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Routine vaccination against MenB

Considerations for implementation

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Effective polysaccharide(conjugate) vaccines against *Neisseria meningitidis* serogroups A, C, W, and Y have been widely used, but serogroup B meningococci remain a major cause of severe invasive meningococcal disease (IMD) worldwide, especially in infants. Recently, a vaccine, 4CMenB (Bexsero®), containing three recombinant proteins, and outer membrane vesicles (OMV) derived from a serogroup B meningococcal strain (MenB) has been licensed in Europe and Australia and is indicated for persons aged 2 mo or older. This article discusses what should be considered to enable a successful implementation of a broad coverage MenB vaccine in national immunization programs. Epidemiology data, vaccine characteristics including vaccine coverage, immunogenicity, post-implementation surveillance and costs are relevant aspects that should be taken into account when selecting an appropriate immunization strategy. The potential impact on strain variation and carriage, as well as monitoring vaccine effectiveness, and rare but potentially serious adverse events are points that need to be included in a post-implementation surveillance plan.

Introduction

Neisseria meningitidis is a Gram-negative bacterium frequently found in the human nasopharynx. Entry of *N. meningitidis* into the bloodstream can result in meningococcal meningitis and/or septicemia. Invasive meningococcal disease (IMD) may result in death within 24 h, even with antibiotic treatment. Patients who survive IMD are also at high risk of suffering at least 1 permanent sequela, which may include limb loss, cognitive deficits, hearing loss, or seizure disorders.[1] Each year approximately 1.2 million cases of IMD with 135 000 deaths are estimated worldwide. IMD affects mainly young children, older children, and young adults. Epidemiology and serogroup distribution differs geographically.[2] *N. meningitidis* has at least 13 serologically distinct groups, classified according to the antigenic structure of the polysaccharide capsule.[1] Six serogroups of *N. meningitidis* (A, B, C, Y, W, and more recently X) are responsible for the majority of IMD cases worldwide.[1,3] The risk of invasive disease is higher for serogroup C and B compared with other serogroups, and is higher for serogroup C than for serogroup B.[4] Disease caused by *N. meningitidis* serogroups (A, C, Y, and W) is preventable using conjugate vaccines targeting the respective serogroup-specific polysaccharide capsules. Currently, most meningococcal disease in developed countries is caused by MenB. In the United States, nearly one-third of all cases of meningococcal disease are caused by capsular group B strains.[5] In many European countries, the proportion is even higher (up to 90%).[6-11] Group B strains cause a disproportionate number of IMD cases in infants <1 y of age[12] (**Table 1**). Rates of IMD infection generally decline with age, although disease prevalence rises slightly during the teenage years, presumably due

Table 1. Epidemiological data of MenB

	% serogroup B per total IMD	Incidence rate per 100 000 per year	% per age per total (MenB) IMD cases	Case-fatality rate	Reference
Europe		0.3–1.1 (2009–12)			
Germany		0.3 (2011)			13
The Netherlands	83% (2010)	0.4–0.7 (2008–11)	19% (<1 y) MenB IMD (2010) 28% (1–4 y) MenB IMD (2010)		7
England-Wales	80% (2011–12)	1.1 (2011–12)	62% (<1 y) MenB IMD 32% (1–4 y) MenB IMD		6
Austria	59% (2010)	0.5–0.9 (0.6 in 2010)	10.5 rate (<1 y) MenB IMD		8
Ireland	82–89% (2010–12)	5.2–0.9 (1999–2012) (0.9 in 2012)	20–32% (<1 y) IMD 53–65% (1–4 y) IMD	2–5% (1999–2012)	9
Poland	52% (2010)	0.6 (2010)	>51% (<5 y) IMD		11
Spain	72% (2009–10)	0.7–1.1 (2004–10)	21% (<1 y) MenB IMD (2009–10) 31% (1–4 y) MenB IMD (2009–10)	7–11% (2004–10)	10
US	28% (2011) 25% MnC (2011) 36% MnY (2011)	0.05 (2011)	24% (<1 y) MenB IMD 24% (1–4 y) MenB IMD		5
Canada Ontario Quebec	36% (2000–10) 22% MnC (2000–10) 22% MnY (2000–10) 68% (1997–2011) 88% (2009–2011)	0.1–0.3 (2000–10) 0.1 (2010) 0.3–0.9 (1991–2011)	21% (<1 y) MenB IMD 15% (<1 y) IMD 14% (1–4 y) IMD 18% (15–19 y) IMD	6% (1997–2011)	15 16
Australia	84% (2011)	0.8 (2011)	18% (<1 y) MenB IMD 17% (1–4 y) MenB IMD 20% (15–19 y) MenB IMD		17
New Zealand	63% (2012) 34% MenC (2012)	1.2 (2012)	14% (<1 y) MenB IMD 16% (1–4 y) MenB IMD 18% (15–19 y) MenB IMD	4.7% (2012)	18

to the high carriage rate in this group attributable to increased peer contact and social behavior.[4]

The most effective prevention strategy for meningococcal disease is vaccination. Since January 2013, the European Commission granted a marketing authorization for the first meningococcal serogroup B (MenB) vaccine, 4CMenB, a vaccine containing three recombinant proteins, and outer membrane vesicles (OMV) derived from MenB. In August 2013, the 4CMenB vaccine was also licensed in Australia. The 4CMenB vaccine is indicated for persons 2 mo of age or older. This article discusses the different aspects that should be considered to enable a successful implementation of this vaccine in national immunization programs.

Epidemiology

Most of the MenB disease is endemic with incidences varying by country over the years; the highest incidence of IMD caused by serogroup B meningococci is in the infant age group (<1 y) (**Table 1**). In Europe, the overall IMD incidence ranges from 0.3 to 1.1 per 100 000 persons (2009–2012).[6-11,13] In the United States, the incidence of MenB disease is historically low, i.e., 0.05 per 100 000 (2011).[5] The epidemiology data of the US from 1998–2007 shows that the incidence of IMD caused by serogroup B peaked among infants aged 0–3 mo, whereas MenC disease peaked among 4–5 mo.[14] In Canada (data from 1991–2011) the MenB disease incidence ranged from 0.1–0.9 per 100 000 per year; A peak in IMD incidence was observed in infants at 4–5 mo.[15,16] In Australia (2011), the incidence rate was 0.8 per 100 000. Infants <1 y accounted for 18% of the cases, children 1–4 y for 17%, and persons aged 15–19 y for 20% of the cases.[17] In New Zealand (2012), the incidence rate was 1.2 per 100 000.[18] More details are presented in **Table 1**.

MenB can also cause severe epidemics dominated by one particular strain, which may persist for 10 y or longer, as seen in the past in Cuba, Brazil, Norway, and New Zealand. Strain-specific OMV MenB vaccines have been proven effective in controlling these epidemics.[19-21]

Table 2. Randomized controlled phase 2–3 studies performed with 4CMenB prior to license

Study description	4CMenB	Total subjects	Results	Reference
Phase 2b/3	1,2 or 3 doses of 4CMenB interval 1,2 or 6 mo	1631 healthy persons, aged 11–17 y	Vaccine was safe. Vaccination with 2 doses with an interval of 6 mo, and not 1 or 2 mo, provided good SBA titers. A 3rd dose provided no additional benefit	39
Phase 2b	3 doses 4CMenB at 2,4,6 mo concomitantly with routine infant vaccination 3 doses 4CMenB at 2,4,6 mo and at 3,5,7 mo routine infant vaccination (intercalated scheme) 3 doses concomitantly at 2,3,4 mo simultaneously routine infant vaccination Only routine infant vaccination at 2,3,4 mo	1885 infants	After each vaccination, fever (≥38 °C) was reported; 76–80% in the groups receiving 4CMenB and the routine vaccines simultaneously, 71% in the intercalated group, and in 51% in the group receiving the routine vaccines only. No influence of clinical significance was observed of 4CMenB vaccination on the immune response to routine vaccination. Higher SBA titers were observed in intercalated vaccination group. In all groups: A SBA titer of ≥1:5 was observed in 99% or more of infants against strains 44/76-SL (fHbp) and 5/99 (NadA), and in 79–86% against the NZ98/254 strain (OMV)	38
Phase 3	Safety: Routine vaccines* alone or concomitantly with 3 doses of 4CMenB or MenC at 2,4,6 mo Immunogenicity: Routine vaccines* alone or concomitantly with 3 doses of 4CMenB Fourth (booster) dose at 12 mo with or without MMRV vaccination	1003 infants 2627 infants 1555 infants	Concomitantly 4CMenB was associated with increased fever (≥38.5 °C) rates. In total 77% (1912 of 2478) of infants had fever after any 4CMenB dose, compared with 45% (295 of 659) after routine vaccines alone, and 47% (228 of 490) with MenC No clear influence of 4CMenB vaccination was observed on the immune response to routine vaccination. A SBA titer of ≥1:5 was observed in 100% of infants against strains 44/76-SL (fHbp) and 5/99 (NadA), and in 84% against the NZ98/254 strain (OMV). In a subset (n = 100), 84% had SBA titer ≥1:5 for NHBA. 95–100% of boost-vaccinated infants had SBA titers ≥1:5 for all antigens with or without concomitant MMRV	37

*Routine vaccination: with 7-valent pneumococcal and combined diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, Hemophilus influenzae type b DTaP-IPV-HepB-Hib vaccine. MenC, serogroup C conjugate vaccine; MMRV, measles-mumps-rubella-varicella vaccine.

Vaccine development

Vaccines against MenB disease have proved difficult to produce, because the capsular polysaccharide on the serogroup B bacterium is poorly immunogenic as it exhibits structural similarity to human neural (adhesion) molecules and is therefore not a useful target.[22] Consequently, vaccine developers focused on other outer membrane structures and initially meningococcal outer membrane vesicles (OMV) were used as basis for the development of several MenB vaccines. OMV produced from a representative outbreak strain has been shown to be successful in controlling various epidemics of MenB disease, such as MeNZB that was used to control an epidemic in New Zealand (2004–6).[19,20] The bactericidal activity induced by these OMV vaccines is largely directed at the PorA outer membrane protein (OMP). However, PorA is a highly variable, and therefore monovalent strain-specific OMV vaccines are not generally useful for prevention of endemic IMD caused by diverse strains. In order to obtain broader protection multivalent PorA OMV vaccines have been developed, such as bivalent, hexavalent, and nonavalent OMV vaccine combinations.[23-27] In addition, OMV vaccine formulations based on *Neisseria lactamica* have been designed to provide broad coverage.[28] More recently, native OMV vaccines, without the use of detergents, based on genetically detoxified LPS have been developed.[27,29] Other approaches that have been applied are vaccines containing multiple recombinant proteins, such as 4CMenB or rLP2086.[19,30] Several of these vaccines are at stages of clinical development, and in January 2013, 4CMenB was the first MenB vaccine that has been approved by the European Medicines Agency (EMA) for use on the European market. 4CMenB is based on novel antigens identified by reverse vaccinology and is composed of factor H binding protein (fHbp), involved in regulation of complement activation, NadA, involved in cell adhesion, invasion and induction of cytokines, and NHBA, heparin-binding protein.[19] NHBA and fHbp were fused to GNA1030 (unknown function) and GNA2091 (unknown function), respectively, to enhance protein stability and immunogenicity.[19,31] In addition to these proteins, OMV from the New Zealand epidemic strain (NZ98/254; P1.7-2,4, ST41/44) were added to the formulation as major (PorA) antigen and for additional potential adjuvant activity besides the alum adjuvant.[19]

Discussion

***N. meningitidis* serogroup B strain typing**

Today, meningococci are classified into serogroups (by type of capsular polysaccharide) usually performed by bacterial agglutination test or PCR[32] and fine types determined by sequencing epitope encoding regions of PorA (VR1, VR2) and FetA.[33] Multilocus sequence typing (MLST) is a molecular technique that has been developed and has been increasingly used for MenB typing.[34] MLST is performed by sequencing of selected genes encoding housekeeping enzymes. The loci of each house-keeping gene define the allelic profile or so-called sequence type (ST). Related STs with identical alleles at four or more loci are grouped together as a clonal complex (CC). The combination of antigen sequence typing of PorA and FetA together with MLST seems to provide a robust framework, which can be complemented by sequence typing of other antigens and measurement of their expression.[34]

After implementation of a MenB vaccine in a national immunization program, it is important to have a surveillance system that provides complete and accurate data of the circulating MenB strains. This is essential to be able to identify antigenic changes that may lead to vaccine failures. *N. meningitidis* has the capability adapt surface structures to changing environments by a variety of genetic mechanisms. Horizontal gene transfer is a common occurrence in the *Neisseria* genus and is responsible for large numbers of genetically heterogeneous MenB strains, especially at the OMP level whereby a variety of combinations are present.[32,33,35] In addition, MenB strains could also escape immune responses against vaccine antigens by changing the expression levels of the target antigens.[19] For example, only 50% of invasive meningococcal isolates are known to produce NadA, present in 4CMenB, in detectable quantities (NadA expression is phase variable) with a significant proportion of the NadA negative isolates not having the NadA gene at all. NHBA on the other hand, appears to be present in all isolates tested so far, but protein sequence variability is high. The fHbp shows significant variability resulting in limited cross-protective antibody responses and immune selection under vaccine pressure may occur.[19] Therefore, in addition to traditional typing of the serogroup, fine and genetic typing, data are required on the fHbp, NHBA and NadA genotypes (DNA sequencing), and phenotypes of invasive circulating strains for the post-implementation surveillance of the 4CMenB vaccine. The meningococcal antigen typing system (MATS) was developed to predict 4CMenB strain coverage, using serum bactericidal antibody assay with human complement (hSBA) taking antigen expression levels and cross protection into account.[36] However, the MATS assay is a complicated assay that cannot be performed in any reference laboratory and it has been suggested that selected reference laboratories should carry out MATS. Moreover, the vaccine producer itself developed the assay and is the only producer so far. Therefore, national public health authorities may not want to rely on it. Also, if post-implementation surveillance methods that take into account antigen expression levels will be used, vaccine failures should be carefully defined. As aforementioned vaccine pressure may drive meningococci to reduce expression of antigens present in the vaccine.

Clinical data

Since no other MenB vaccine has completed clinical development, this article focuses on clinical data obtained with 4CMenB (**Table 2**). Three large phase 2–3 randomized controlled clinical studies have been performed to study the immunogenicity and safety of the investigational vaccine, 4CMenB, in adolescents, and infants (2–12 mo).[19,37-39] The immunogenicity of 4CMenB was determined by measuring serum bactericidal antibody (SBA) titers against MenB reference strains that primarily expressed just one particular vaccine antigen, i.e., strain 44/76-SL (matched with the vaccine for fHbp), strain 5/99 (matched with the vaccine for NadA), and strain NZ98/254, the vaccine strain for the OMV component.[19] Summarizing, 4CMenB was shown to be safe in adolescents and infants (primary series and booster dose). However, high fever (≥38–38.5 °C) rates, up to 80%, were reported in the infant groups, especially when 4CMenB was given concomitantly with routine vaccines. Evidence suggests that the rise in body temperature induced by the vaccine can be tempered by prophylactic use of paracetamol without influencing the immunogenicity.[40] In general, good SBA titers were found against the selected MenB reference strains and no influence of clinical relevance was observed regarding the immune response against routine infant vaccines. The potential of 4CMenB to protect against wild-type circulation strains should be proven after implementation of the vaccine in routine schemes.

In a recent study, waning of SBA titers was observed at 40 mo of age after primary immunization with 4CMenB at 6, 8, and 12 mo of age.[41] Thus, a robust surveillance program post-implementation is recommended, allowing early recognition of any decline in vaccine effectiveness and the need for a booster vaccination later in childhood or adolescence.

Carriage

N. meningitidis is transmitted between individuals via respiratory secretions. Carriage is considered a prerequisite for the development of IMD. Asymptomatic nasopharyngeal carriage of *N. meningitidis* is common, with an average carriage rate of approximately 10%.[4,42,43] Commensal association of particular strains with a host is a long-term relationship, often lasting several months.[43] In contrast to IMD, which is most common in infants and declines through childhood, the prevalence of *N. meningitidis* carriage is highest among teenagers and low in young children. The carriage rate was shown to be <3% in children younger than 4 y and increased up to 24–37% in the age-group 15–24 y, but may differ per country and over the time.[4,42-44] Apart from age, other risk factors for higher carriage are active and passive smoking, gender (slightly more male), recent respiratory infections, and regular visits to public venues, such as youth clubs and discotheques.[42-44]

Asymptomatic infection with or carriage of pathogenic and non-pathogenic strains may help to protect against meningococcal disease.[4,42,43,45] This may explain the higher risk of disease in infants that may have never been a carrier (naive). Carriage of *meningococci* has been shown to cause an increased bactericidal antibody response. The humoral response may last several months after the carried strains have been lost.[42,45] Cellular immunity and cytokine production in relation to meningococcal disease and carriage are poorly understood and deserve more attention. There is evidence that the loss of capsule enhances the capability of meningococci to colonize the human nasopharynx and to avoid human defense systems. Capsule production in meningococcal strains can be switched on and off at a high frequency.[42] Moreover, meningococci can change from serogroup by capsular switching. In a population-based study, a substantial proportion of invasive serogroup B, C, and Y isolates demonstrated capsular switching, indicating that this is a common natural phenomenon. The implementation of MenB vaccination in national immunization programs might have an effect on population-level meningococcal carriage state. This phenomenon should be further explored in post-implementation surveillance programs.

Implementation in national immunization programs

The highest incidence of IMD caused by serogroup B is in the infant age group (<1 y). Therefore, implementation of a new MenB vaccine in existing routine infant immunization schedules seems the most logical strategy. However, it is noteworthy that a substantial disease burden occurs in very young infants (i.e., those younger than 3–5 mo of age),[14,15] and these cases will probably not be vaccine-preventable using a 2-, 4-, and 6-mo schedule. Results from clinical trials suggest that a 2-, 3-, or 4-mo infant schedule may be acceptable, although further information is needed given the lower immunogenicity that was observed using this schedule.[38] In some countries, this accelerated schedule fits well in the national immunization program, while in other countries the routine infant vaccinations are given at a 2-, 4-, and 6-mo schedule. This should also be taken into account. Official recommendations for infants is, according to the product information, three primary doses starting at the age of 2 mo and a booster vaccination between the age of 12 and 23 mo. 4CMenB can be given concomitantly with vaccines against diphtheria, tetanus, acellular pertussis, *Hemophilus influenza* type b, inactivated poliomyelitis, hepatitis B, heptavalent pneumonoccal conjugate, measles, mumps, rubella or varicella.

Another strategy may be maternal vaccination, however, because young children remain vulnerable for IMD in the first years of their life, the infants will not be protected when maternal antibody levels have diminished. Probably multiple vaccinations are then still necessary to prevent MenB IMD during young childhood.

After the implementation of the MenB vaccine, it is recommended to investigate the influence on meningococcal carriage. So far, three studies have examined the effect of MenB OMV vaccines on carriage; in these studies high vaccine coverage had no effect on rates of meningococcal carriage.[32] Recently, results were presented of a large study in the UK of nearly 3000 young adults immunized with 4CMenB and/or quadravalent meningococcal A, C, W, Y conjugate vaccines examining the effect on meningococcal carriage rates. In this study, prior to vaccination 33% of the samples (n = 930) yielded *Neisseria* cultures, mostly N. meningitides (98%), mainly of serogroups B and Y. Primary analysis at one month after the vaccination series did not reveal significant impact of the 4CMenB vaccine, but at later time points 4CMenB was associated with a decrease in carriage of MenBCWY strains (24.2%).[46] These results raise the possibility of an impact on individual carriage, which may lead to greater herd protection in settings where the vaccines are implemented broadly. If immunization with a MenB vaccine were to influence nasopharyngeal carriage, a mass immunization campaign of adolescents and young adults, the age of peak nasopharyngeal carriage, may reduce circulation of strains covered by the vaccine leading to reduced rates of disease (i.e., herd immunity). This strategy alone, however, is probably not sufficient to protect young children.

Based on modeling data that have been published regarding the cost-effectiveness of a new MenB vaccine it is not expected that the vaccine is cost-effective at present, considering the commonly accepted threshold of €50 000 per QALY. Only when the MenB incidence will increase considerably or the vaccine price will become very competitive it may become cost-effective.[47,48] Another important influence on cost-effectiveness will be whether the vaccine results in herd effects, by reduction of carriage rate, which is not yet known.[32,47,48] The duration of protection and the need for booster doses in childhood will be other key cost considerations.[32,47,48] Apart from cost-effectiveness, the success of a vaccine program is dependent on public acceptability and feasibility. Meningococcal disease is highly feared by the public, which may encourage the uptake of the MenB vaccine. On the other hand, parental acceptability may be influenced by vaccine concerns, which include safety, undefined effectiveness, or more practical concerns regarding many vaccines and multiple injections at single visits.[32] With respect to vaccine safety, parents can fear the risk of fever associated with 4CMenB vaccine, when administered to infants. An adequate system of post-implementation surveillance to detect and evaluate (potentially rare and serious) adverse effects and will be an essential component of maintaining public confidence. In addition, post-implementation surveillance data should be sufficient to monitor the vaccine effectiveness and to be able to detect possible changes in the clonal, antigenic, and phenotypic profiles of circulating strains under vaccine selection pressure.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Author's Contributions

P.K. drafted the outline and the text of the manuscript. A.v.d.E., expert in medical microbiology focus area meningitis, has contributed to the intellectual content with respect to strain typing and variation and IMD incidence data of the Netherlands. W.L., advisor in vaccination strategies, gave critical input regarding the evaluated vaccination strategies. All authors were actively involved in reviewing the content and editing the text of the manuscript. All authors read and approved the final version of the manuscript.

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