**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. 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. *N. meningitidis* has at least 13 serologically distinct groups, classified according to the antigenic structure of the polysaccharide capsule. Six serogroups of *N. meningitidis* (A, B, C, Y, W, and more recently X) are responsible for the majority of IMD cases worldwide. 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. 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.6-11 Group B strains cause a disproportionate number of IMD cases in infants <1 y of age (Table 1). Rates of IMD infection generally decline with age, although disease prevalence rises slightly during the teenage years, presumably due...
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).7 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 New Zealand (2012), the incidence rate was 1.2 per 100 000.18 More details are presented in Table 1.

| 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) | | | |
| 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 | | 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) | | 10 |
| US | 28% (2011) 25% MenC (2011) 36% MenY (2011) | 0.05 (2011) | 24% (<1 y) MenB IMD 24% (1–4 y) MenB IMD | | 5 |
| Canada Ontario Quebec | 36% (2000–10) 22% MenC (2000–10) 22% MenY (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 | | 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 | | 18 |
Vaccine development

Vaccines against MenB disease have proved difficult to produce, because the capsule 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. 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). 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. In addition, OMV vaccine formulations based on Neisseria lactamica 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.

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 and fine types determined by sequencing epitope encoding regions of PorA (VR1, VR2) and FetA. Multilocus sequence typing (MLST) is a molecular technique that

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.

Table 2. Randomized controlled phase 2–3 studies performed with 4CMenB prior to license
has been developed and has been increasingly used for MenB typing.\textsuperscript{34} MLST is performed by sequencing of selected genes encoding housekeeping enzymes. The loci of each housekeeping 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.\textsuperscript{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. \textit{N. meningitidis} has the capability to adapt surface structures to changing environments by a variety of genetic mechanisms. Horizontal gene transfer is a common occurrence in the \textit{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.\textsuperscript{32,33,35} In addition, MenB strains could also escape immune responses against vaccine antigens by changing the expression levels of the target antigens.\textsuperscript{39} 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.\textsuperscript{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.\textsuperscript{50} 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).\textsuperscript{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 NZ298/254, the vaccine strain for the OMV component.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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**

\textit{N. meningitidis} is transmitted between individuals via respiratory secretions. Carriage is considered a prerequisite for the development of IMD. Asymptomatic nasopharyngeal carriage of \textit{N. meningitidis} is common, with an average carriage rate of approximately 10%.\textsuperscript{4,42,43} Commensal association of particular strains with a host is a long-term relationship, often lasting several months.\textsuperscript{42,44} In contrast to IMD, which is most common in infants and declines through childhood, the prevalence of \textit{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.\textsuperscript{4,44} 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.\textsuperscript{42,44}

Asymptomatic infection with or carriage of pathogenic and non-pathogenic strains may help to protect against meningococcal disease.\textsuperscript{42,43,45} This may explain the higher risk of disease in infants that may have never been a carrier (naive). Carriage of \textit{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.\textsuperscript{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. 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), 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. 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 pneumococcal 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. Recently, results were presented of a large study in the UK of nearly 3000 young adults immunized with 4CMenB and/or quadrivalent 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%). 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. 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. The duration of protection and the need for booster doses in childhood will be other key cost considerations. 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. 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.

**References**

1. Granoff DM, Harrison LH, Borrow R. Vaccines, 5th Ed. Philadelphia: Saunders Elsevier, 2008.
2. Bai X, Findlow J, Borrow R. Recombinant protein meningococcal serogroup B vaccine combined with outer membrane vesicles. Expert Opin Biol Ther 2011; 11:969-85; PMID:21615224; http://dx.doi.org/10.1517/14712598.2011.585965
3. Xie O, Pollard AJ, Mueller JE, Norheim G. Emergence of serogroup X meningococcal disease in Africa: need for a vaccine. Vaccine 2013; 31:2852-61; PMID:23623866; http://dx.doi.org/10.1016/j.vaccine.2013.04.036
18. Health Intelligence Team of the Institute of Environmental Science and Research Limited. The epidemiology of meningococcal disease in New Zealand. Surveillance report 2012; Available via the Internet: [http://www.surv.esristi.nz/PDF_surveilance/MeningococcalDisease/2012/2012AnnualRpt.pdf](http://www.surv.esristi.nz/PDF_surveilance/MeningococcalDisease/2012/2012AnnualRpt.pdf)

19. Goringe AR, Pajon R, Bexsero: a multicomponent vaccine for prevention of meningococcal disease. Hum Vaccin Immunother 2012; 8:174-83; PMID:22426368; [http://dx.doi.org/10.1080/16181629](http://dx.doi.org/10.1080/16181629)

20. Arnold R, Galloway Y, McNicholas A, O’Hallahan J. Effectiveness of a vaccination programme for an epidemic of meningococcal B in New Zealand. Vaccine 2011; 29:7610-1; [http://dx.doi.org/10.1016/j.vaccine.2011.06.120](http://dx.doi.org/10.1016/j.vaccine.2011.06.120)

21. van Alphen L, van den Dobblesteen G. Meningococcal B vaccine development and evaluation of efficacy. Hum Vaccin 2008; 4:1458-61; PMID:18854894; [http://dx.doi.org/10.1080/16181629](http://dx.doi.org/10.1080/16181629)

22. Finne J, Leinonen M, Makela P. Antigenic similarities between brain components and bacteria causing meningitis. Implications for vaccine development and pathogenesis. Lancet 1983; 2:355-7; PMID:6158800; [http://dx.doi.org/10.1016/S0140-6736(83)90340-9](http://dx.doi.org/10.1016/S0140-6736(83)90340-9)

23. Sandbu S, Domingo J, Oster A, Billmark O, Bakke HS, Naess LM, Aase A, Hveberg IS, Kristoffersen AC, Rydlund KM, et al. Immunogenicity and safety of a combination of two serogroup B meningococcal outer membrane vesicle vaccines. Clin Vaccine Immunol 2007; 14:1062-9; PMID:17607345; [http://dx.doi.org/10.1128/CVI.00094-06](http://dx.doi.org/10.1128/CVI.00094-06)

24. Bouriaud D, Poolman J, Borrow R, Findlow J, Domingo JD, Puig-Barbera J, Baldi JM, Planelles V, Juberit A, Colomer J, et al. Immunogenicity and safety of three doses of a bivalent (B-4:p1,19,15 and B-4:p1,7,9) meningococcal outer membrane vesicle vaccine in healthy adolescents. Clin Vaccine Immunol 2007; 14:65-73; PMID:17065257; [http://dx.doi.org/10.1128/CVI.00230-06](http://dx.doi.org/10.1128/CVI.00230-06)

25. de Kleijn ED, de Groot R, Labadie J, Lefeber AF, van den Dobblesteen G, van Alphen L, van Dijken H, Kuipers B, van Omme GW, Mala W, et al. Immunogenicity and safety of a hexavalent meningococcal outer-membrane-vesicle vaccine in children of 2.3-7 and 7-8 years of age. Vaccine 2000; 18:1456-66; PMID:11081109; [http://dx.doi.org/10.1016/S0264-410X(00)00423-5](http://dx.doi.org/10.1016/S0264-410X(00)00423-5)

26. van den Dobblesteen GP, van Dijken HH, Pillai S, van der Vlugt M, Ronkiewicz P. M, et al. Surveillance of invasive meningococcal disease in the Netherlands. Submitted for publication; Available via the Internet: [http://revista.isciii.es/publicacio/1/pdf_92.pdf](http://revista.isciii.es/publicacio/1/pdf_92.pdf).

27. Donnelly J, Medini D, Boccardo G, Giuberti L, Ward J, Frisch C, Moxon ER, Stella M, Comanducci M, Bambini S, et al. Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein-based vaccines. Proc Natl Acad Sci U S A 2010; 107:19490-5; PMID:20926228; [http://dx.doi.org/10.1073/pnas.0917580107](http://dx.doi.org/10.1073/pnas.0917580107)

28. Vesikari T, Esposito S, Pryymula R, Ypma E, Kohl I, Toneatto D, Dull P, Riminucci B, Adolescent Vaccine Study Group. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. Lancet 2013; 381:825-35; PMID:23324563; [http://dx.doi.org/10.1016/S0140-6736(12)61961-8](http://dx.doi.org/10.1016/S0140-6736(12)61961-8)

29. Gesquer N, Snape MD, Yu LM, Finn A, Bona G, Esposito S, Principi N, Diez-Domingo J, Sokal E, Bejel K, et al; European MenB Vaccine Study Group. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. JAMA 2012; 307:573-82; PMID:22318278; [http://dx.doi.org/10.1001/jama.2012.85](http://dx.doi.org/10.1001/jama.2012.85)

30. Santolaya ME, O’Ryan ML, Valenzuela MT, Prado V, Vergara R, Muñoz A, Toneatto D, Graña G, Wang H, Clemens R, et al; V72P10 Meningococcal B Infant Vaccine Study group. Immunogenicity and safety of a multicomponent vaccine, recombinant meningococcal serogroup B (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. Lancet 2013; 381:825-35; PMID:23324563; [http://dx.doi.org/10.1016/S0140-6736(12)61961-8](http://dx.doi.org/10.1016/S0140-6736(12)61961-8)
40. Prymula R, Esposito S, Kretel C, Kohl I, Toneatto D, P. D. Prophylactic paracetamol in infants decreases fever following concomitant administration of an investigational meningococcal serogroup B vaccine with routine immunizations. 29th Annual Meeting of the European Society for Paediatric Infectious Diseases; The Hague, Netherlands; June 7–11, 2011 Available via internet: http://www.kenes.com/espid2011/cd/PDF/O219.pdf?zoom_highlightsub=p

41. Snape MD, Philip J, John TM, Robinson H, Kelly S, Gossger N, Yu LM, Kretel C, Toneatto D, Dull PM, et al. Bactericidal Antibody Persistence 2 Years After Immunization With 2 Investigational Serogroup B Meningococcal Vaccines at 6, 8 and 12 Months and Immunogenicity of Preschool Booster Doses: A Follow-on Study to a Randomized Clinical Trial. Pediatr Infect Dis J 2013; 32:1116-21; PMID:23958808; http://dx.doi.org/10.1097/INF.0b013e31829cfff2

42. Yazdankhah SP, Caugant DA. Neisseria meningitidis: an overview of the carriage state. J Med Microbiol 2004; 53:821-32; PMID:15314188; http://dx.doi.org/10.1099/jmm.0.45529-0

43. Caugant DA, Tzanakaki G, Kritz P. Lessons from meningococcal carriage studies. FEMS Microbiol Rev 2007; 31:52-63; PMID:17233635; http://dx.doi.org/10.1111/j.1574-6976.2006.00052.x

44. Bogaert D, Hermans PW, Beelens H, Sluijter M, Luijendijk A, Rumke HC, Koppen S, van Belkum A, de Groot R, Verbrugh HA. Epidemiology of nasopharyngeal carriage of Neisseria meningitidis in healthy Dutch children. Clin Infect Dis 2005; 40:899-902; PMID:15736029; http://dx.doi.org/10.1086/428351

45. Jones GR, Christodoulides M, Brooks J, Miller AR, Cartwright KA, Heckels JE. Dynamics of carriage of Neisseria meningitidis in a group of military recruits: subtype stability and specificity of the immune response following colonization. J Infect Dis 1998; 178:451-9; PMID:9697726; http://dx.doi.org/10.1086/515622

46. Read R, Baxter D, Chadwick DR, Faust SN, Finn A, Gordon SB, et al. Impact of a quadrivalent conjugate (MenACWY-CRM) or a serogroup B (4CMenB) meningococcal vaccine on meningococcal carriage in English university students Presentation at the 20th European Monitoring Group on Meningococccies (EMGM); Bad Loipersdorf, Austria; Sept 17–19, 2013

47. Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. Vaccine 2013; 31:2638-46; PMID:23566946; http://dx.doi.org/10.1016/j.vaccine.2013.03.034

48. Pouwels KB, Hak E, van der Ende A, Christensen H, van den Dobbelsteen GP, Postma MJ. Cost-effectiveness of vaccination against meningococcal B among Dutch infants: Crucial impact of changes in incidence. Hum Vaccin Immunother 2013; 9:1129-38; PMID:23406816; http://dx.doi.org/10.4161/hv.23888