in adulthood [7, 8].

Based on the chemical composition of the polysaccharide capsule, *N. meningitidis* strains can be classified into 13 different serogroups, five of which (serogroups A, B, C,W-135, and Y) are responsible for the majority of the invasive diseases [9].

The epidemiology of meningococcal disease is dynamic, varying over time and across regions. 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), the major disease burden is in developing countries [1].

Serogroups B and C are predominant in Europe and United States. In USA serogroup Y, accounting for only 2% of meningococcal infections in 1989-1991, emerged over the past decade and now is a major cause of meningococcal disease (37%) [10]. In Europe, particularly in countries that have introduced serogroup C meningococcal conjugate vaccine, the majority of cases (90%) is caused by serogroup B [11].

Serogroup A is responsible for large epidemics in Africa, in which the incidence approaches 1000 cases per 100,000 persons (and may involve environmental fac-

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tors), whereas serogroups B and C cause disease predominantly in industrialized and newly industrialized countries.
Recently, serogroups W-135 and X (predominantly in Africa) have become increasingly prominent in this region, the latter serogroup being of concern in part because the incidence during outbreaks has exceeded 25 cases per 100,000.
Serogroup W-135 emerged as an important cause of invasive meningococcal disease following outbreaks during and after the 2000 and 2001 Hajj pilgrimages [12].

Meningococcal vaccines

Vaccines against the various meningococcal serogroups were developed during the twentieth century. Meningococcal monovalent conjugate vaccines against serogroups A and C and tetravalent (A,C,W-135 and Y) conjugate vaccines are currently available. No vaccine is licensed for the prevention of serogroup B meningococcal disease.
Although capsular polysaccharide vaccines against meningococcal serogroups A, C, Y, and W-135 have been available for over 30 years, their use has been restricted because they do not induce long-term memory and they are not effective in young children who are at particularly high risk from invasive meningococcal infections [9].
Polysaccharide vaccines can also induce subsequent hyporesponsiveness, in particular with serogroup C [13].
Meningococcal polysaccharides can stimulate a B-lymphocyte response leading to functional antibody, but they fail to stimulate T lymphocytes. As a result, the response to polysaccharide antigen is short-lived and incapable of generating an anamnestic response when the recipient is later exposed to the same antigen. In addition, meningococcal polysaccharide vaccines are poorly immunogenic in infants and young children.
Vaccines produced by conjugation of bacterial capsular polysaccharide to a protein carrier elicit a T cell-dependent response, resulting in increased antibody titres and polysaccharide-specific immunological memory in infants and young children.
Conjugate vaccines induce herd immunity and do not induce immunologic hyporesponsiveness [14].
In 1999, the United Kingdom became the first country to introduce the meningococcal serogroup C 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. Vaccine efficacy for toddlers and teenagers was 88% and 96% respectively in the first 16 months after immunization. The number of serogroup C cases fell rapidly in the targeted age groups, with an overall reduction of 81% of confirmed cases of invasive meningococcal C disease. The reduction occurred also among the unimmunized population through a decrease in pharyngeal carriage of serogroup C *Neisseria meningitidis* [15, 16].
Universal implementation of these MenC vaccines led to the dramatic control of invasive serogroup C disease in the United Kingdom and elsewhere [17-19].
On the basis of the success of MenC vaccine, a serogroup A conjugate vaccine (MenAfriVac) was developed by the Meningitis Vaccine Project. This vaccine has been safe and immunogenic in phase 2 and 3 trials in Africa and India [20].
An unconjugated quadrivalent (serogroups A, C, W-135, and Y) polysaccharide vaccine has been available since 1981 in the United States; however this vaccine provided protection for a limited time and was not effective in children under 2 years of age.
A quadrivalent A, C, W-135, and Y diphtheria toxoid protein-conjugated meningococcal vaccine (MenACWY-D, Menactra, Sanofi Pasteur) was licensed in 2005 for use in persons 2-55 years of age in the United States and is currently recommended for routine use in adolescents (11-18 years of age) as well as other high-risk groups (college freshmen living in dormitories, military recruits, microbiologists, travelers in countries in which *N. meningitidis* is hyperendemic or epidemic, persons with asplenia or complement deficiency) [21].
The licensed tetravalent glycoconjugate vaccine was immunogenic and well tolerated in children (2-10 years) and adolescents but resulted poorly immunogenic in infants, the group with the highest risk of meningococcal disease [22-24].
In the last decade other multivalent vaccines have been developed, including a quadrivalent (serogroups A, C, W-135, and Y) vaccine conjugated to tetanus toxoid (Men ACWY-TT) and a novel quadrivalent conjugate vaccine in which the capsular oligosaccharides are conjugated to CRM_{197}, a non toxic mutant of the diphtheria toxin (MenACWY-CRM, Menveo®, Novartis).
Compared to the licensed quadrivalent polysaccharide vaccine, Men ACWY-TT showed similar bactericidal antibody persistence at 3 years for serogroups A and C and higher for serogroups W-135 and Y in young adults [25].
MenACWY-CRM has provided good seroprotection in all age groups. In children 2-10 years of age, MenACWY-CRM has been well tolerated and immunogenic, inducing a persistent immune response one year after immunization [26].
In adolescents, MenACWY-CRM induced robust immune responses to serogroups A, C, W-135, and Y, and was generally safe and well tolerated [27]. Persistence of immunogenicity has been observed for periods of up to 5 years in clinical trials [28, 29]. Concomitant administration with a combined tetanus, reduced diphtheria, and acellular pertussis vaccine didn't affect immunogenicity in adolescents [30].
In infants, unlike the quadrivalent ACWY diphtheria toxoid-conjugate vaccine, MenACWY-CRM has provided good protection [31]. Snape et al. demonstrated that a primary immunization course of MenACWY-CRM was well tolerated and immunogenic for serogroups A, C, W-135, and Y when given to healthy infants with different primary schedules (2,4 months; 2, 3, and 4 months;

2, 4, and 6 months) and a booster dose at 12 months of age. Although lower seroprotection rates for serogroup A in the 2-dose primary series was observed, the administration of a booster dose of MenACWY-CRM resulted in at least 95% of participants achieving seroprotection against each of the serogroups C, W-135, and Y and at least 84% for serogroup A.
In February, 2010, the Food and Drug Administration (FDA) licensed the quadrivalent meningococcal MenACWY-CRM (Menveo®) vaccine for use in a single dose in persons aged 11–55 years [32].
In March, 2010 the EMEA (European Medicines Agency) licensed MenACWY-CRM (Menveo®) vaccine for use in subjects aged over 11 years. Menveo® is recommended for teenagers and adults at risk in some European countries.
Recently the FDA recommended the use of quadrivalent meningococcal diphtheria toxoid-conjugate vaccine (MenACWY-D) among children aged 9 through 23 months at increased risk for invasive meningococcal disease [33].

Meningococcal serogroup B vaccines

With the increasing introduction of a quadrivalent polysaccharide conjugate vaccine against serogroups A, C, W135 and Y, serogroup B now remains the major challenge in industrialized countries.
Meningococcal serogroup B vaccine development has followed a different approach from that used for the preparation of conjugate vaccines for serogroups A, C, W-135 and Y. The capsular-polysaccharide strategy cannot be applied because serogroup B polysaccharide has a structural homology to the polysialic acid present in many human glycoprotein of neural cell adhesion molecules, resulting in poor immunogenicity and the potential for induction of autoimmune antibodies [34].
Therefore the development of Men B vaccines has focused on subcapsular antigens either as outer membrane vesicles (OMV) or as individual antigens [35].
Serogroup B vaccines based on outer membrane vesicles containing proteins (especially the PorA protein) have been successful in the control of clonal outbreaks of serogroup B disease, but, due to meningococcal surface structure heterogeneity and genetic recombination, these vaccines are not candidates for routine prevention of endemic serogroup B disease.
Based on the knowledge of the meningococcal genome, a new approach named "reverse vaccinology" has led to the identification of 350 genes from the *N. meningitidis* genome encoding potential surface-exposed protein antigens, which were evaluated for their ability to elicit bactericidal antibodies [35].
Novartis developed a four component Men B vaccine (4CMenB) containing three novel surface-protein antigens (factor H binding protein, neisserial adhesion A, neisserial heparin binding antigen) combined with a PorA-containing outer membrane vesicle preparation [36].
One of these antigens, the fHBP (factor H Binding Protein), was independently identified and included in another Men B vaccine developed by Pfizer, currently being assessed in phase II and III clinical trials [37].
Recently, Santolaya and coll. assessed the immunogenicity and safety of 4CMenB in healthy Hispanic adolescents, demonstrating seroprotective titres against the reference strains in 99-100% of participants after two 4CMenB doses, while no additional immunological benefit were observed after a third dose. Local and systemic reaction rates were similar after each 4CMenB injection and didn't increase with subsequent doses, but remained higher than placebo. No significant safety signals were identified [38].
Gossger and coll assessed the immunogenicity and reactogenicity of 4CMenB in infants when given in two different schedules (2,3,4 months; 2,4,6 months), concomitantly or separately from routine vaccines. [39] More than 99% of participants had human serum bactericidal antibody titers of 1:5 or greater in response to the strains specific for the fHbp and NadA components of the vaccine; 79% to 81.7% of participants had responses to the strain specific for the OMV component, depending on the schedule used. The study demonstrated that the responses to routine vaccines given with 4CMenB were non inferior to routine vaccines alone for all antigens, except for the responses to pertactin in the pertussis vaccine and to serotype 6b in the 7-valent pneumococcal vaccine. Although the overall safety profile of the 4CMenB vaccine was similar to that of other routine infant vaccines, the rates of fever were higher.

Conclusions

Because of its devastating effects, meningococcal infection continues to be a global threat to human health.
Serogroup C meningococcal conjugate vaccine has been demonstrated to be safe, immunogenic and efficacious in all group of age, with a documented rapid decline in meningococcal C disease in countries in which MenC vaccines have been introduced in national mass immunization campaign [40].
Given the dynamic epidemiology of meningococcal disease and the recent emergence of meningococcal serogroups different from B and C, the availability of multivalent meningococcal conjugate vaccine represents a substantial progress toward worldwide prevention of invasive meningococcal disease.
In future years, tetravalent meningococcal conjugate vaccine diffusion and inclusion in new immunization strategies (such as universal infant vaccination, booster vaccination in various age groups and as a travel vaccine), will offer the opportunity to protect broad populations against emergent meningococcal serogroups.
The new meningococcal serogroup B vaccine could potentially provide improved protection for infants against meningococcal disease beyond the protection provided by currently licensed vaccine.

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