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Meningococcal B Vaccination: Real World Experience and Future Perspectives

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Abstract:	Invasive meningococcal disease (IMD) represents a severe risk for health. It can be considered the most dangerous vaccine-preventable disease due to the high probability of related permanent sequelae and death. The introduction in many countries of the conjugate vaccines against A, C, W135 and Y meningococcal serogroups influenced significantly the impact of the disease. Recently, the difficulties in obtaining an effective vaccine against meningococcal serogroup B (MenB) have been get over through the reverse vaccinology, enabling the recognition of some antigens providing a response against most of circulating MenB strains worldwide. The new 4cMenB vaccine is recommended in Europe, Canada, Australia, USA and some Latin American countries. Even if sound data on efficacy and safety profile are available, the results in terms of effectiveness are still limited. The management of the MenB outbreaks in two US universities demonstrated the ability to quickly achieve high vaccination coverage rates and no new cases among immunized subjects were assessed. It is desirable that the opportunity to complete preventive intervention against IMD offered by the new 4cMenB vaccine should be recognized and that this vaccine is included in the vaccination schedule to complete the panel of immunization against Neisseria meningitidis.

Sir,

thanks for the Reviewer's and Editor's comments that have allowed us to greatly improve our manuscript.

Please find the following detailed response to each comment (highlighted in green).

Reviewer #1

This review focuses on the recently implemented vaccine against serogroup B meningococcal disease. The review is concise, sufficiently precise and adequately written and provides a general description of the post implementation data available as of today with the vaccine. Furthermore, it expands on the immunization regimens that are suggested and adopted in the different countries. This review is intended for a general audience and particularly for scientists not fully exposed to this field, as not too many details are provided here.

Main suggestions:

1. Not enough space is devoted to the review of the clinical data (particularly immunogenicity in the different age groups, and tolerability) that have ultimately led to the registration of the vaccine. For instance, the section starting at the end of page 6 ("Besides...") could be moved earlier.

2. The Meningococcal Antigen Typing System (MATS) is the method that has allowed to generate strain coverage estimates for the vaccine in the different geographic settings, and therefore has been crucial for the registration of the vaccine. This method is not mentioned here. I think it would be important to discuss this assay and to cite the relevant references

3. The composition of the 4CMenB vaccine is mentioned very briefly. I think it would be important to spend a couple of sentences describing the antigens

present in the vaccine and the role that these antigens have in the pathophysiology of the meningococcal disease. A few key references should also be cited here.

4. Finally, the section on Epidemiology is very concise, and it would be important extend a bit on this section particularly to explain the difficulties of developing a universal MenB vaccine and to show the value of a multicomponent vaccine in order to protect against a multiplicity of heterogeneous MenB strains.

OK. We think that we have summarized the epidemiological impact of MenB in the "Epidemiology" section, reporting data from all over the world. For this reason we would prefer not to expand too much this section. We have just added this part in page 3:

The molecular epidemiology studies have confirmed that several hundred PorA genotypes have been identified among capsular group B isolates worldwide. Anyway, even if the disease is caused by relatively few PorA subtypes, the development of a vaccine against MenB has been hampered by the requirement to obtain a broad protection against heterologous strains (PorA subtypes). However, the point raised by the Reviewer is relevant and the difficulties of developing a universal MenB vaccine as well as the value of a multicomponet approach has been added in the "Vaccines" section.

In the same section we have also included some parts related to the points 1, 2 and 3. In detail, we have added the following parts:

page 4:

The design of protein-based meningococcal vaccines is complicated by the important level of genetic and antigenic diversity expressed by the meningococcus. In fact, a variety of genetic mechanisms allow surface structures to adapt to changing environments[27] To give broad protection against MenB, a vaccine must take into account a high level of antigenic diversity/variability as well as the risk of escape mutants.[28]

pages 5 and 6:

In detail, fHbp is a surface lipoprotein that binds to human factor H and by blocking this inhibitor of the alternative complement pathway favours enhanced meningococcal killing. Nad A is a surface protein that mediates the adhesion and the entrance of the pathogen in the nasopharingeal epithelial cells; 5 variants of this adhesin have been identified.[33] NHBA (Neisserial Heparin Binding Antigen) is a surface lipoprotein able to bind heparin in vitro and to induce bactericidal antibodies. OMVs are outer membrane blebs released by meningococci able to induce protective antibodies against the homologous strain[34]

The vaccine has been proven effective and without significant side effects. Two randomized controlled multicenter phase II and III studies in several European countries on a large cohort of children have shown excellent results in terms of immunogenicity without any clinically relevant interference with routine vaccines[32,35]. In terms of reactogenicity, both studies have shown a higher incidence of fever when 4CMenB has been given concomitantly with other vaccines; anyway, fever was not higher or more frequent than the one usually related to the administration of other pediatric vaccines[32,35]. An innovative method, called MATS (Meningococcal Antigen Typing System) has been developed to estimate the percentage of circulating strains in a given country that may be covered by the immune response induced by 4CMenB vaccine.[36]A survey on 1,052 isolates of invasive MenB, collected from 2007 to 2008 in 5 European countries, has shown that, depending on the country of origin, between 73% and 87% of the isolates had an antigenic asset susceptible to be covered by the vaccine.[37]

Since the antigens contained in 4CMenB are also present in other meningococcal serogroups, this vaccine may offer some protection even against non-MenB strains.[38]

A study carried out on 147 strains belonging to serogroups C, W and Y isolated in UK, Germany, France and Brazil highlighted that the sera of subjects immunized with 4CMenB vaccine were capable of inducing a complement mediated killing of Men C, W and Y in a range from 45% to 90%, suggesting that 4CMenB can potentially have an impact on meningococcal disease caused by non-MenB strains.[39]

In a study involving 10 reference laboratories all around the world (Australia, Brazil, Canada, Czech Republic, England and Wales, France, Germany, Greece, Italy,

Norway,Spain, and the United States), MATS was used to estimate strain coverage. The global predicted coverage by 4CMenB was 78% (95% CI 63–90%) of all MenB strains contained in the vaccine, ranging from 66% in Canada (95% CI, 43–78%) to 91% in the US (95% CI, 72–96%) [40].

5. Regarding the implementation of 4CMenB on Quebec, it should be mentioned that the rate of fever was lower than expected.

Ok. This point has been mentioned in page 8 as follows:

The percentage of children, adolescents and young adults with fever ≥ 40.5°C was equal to 0.1%; no cases of fever ≥ 40.5 ° C were observed in children who had received 4CMenB concomitantly with other routine vaccinations. Overall, the average maximum temperature was lower than expected; as a matter of fact, the average maximum temperature resulted 38.9°C (38.8°C in children less than two years of age and 39°C in 2-20 year-old subjects).[70]

Minor comments:

1.According to the new nomenclature, MenW135 is now defined as MenW

Ok. Done

2. At page 4, when dealing with recommendation of the vaccine, it should be mentioned that Italy has recommended the vaccine on a regional basis

Ok. Done

3. The last sentence at page 4 ("Inconsistent...") should be omitted as these data have not been considered to have a statistically significant relevance.

Ok. Done

4. page 5, line 18, "supported by" should be changed with "caused by". "serogroups" should be changed with "clones"

Ok. Done

5. page 6, line 7: the term "peculiar" is not appropriate here and should be changed

This sentence has been changed as follows: To date, the CDC recommends that all university students, graduates and all members of the university community in Princeton can receive a free immunization against the MenB.

7. First sentence of the Discussion is not clear and should be rephrased.

Ok. This sentence has been rephrased as follows:

The availability of the new 4CMenB vaccine allows to improve the possibilities of prevention towards meningococcal diseases, as it is directed against one of the most epidemiologically relevant serogroups of *Neisseria meningitidis*.

Reviewer #2:

The title of the manuscript suggests that this is a review of meningococcal B vaccines but this only covers 4CMenB and ignores Trumenba licensed in the US. Either the title should be adjusted or the review should be expanded.

The review has been expanded in pages 9 and 10, considering also the MenB-FHbp vaccine (Trumenba):

In the United States (USA), another new vaccine was recently approved by the Food and Drugs Administration (FDA) for use in persons aged 10-25 years: MenB-FHbp[76].It contains two purified recombinant lipidated factor H binding protein (FHbp) antigens, both FHbp subfamily (A and B). The vaccine is registered as a 3-dose series, with the second and third doses administered 2 and 6 months, respectively, after the first dose. The immunogenicity and safety in adolescents and young adults were evaluated in several clinical trials conducted in USA and in Europe on adolescents aged 11-18 years. They showed similar results in terms of immunogenicity and no immunogenic interference when MenB-FHbp was administered with other vaccines, except for the antibody response to HPV type 18[77,78]. Antibody persistence through 48 months after the 3rd dose was evaluated in a

clinical trial, that demonstrated an initial rapid decline in antibodies after vaccination followed by a flattening out of the antibody curve after 6 months. More than 50% of vaccinated subjects continued to demonstrate hSBA titers greater than or equal to the lower limit of quantification against three of the four strains tested after 48 months[76]. The most common solicited adverse reactions observed in the 7 days after receipt of MenB-FHbp in the clinical trials were pain at the injection site (≥85%), fatigue (≥40%), headache (≥35%), myalgia (≥30%), and chills (≥15%)[78]. In addition a study on laboratory personnel was conducted due to the greater estimated risk for meningococcal infection in workers occupationally exposed to *N. meningitidis* serogroup B (more than 40-fold higher than for all adults aged 30–59 years). A seroprotective and broad antibody response was elicited while local reactions, systemic events, and adverse events were commonly mild to moderate in severity, and no potentiation with subsequent doses was demonstrated[79]. According to these findings, the US Advisory Committee on Immunization Practices (ACIP) recommends MnB vaccination for individuals at higher risk for meningococcal infection, including microbiologists[80].

A brief consideration was also added in section "Dicussion and Conclusion":

The availability of new vaccines against MenB allows to improve the possibilities of prevention towards meningococcal diseases, as it is directed against one of the most epidemiologically relevant serogroups of *Neisseria meningitidis*. Both vaccines are immunogenic and safe but recommended for different age groups and available in different countries. In addition, antibody levels within six months post-dose 3 for MenB-FHbp, appears to decline, while for 4CMenB a modest antibody waning was observed through 24 months post-dose 2 [50].

The manuscript requires a review and redraft for English (both grammar and choice of wording).

Ok. We have reviewed the manuscript. Grammar and choice of wording have been checked

There are many scientific inaccuracies which are too numerous to individually list. The manuscript requires a redraft from this perspective.

There is no mention of some key issues which must be included

a) Breadth of vaccine coverage.

b) Cross protection to other serogroups.

c) Fever rates in infants and recommended use of paracetamol.

d) Serology data is now available from the Princeton implementation.

Ok. Accordingly to the parts previously illustrated, we have taken into account most of these points.

Editor:

There are many positive comments and points of improvement mentioned below by our reviewers. I would also like to suggest that you elaborate more on a worldwide perspective. As reviewer #2 points out, there is little reference to the US and other countries where not only 4CMenB is available. Please seek to create a more universal balance, taking into consideration vaccines' implementation worldwide.

We hope to have taken into account most of the points raised by the Reviewers.

Due to the update of the references, we have to modify the table 3 that we upload in the revised version.

I hope you find our revised manuscript suitable for publication and look forward to hearing from you.

Best regards,

Armando Stefanati.

Title Page

Title: Meningococcal B Vaccination: Real World Experience and Future Perspectives

Type of Article: Review Article

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Conflict of interest statement:

GG received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, and Pfizer for being consultant or taking part in advisory board, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials; AS, PK, SL, NV have no competing interest.

Abstract: Invasive meningococcal disease (IMD) represents a severe risk for health. It can be considered the most dangerous vaccine-preventable disease due to the high probability of related permanent sequelae and death. The introduction in many countries of the conjugate vaccines against A, C, W135 and Y meningococcal serogroups influenced significantly the impact of the disease. Recently, the difficulties in obtaining an effective vaccine against meningococcal serogroup B (MenB) have been get over through the reverse vaccinology, enabling the recognition of some antigens providing a response against most of circulating MenB strains worldwide. The new 4cMenB vaccine is recommended in Europe, Canada, Australia, USA and some Latin American countries. Even if sound data on efficacy and safety profile are available, the results in terms of effectiveness are still limited. The management of the MenB outbreaks in two US universities demonstrated the ability to quickly achieve high vaccination coverage rates and no new cases among immunized subjects were assessed. It is desirable that the opportunity to complete preventive intervention against IMD offered by the new 4cMenB vaccine should be recognized and that this vaccine is included in the vaccination schedule to complete the panel of immunization against *Neisseria meningitidis*.

Keywords: Immunization, Meningococcal Disease, *Neisseria meningitides*, Serogroup B.

Title Page

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Type of Article: Review Article

Introduction

Invasive meningococcal disease (IMD) poses a serious threat for health and is considered to be the most dangerous vaccine-preventable disease by the population. IMD is regarded as a dramatic event due to the high probability of related permanent sequelae and death. Although the role played by the most epidemiologically relevant serogroups of *Neisseria (N.) meningitidis* (A, B, C, W and Y) varies considerably in relation to season and geographical area and their epidemiological impact is greatly underestimated, meningococci are a worldwide major public health problem.[1,2] The availability of conjugate vaccines against A, C, W and Y meningococcal serogroups and their introduction in many countries significantly impacted on the disease. Recently, the difficulties in developing an effective vaccine against meningococcal serogroup B (MenB) has been overcome by reverse vaccinology methodology, that enabled the identification of some antigens inducing a response against most of circulating MenB strains in the world.[3]

The new vaccine (4CMenB), already approved in Europe, Canada, Australia, USA and some Latin American countries, allows to complete the panel of immunization prevention against IMD.[4,5]

Microbiological and clinical overview

N. meningitidis is a Gram-negative aerobic diplococcus, hosted exclusively by men. It is an opportunistic pathogen, usually living as a commensal in the nasopharynx, colonizing the upper respiratory tract, without causing damage to the host.[6,7] The highest rates of nasopharyngeal carriage are reported in adolescents and young adults. The asymptomatic carriage prevalence increases from 4.5% in childhood, with a peak of 23.7% in 19-year-old individuals, and then decreases to 7-8% in adulthood.[8] The different *N. meningitidis* strains are divided in 12 serogroups (A, B, C, 29E, H, I, K, L, W, X, Y and Z; serogroup D is currently classified as a not encapsulated variant of serogroup C) on the basis of the

capsular polysaccharides immuno-histochemical characteristics; serogroups A, B, C, W and Y are responsible of most IMD cases worldwide. Further classification into serotypes/subserotypes or immunotypes is established on major outer-membrane class 1 (PorA) and class 2 or 3 (Por B) proteins or on lipopolysaccharides (LPS), respectively.[9]

The main route of transmission is direct contact with Flügge's droplets from people with IMD or, more frequently, from asymptomatic carriers. Usually the humoral response is sufficient to stop the spreading of the microorganism and avoid IMD; but, when the antibody response is not optimal, through mechanisms still incompletely understood, bacteremia occurs,[10] causing endothelial damage, increasing vascular permeability and inducing a prothrombotic state.[11] The real meningococcal disease is a very uncommon complication of bacterial colonization and usually manifests itself with meningitis (over than 50% of cases), bacteremia and septicemia.[12] The disease may occur in endemic, with sporadic cases, or in epidemic form, with outbreaks of varying extent and duration. The main risk groups are: newborns and children <1 year (in which natural immunity is particularly low), adolescents (since their behaviors promote close interpersonal contact and have higher carriage rates), travelers in highly endemic zones (sub-Saharan Africa), patients with immunosuppression and elderly subjects.[3,13] The characteristics of IMD are the quick clinical progression and the presence of skin rash, often starting from lower limbs; however, patients frequently experience aspecific clinical pictures.[14] In contrast to other most common infectious meningitis, IMD manifests itself less frequently with seizures or focal neurological signs [15] and the most commonly sequelae include deafness, spasticity, seizures, learning and attention disabilities.[11]

Every year MenB causes 500,000 cases of septicemia and meningitis worldwide; although the incidence of the invasive form is generally low, it is matter of great concern for health professionals due to the quick onset and course of the disease, the difficult of early diagnosis, the major post-infection sequelae (brain damage, deafness, kidney failure and lower limb amputation) and high fatality rates (up to 5-15%).[14,16-18]

Epidemiology

The overall incidence of the meningococcal disease varies around the world: in North America, Europe and Australia the rate is 0.3-3 cases per 100,000[13], while it can reach 10-

1,000/100,000 in Africa, during an epidemic. The same serogroups have different geographical distribution: events sustained by the group A are more common in Africa and Asia, while groups B and C have a greater dissemination in North America and Europe. In the United States, the incidence of MenB disease is historically low (0.05 per 100,000); in Canada in the period 1991–2011, the MenB disease incidence ranged from 0.1–0.9/100,000 per year. In Australia (2011), the incidence rate was 0.8/100,000 and in New Zealand (2012) was 1.2/100,000[4]. In 2009, 29 European countries have reported a meningococcal disease incidence of 0.92 cases per 100,000; the Republic of Ireland (3.4/100,000) and the UK (2.0/100,000) showed the highest rates. In 2011, MenB was responsible of 73.6% of reported cases, followed by serogroups C (14.4%) and Y (8.2%).[19] Nonetheless the incidence of meningococcal disease in Europe declined over the past decade, mainly due to the introduction of the conjugate vaccine against meningococcus C (MenC).

In Italy, IMD is historically associated with an alternation of serogroups B and C. From the '90s, up to 2001, MenB prevailed, while in 2003-2004 there was a reversed trend with a predominance of MenC. In 2006, with the extensive use and implementation of the MenC conjugate vaccine, the epidemiological situation changed again, making MenB the principal agent of meningitis and septicemia, mainly affecting children in the first months of life and adolescents.[1,20]

The molecular epidemiology studies have confirmed that several hundred PorA genotypes have been identified among capsular group B isolates worldwide. Anyway, even if the disease is caused by relatively few PorA subtypes, the development of a vaccine against MenB has been hampered by the requirement to obtain a broad protection against heterologous strains (PorA subtypes).[21, 22]

Vaccines

Immunization is the most effective strategy for the prevention of meningococcal disease. Polysaccharide vaccines against meningococcal A, C, Y and W serogroups are available since the ‘70s and ‘80s. However they suffer several limitations. Conjugate vaccines were later produced: the conjugation of a polysaccharide to a protein carrier allows a T-dependent immune response with the advantage of generating high affinity antibodies, immunological memory and responsiveness to booster doses. The conjugate vaccines are

effective in infants, induce a reduction in the carriage state and favors herd immunity. The vaccines currently available include monovalent and polyvalent polysaccharidic vaccines containing antigens of type A, C, Y, W; a monovalent conjugate MenA vaccine (recently introduced in Sub-Saharan Africa)[20]; a conjugate MenC vaccine and two types of quadrivalent conjugate vaccine (MenACYW). The quadrivalent vaccine conjugated with non-toxic mutant of diphtheria toxin[23] is indicated in children ≥2 years, adolescents and adults; the quadrivalent vaccine, conjugated with tetanus toxoid, is administered from 12 months of life.[24]

The Italian National Vaccination Plan (PNPV) 2012-2014 [25] included the MenC conjugate vaccine in the immunization schedule with the aim of achieving and maintaining a coverage rate ≥ 95% in newborns and adolescents (11-18 years) and establishes the vaccination with one dose of vaccine against MenC in children 13-15 months or a dose in adolescents not immunized in childhood. It also recommends the identification and vaccination of individuals at risk of IMD.

For many years, it has been attempted to develop a vaccine also against serogroup B, but no satisfying results were obtained because the capsule of the MenB is a self-antigen, and then the polysaccharides B are not very immunogenic and are potentially able of inducing autoimmunity.[9,26] The design of protein-based meningococcal vaccines is complicated by the important level of genetic and antigenic diversity expressed by the meningococcus. In fact, a variety of genetic mechanisms allow surface structures to adapt to changing environments[27] To give broad protection against MenB, a vaccine must take into account a high level of antigenic diversity/variability as well as the risk of escape mutants.[28]

To overcome these issues, vaccines containing outer membrane vesicles (OMV) have been formulated. They are clone-specific, and therefore effective only in the epidemiological context in which a specific clone circulates .[3,29] Their use provided good results in terms of containment of outbreaks in Cuba, New Zealand, Norway and France (Normandy).[30,31] In January 2013, the European Commission granted marketing authorization of the vaccine against the MenB (4CMenB), containing three recombinant proteins and OMV derived from NZ98/254 MenB strain. This vaccine has been produced using the innovative technique of reverse vaccinology, which led to the identification of new MenB antigens

able to induce a bactericidal response. The vaccine is composed by the proteins fHbp (factor H binding protein), NadA (Neisserial adhesin A) and NHBA (Neisserial heparin binding antigen). The OMVs of the epidemic strain of the New Zealand NZ98/254, able to induce a robust antibody response, were also added.[31,32]

In detail, fHbp is a surface lipoprotein that binds to human factor H and by blocking this inhibitor of the alternative complement pathway favours enhanced meningococcal killing. Nad A is a surface protein that mediates the adhesion and the entrance of the pathogen in the nasopharingeal epithelial cells; 5 variants of this adhesin have been identified.[33] NHBA (Neisserial Heparin Binding Antigen) is a surface lipoprotein able to bind heparin in vitro and to induce bactericidal antibodies. OMVs are outer membrane blebs released by meningococci able to induce protective antibodies against the homologous strain[34]

The vaccine has been proven effective and without significant side effects. Two randomized controlled multicenter phase II and III studies in several European countries on a large cohort of children have shown excellent results in terms of immunogenicity without any clinically relevant interference with routine vaccines[32,35]. In terms of reactogenicity, both studies have shown a higher incidence of fever when 4CMenB has been given concomitantly with other vaccines; anyway, fever was not higher or more frequent than the one usually related to the administration of other pediatric vaccines[32,35]. An innovative method, called MATS (Meningococcal Antigen Typing System) has been developed to estimate the percentage of circulating strains in a given country that may be covered by the immune response induced by 4CMenB vaccine[36].

A survey on 1,052 isolates of invasive MenB, collected from 2007 to 2008 in 5 European countries, has shown that, depending on the country of origin, between 73% and 87% of the isolates had an antigenic asset susceptible to be covered by the vaccine.[37]

Since the antigens contained in 4CMenB are also present in other meningococcal serogroups, this vaccine may offer some protection even against non-MenB strains.[38]

A study carried out on 147 strains belonging to serogroups C, W and Y isolated in UK, Germany, France and Brazil highlighted that the sera of subjects immunized with 4CMenB vaccine were capable of inducing a complement mediated killing of Men C, W and Y in a

range from 45% to 90%, suggesting that 4CMenB can potentially have an impact on meningococcal disease caused by non-MenB strains.[39]

In a study involving 10 reference laboratories all around the world (Australia, Brazil, Canada, Czech Republic, England and Wales, France, Germany, Greece, Italy, Norway, Spain, and the United States), MATS was used to estimate strain coverage. The global predicted coverage by 4CMenB was 78% (95% CI 63–90%) of all MenB strains contained in the vaccine, ranging from 66% in Canada (95% CI, 43–78%) to 91% in the US (95% CI, 72–96%) [40].

A year after its approval, the new 4CMenB vaccine has been recommended for pediatric immunization in several countries, including Australia, Canada, UK and Italy; in this latter country the vaccine is recommended on a regional basis.[41] According to the technical datasheet of the vaccine,[42] active immunization is provided to subjects >2 months. The recommended dosage, according to age group, is summarized in Table 1. There are two different possibilities for the inclusion of the vaccine in the pediatric immunization schedule: an "intercalated" schedule ("3+1 intercalated"), with 4CMenB dedicated sessions alternated by 15 days compared to routine sessions, and a "3+1 concomitant" schedule, in which the 4CMenB vaccine is administered at the third and fifth month along with routine vaccinations, and at the seventh month as a single injection. For both proposals, the booster dose is administered at 13-15 months of age. The vaccine (injected into a separate injection site) may be co-administered with vaccines against diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, HBV, pneumococcus (conjugate), measles, mumps, rubella and chickenpox, without any interference on antibody response. Low results were observed with regard to the responses to inactivated poliovirus type 2 and the conjugate pneumococcal serotype 6B and lower antibody titers against pertactin antigen of pertussis were reported. However, these data do not suggest a clinically significant interference. Considering these data and the increased frequency of fever and systemic and local reactions in the case of co-administration with other vaccines, the "Immunization Schedule for Life" sustained by several Italian Scientific Societies, while leaving at territorial policy makers the decision of the best schedule to adopt, suggests the "3 +1 intercalated" vaccination schedule. This choice, though causing the inconvenience of

three additional immunization sessions during the first year of life, has some advantages: carrying out the three doses of 4CMenB immunization more quickly, administration of no more than two vaccines in a single session and minimizing the possibility of increased adverse events. Starting vaccination after the sixth month of age implies a scheme 2+1, with administration at month 6, 8, and a booster dose during the second year of life. Such schedule would have the advantage of reducing the additional immunization sessions to three, but the disadvantage of the theoretical lack of prevention of cases that could occur in the first months of life. The schedule 2+1 would be beneficial if the activation of herd immunity, that can indirectly protect subjects in the first months of life, would be confirmed. Vaccination against MenB should be actively offered to subjects at any age, in the presence of concomitant diseases, in workers at risk and to close contacts of patients, in case of outbreaks and epidemics.[43,44] Immunization schedules adopted in Italian Regions are summarized in Table 2.

The first large-scale use of 4CMenB started in USA in 2013, during two meningitis outbreaks occurred in two universities and caused by different MenB clones (ST409 in Princeton and ST32 in Santa Barbara). The first episode occurred at Princeton University; since the declaration of epidemic cluster, the Department of Health of New Jersey (NJDOH) first activated a wide educational campaign to inform all students about the pathogen transmission way and, then, undertook an antibiotic prophylaxis for all close contacts of cases. The identification of the fifth case led the Centers for Disease Control and Prevention (CDC), the NJDOH and the Princeton University to consider the undertaking of a vaccination campaign, in the awareness of having to require the Food and Drug Administration (FDA) authorization for the use of 4CMenB, not yet licensed in the USA. The permission for the experimental vaccine use was released just before the identification of the eighth case and the first vaccinations were planned in early December. The strategy included the administration of two doses and overall vaccination coverage reached over 90%. The second epidemic outbreak occurred at Santa Barbara University (California) in November 2013. As in Princeton's outbreak, the Department of Health of Santa Barbara (SBPHD) coordinated the activities of prevention, first with antibiotic prophylaxis, then administrating two doses with a scheme similar to that adopted in

Princeton.[45-47] Following these events, in June 2014, the FDA announced the authorization for extensive use of the vaccine in the US for adolescents and young adults between 10 and 25 years of age.[48] To date, the CDC recommends that all university students, graduates and all members of the university community in Princeton can receive a free immunization against the MenB.[49] Data on seroprevalence obtained from Princeton students are available by means of a cross-sectional survey launched in April 2014, that enrolled 607 participants. Focusing on the largest group of subjects who received both doses, approximately 66% of subjects had an hSBA titer > 1:4 against the outbreak strain, two months after the second dose of 4CMenB. In a subgroup of 245 subjects immune response against one of the vaccine strains was assessed. After 2 doses, almost all of them showed a protective titer (hSBA titers > 1:4). In addition, the geometric mean titers (GMTs) were higher for the strain contained in the vaccine than the outbreak strain[50].

Immunization recommendations adopted by several countries and their references are summarized in Table 3.[51-68] Since the suitability of a new vaccine can be influenced by concerns regarding the safety, the effectiveness or multiple injections requirement, the presence of an adequate surveillance system is fundamental to detect possible adverse events, even rare and potentially serious, following vaccination.[69] In this regard, a recent study has been carried out in Canada. In order to control the spreading of the MenB disease, in Saguenay–Lac-Saint-Jean Region of Quebec, a vaccination campaign with 4cMenB was addressed to subjects resident or attending school in the area, aged from 2 months to 20 years. In May-June 2014, during the first dose administration, an active and passive surveillance system was implemented in order to recognize and monitor any related adverse event within the first 7 days following vaccination, particularly high fever (≥ 40.5 ° C), febrile convulsions, transient arthralgia and to assess whether and how they could negatively affect the availability of the subjects to receive the second dose of vaccine. The surveillance system reported a significant incidence of painful local reactions, fever (14-15% of children aged 2 to 23 months) and general malaise. The percentage of children, adolescents and young adults with fever ≥ 40.5°C was equal to 0.1%; no cases of fever ≥ 40.5 ° C were observed in children who had received 4CMenB concomitantly with other routine vaccinations. Overall, the average maximum temperature was lower than expected;

as a matter of fact, the average maximum temperature resulted 38.9°C (38.8°C in children less than two years of age and 39°C in 2-20 year-old subjects)[70] .

No serious or unexpected reactions were reported, so the majority of vaccinated subjects expressed the intention to receive the second dose.[71] The coverage rate reached 83% for the first dose and was 73% for the second dose. No cases of invasive meningococcal disease occurred among both young and older people, from the start of the vaccination campaign. This observation is congruent with the hypothesis of a positive effect of the vaccine.[72]

Besides, four randomized clinical trials in adolescents 11 to 18 years, showed that the vaccine is well tolerated and safe. The most frequent reactions were local as pain at the injection site (86%), while the most common general reaction was malaise (51%); fever occurred between the first and the second day after vaccination in a very low percentage of vaccinated subjects (0.2%)[73].

The use of paracetamol (Prophylactic acetaminophen) has been recommended in order to reduce the incidence of post-vaccination fever in children. Acetaminophen, administered at the time of vaccination, followed by two subsequent doses at 4-6 hour intervals, reduced the incidence of fever of 51-65% in the seven days following vaccination. The use of the drug does not have an impact on the immunogenicity of the vaccine and does not interfere with the response to other routine vaccines[74]. From 1 September 2015, the MenB vaccination was added to the NHS Childhood Immunisation Programme in England with the other routine vaccinations at 2 months, 4 months and 12 to 13 months of age, that makes the UK the first country in the world to offer a national, routine and publicly funded MenB vaccination programme[75].

In the United States (USA), another new vaccine was recently approved by the Food and Drugs Administration (FDA) for use in persons aged 10-25 years: MenB-FHbp[76].It contains two purified recombinant lipidated factor H binding protein (FHbp) antigens, both FHbp subfamily (A and B). The vaccine is registered as a 3-dose series, with the second and third doses administered 2 and 6 months, respectively, after the first dose. The immunogenicity and safety in adolescents and young adults were evaluated in several clinical trials conducted in USA and in Europe on adolescents aged 11-18 years. They showed similar results in terms of immunogenicity and no immunogenic interference when

MenB-FHbp was administered with other vaccines, except for the antibody response to HPV type 18[77,78]. Antibody persistence through 48 months after the 3rd dose was evaluated in a clinical trial, that demonstrated an initial rapid decline in antibodies after vaccination followed by a flattening out of the antibody curve after 6 months. More than 50% of vaccinated subjects continued to demonstrate hSBA titers greater than or equal to the lower limit of quantification against three of the four strains tested after 48 months[76]. The most common solicited adverse reactions observed in the 7 days after receipt of MenB-FHbp in the clinical trials were pain at the injection site (≥85%), fatigue (≥40%), headache (≥35%), myalgia (≥30%), and chills (≥15%)[78]. In addition a study on laboratory personnel was conducted due to the greater estimated risk for meningococcal infection in workers occupationally exposed to *N. meningitidis* serogroup B (more than 40-fold higher than for all adults aged 30–59 years). A seroprotective and broad antibody response was elicited while local reactions, systemic events, and adverse events were commonly mild to moderate in severity, and no potentiation with subsequent doses was demonstrated[79]. According to these findings, the US Advisory Committee on Immunization Practices (ACIP) recommends MnB vaccination for individuals at higher risk for meningococcal infection, including microbiologists[80].

Discussion and Conclusion

The availability of new vaccines against MenB allows to improve the possibilities of prevention towards meningococcal diseases, as it is directed against one of the most epidemiologically relevant serogroups of *Neisseria meningitidis*. Both vaccines are immunogenic and safe but recommended for different age groups and available in different countries. In addition, antibody levels within six months post-dose 3 for MenB-FHbp, appears to decline, while for 4CMenB a modest antibody waning was observed through 24 months post-dose 2 [50]. The highest spreading of MenB in children <1 year suggests that the most effective prevention strategy is to focus the immunization intervention in this age group by means of the 4CMenB vaccine, according to the vaccination schedules indicated in the technical datasheet. As the vaccine was only recently added in vaccine schedules in several countries, compared to sound data in terms of efficacy and safety profile, the results

in terms of effectiveness on the field are still limited. The management of the outbreaks in the US universities demonstrated how the meningococcal disease is perceived as a true medical emergency by the population and by health authorities. The adopted immunization practices, while not structured to allow an evaluation of the effectiveness of vaccination, showed the ability to quickly achieve high vaccination coverage rates and no new cases among subjects immunized were assessed. It is desirable that the opportunity to complete preventive intervention against the meningococcal disease offered by the availability of the new MenB vaccines should be recognized and that these vaccines are included in the vaccination schedule of different countries.

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Legend:

Table 1: Recommended dosing of 4CMenB according to age group

Table 2: Immunization schedules adopted by Italian Regions offering MenB vaccination

Table 3: MenB immunization recommendations adopted by several countries

Abbreviations:

IMD: Invasive Meningococcal Disease; **Men B:** *Neisseria meningitidis* serogroup B; **PorA:** porin A, formerly class 1 protein; **PorB:** porin B, formerly class 2/3 protein; **LPS:** lipopolysaccharide; **MLST:** multi-locus sequence typing; **ST:** sequence type; **IgA:** immunoglobulin A; **TNF-α:** tumor necrosis factor α; **IL:** interleukin; **HIV:** human immunodeficiency virus; **Men C:** *Neisseria meningitidis* serogroup C; **OMV:** outer membrane vesicles; **fHbp**: factor H binding protein; **NadA:** Neisserial adhesin A; **NHBA:** Neisserial heparin binding antigen; **4CMenB:** Four-component meningococcal serogroup B vaccine; **PNPV:** Italian National Vaccination Plan; **NJDOH:** Department of Health of New Jersey; **CDC:** Centers for Disease Control and Prevention; **FDA:** Food and Drug Administration; **SBPHD:** Department of Health of Santa Barbara.

Age group	Primary Immunisation	Intervals between Primary Doses	Booster
Infants, 2-5 months	Three doses each of 0.5 ml, with first dose given at 2 months of age[a]	Not less than 1 month	One dose between 12 and 23 months [b,c]
Unvaccinated infants, 6-11 months	Two doses each of 0.5 ml	Not less than 2 months	One dose in the second year of life with an interval of at least 2 months between the primary series and booster dose [c]
Unvaccinated infants, 12-23 months	Two doses each of 0.5 ml	Not less than 2 months	One dose with an interval of 12 months to 23 months between the primary series and booster dose[c]
Children, 2-10 years	Two doses each of 0.5 ml	Not less than 2 months	Need not established
Adolescents (from 11 years) and adults*	Two doses each of 0.5 ml	Not less than 1 month	Need not established

[a] The first dose should be given at 2 months of age. The safety and efficacy in infants less than 8 weeks of age has not yet been established. No data are available.

[b] In case of delay, the booster should not be given later than 24 months.

[c] The need for, and timing of, further booster doses has not yet been determined.

[*] There are no data in adults above 50 years of age.

Adapted from:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Summary_for_the_public/human/002333/WC500137857.pdf.

Datasets

Region	Schedule	Primary cycle			Booster dose
		First dose	Second dose	Third dose	
Basilicata	3+1 intercalated	3rd month+15 days /4th month	5th month+15 days/6th month	7th -8th month	from 13th month
Apulia	3+1 intercalated	3rd month+15 days	4th month+15 days	6th month	15th month
Tuscany	3+1 intercalated	3rd month+15 days	4th month+15 days	6th month	13th month
Liguria	3+1 intercalated	3rd month+15 days	4th month+15 days	6th month	15th month
Sicily	3+1 intercalated	4th month	6th month	7th -8th month	15th-18th month
Veneto	2+1	7th month	9th month		
Friuli Venezia Giulia	2+1	7th month	9th month		15th month
Autonomous Province Bolzano	2+1	7th month	9th month		

Datasets

Country	*Organization and indications*	*Date*	*Ref.*
France	HCSP: high-risk subjects, outbreak, epidemic, iperepidemics	Oct. 2013	50
Germany	SIKO (Saxony): 2 months -18 years DAKJ: children > 2 months; Adults >50 years (voluntary repayment insurance-based)	Dec. 2013	51 52-53
Australia	ATAGI: children <2 years; 15-19 years	Mar. 2014	54
Czech Republic	NIKO: children >2 months to 10 years and young people 13-15 years		55
Canada	NACI : children >2 months, high-risk subjects, outbreaks, epidemics, iperepidemics		56
Austria	Impfaussschuss des OSR: children >2 months, toddlers, adolescents, high-risk subjects and HCW	Jun. 2014	57
Portugal	SIP and SPP: children >2 months		58
Ireland	NIAC: high-risk groups (age ≥1year), outbreak		59
Chile	Instituto de Salud Publica, Ministero da Salud, Gobierno de Chile: children >2 months		60
Spain	AEP: children >2 months	Aug. 2014	61
Hungary	OEK: children >2 months, high-risk subjects, HIV positive, splenectomized subjects		62
Poland	Sanitary – Epidemiological Council: children and adults at risk, lab worker, HCW, close contacts, travelers, army	Oct. 2014	63
Greece	National Pediatric Society : children >2 months	Dec. 2014	64
Uruguay	Ministerio de Salud Publica: subjects aged from 2 months to 50 years	2014	65
Brazil	Sociedade Brasileira de Infectologia: subjects aged from 2 months to 50 years	Jan. 2015	66
USA	US FDA : use limited in adolescents and young adults	Jan .2015	67

Abbreviations: **HCSP:** *Haut Conseil de la Santé Publique*; **SIKO:** Sächsische Impfkommission; **DAKJ:** Deutsche Gesellschaft für Kinder und Jugendmedizin**; ATAGI:** Australian Technical Advisory Group on Immunisation; **SIP:** Comissão de Sociedade de Infeciologia Pediatrica; **SPP:** Sociedade Portuguesa de Pediatria; **HCW:** Health Care Workers; **NIKO:** Národní Imunizační Komise; **NACI:** National Advisory Committee on Immunization; **OEK:** Országos Epidemiológiai Központ ; **NIAC:** National Immunisation Advisory Committee; **FDA:** Food and Drugs Administration.