

Review

Vaccination with a multicomponent meningococcal B vaccine in prevention of disease in adolescents and young adults



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ABSTRACT

Vaccination programs employing capsular-based meningococcal vaccines have proved successful in a variety of settings globally since first introduced over 40 years ago. Similar successes have been demonstrated using meningococcal vaccines for use against serogroup B (MenB) outbreak strains but the diversity of MenB strains has limited vaccine use outside targeted geographic regions. MenB continues to be a significant cause of outbreaks in adolescents and young adults, as recently demonstrated in university settings in the US (Princeton, New Jersey and Santa Barbara, California) and has the potential for hyperendemic disease levels such as currently experienced in Québec and the United Kingdom. In adolescents, increased endemic disease rates and outbreak potential are likely associated with social behaviors putting individuals at risk for carriage acquisition and may explain regional and temporal variations in epidemiology. A protein-based, multi-component MenB vaccine (4CMenB) is currently licensed for use in 37 countries including EU/EEA countries, Australia, Canada, Chile, Colombia, Uruguay, and the US. In this article we review the most recent clinical trial data with 4CMenB with a focus on adolescents and young adults. The vaccine appears to have an acceptable safety profile and is well-tolerated in adolescents and young adults while providing robust, persistent levels of bactericidal antibodies considered protective for each of the four antigenic components of the vaccine. With the recent availability of this vaccine, health care providers have the first comprehensive opportunity to control meningococcal disease, a highly disruptive public health problem with a disproportionate impact on adolescents and young adults.

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1. Introduction

The bacterium *Neisseria meningitidis*, also known as meningococcus, can cause infections of the meninges as well as sepsis. *N. meningitidis* infection can lead to invasive meningococcal disease

(IMD) which is responsible for serious morbidity and mortality with global estimates of 50,000–135,000 deaths annually [1,2]. Sequelae can include limb loss, cognitive impairment, developmental delays, and focal neurological deficits [3]. Both disease burden and serogroup distribution vary across geographic regions and over time. The vast majority of IMD cases are caused by serogroups A, B, C, W, and Y.

Meningococcal disease due to serogroup B (MenB) remains endemic in many countries in Europe, Western Pacific, and the Americas where incidence rates are dynamic over time. The majority of IMD cases across Europe from 2008–2009 were caused by serogroup B (71%), and the incidence rate for adolescents aged 15–19 years in 2009 was approximately 1.7 cases per 100,000 population [4]. Australia and New Zealand report similar incidence rates [5–8]. Low to moderate endemic rates (of predominant serogroup B) in the Americas range from 0.3 to 4 cases per 100,000 population [1,5,9].

Abbreviations: IMD, invasive meningococcal disease; MenC, serogroup C meningococcal disease; MenB, serogroup B meningococcal disease; MCCV, meningococcal serogroup C conjugate vaccine; MenACWY, serogroups A, C, W, Y meningococcal disease; OMV, outer membrane vesicle; fHbp, factor H-binding protein; NadA, *Neisseria* adhesin A; NHBA, *Neisseria* Heparin Binding Antigen; hSBA, human complement serum bactericidal antibody; MATS, meningococcal antigen typing system; UCSB, University of California at Santa Barbara.

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Adolescents and young adults are unique in both their susceptibility to IMD and as vaccine targets to impact carriage rates, thereby leading to 'herd protection'. While the incidence of meningococcal disease is highest in infants <1 year of age, there tends to be a second peak in adolescents, aged 11–19 years [1]. Nasopharyngeal carriage is more prevalent among adolescents [10]. The high carriage rate and peak of disease incidence in adolescents and young adults is thought to be due largely to factors associated with social behaviors. Various studies have shown that increased meningococcal disease incidence, carriage, and transmission among adolescents is linked to activities such as close living quarters (e.g. university dormitories, military barracks), crowded venues (e.g. bars, clubs), intimate contact (e.g. kissing, sharing drinks), smoking, and sleep deprivation [11–13]. While incidence peaks in adolescents are common in countries like the US, Canada, and Europe, some countries in Latin America do not exhibit such a prominent peak in its adolescent population [14–17]. This observation may be in part due to differences in college/university systems where, for example, dormitory housing is more common in the US but not in Chile.

When new meningococcal clones circulate in a naïve population, there tends to be a typical epidemiologic age distribution. In Québec, Canada, as previously reported in Oregon, US, an increase in disease incidence associated with a MenB clonal complex was first seen in 15–24 year-olds prior to its general distribution across the population [18,19]. This observation, in addition to the high carriage rate and increase in disease incidence among adolescents, highlights the potential impact of vaccinating adolescents and young adults, not only to protect vaccinated individuals from IMD but also to build 'herd protection'. Vaccinating adolescents prior to carriage acquisition could potentially impact carriage in this high risk age group that currently acts as a reservoir of meningococcal disease. This is an important public health goal because population immunity makes it less likely for future outbreaks to occur in any age group [10].

Decades of investigations into the etiology, pathogenesis, and interventions to treat or prevent IMD have reduced its impact globally, but serogroup B meningococcal disease remains feared and its prevention an unmet medical need. Apart from infants who are at highest risk, adolescents and young adults are at particular risk, with demonstrated increased risk for outbreaks and hyperendemic disease. The recent licensure of 4CMenB (Bexsero®, Novartis Vaccines), a multicomponent, protein-based MenB vaccine, provides a promising opportunity to impact MenB disease. Here, we review meningococcal vaccination strategies in adolescents and the available data from adolescents and young adults after vaccination with 4CMenB, and discuss the potential benefits of this vaccine in protecting against IMD, particularly in these vulnerable age groups.

2. Worldwide meningococcal vaccination strategies in adolescents

There are several examples in which comprehensive meningococcal disease control has been accomplished on a national level, using either capsular-based or protein-based meningococcal vaccines. The UK introduced a meningococcal conjugate vaccine against serogroup C (MCCV) in 1999, initially for individuals up to 18 years of age, and infections due to serogroup C were reduced by 86.7% thereafter [20,21]. The health ministry in the Netherlands offered a MenC conjugate vaccine in 2002 to toddlers at 14 months of age followed by a national catch-up campaign for those aged 1–18 years [22]. Canada and the US currently recommend a quadrivalent conjugate vaccine (MenACWY) for routine use in adolescents aged 11–18 years. Although a cause and effect relationship cannot be definitively established in each of these examples, current

disease incidence of meningococcal serogroups targeted by these vaccines remains at historically low levels.

Countries like New Zealand and Cuba have implemented national or regional immunization campaigns to control MenB disease epidemics that included children, adolescents, and/or young adults utilizing outer membrane vesicle (OMV)-based vaccines. Cuba mandated a nationwide intervention in 1989 to immunize individuals less than 20 years of age against meningococcal serogroups B and C using the VA-MENGOC-BC vaccine [23]. This vaccine strain (Cu385/83; B:4:P1.15) consisted of lipooligosaccharide-depleted outer membrane proteins and group C polysaccharide enriched with enveloped proteins [23]. After vaccine introduction, from 1984–1994 the incidence fell from 14.1 to 0.8 cases per 100,000 person-years [24]. In another instance, New Zealand implemented an infant and adolescent vaccination strategy from 2004 to 2008 to curb a 13-year epidemic against a clonal outbreak of MenB [25]. The vaccine used was a meningococcal OMV vaccine (MeNZB®), which was offered to high risk groups aged 6 months to 19 years. Studies have shown a substantial vaccine-attributable decline of the epidemic [26].

2.1. Strengths and limitations of immunizing adolescents and young adults

These national campaigns that aimed to reduce MenB or MenC disease incidence by including all age groups at increased risk for meningococcal disease in order to both control IMD and to prevent future outbreaks appear to have been successful. For example, in the MenC campaign in the UK that began in 1999, MCCV was offered to adolescents aged 15–17 years (the highest risk group), followed by catch-up vaccination for 12–15 year-olds while also offered to infants in order to cover the high-risk groups. In 2000, a conjugate or polysaccharide MenC vaccine was then offered to first-year university students and was subsequently made available to children and young adults ≤25 years of age [21]. As expected, a decrease in IMD cases was first observed in the age groups that were first immunized, followed by reductions in other age groups. The number of cases continued to decrease and in 2007/2008 had dropped to levels 97% below those reported in 1998/1999 [21].

Vaccine compliance tends to be sub-optimal in adolescents, particularly for multi-dose vaccine series [27–29]. Reasons for sub-optimal compliance in adolescents include but are not limited to: infrequent healthcare visits, lack of health insurance, poor provider communication on the need to complete vaccine series, and patient/parent failure to return for completion of dose-series [29]. Vaccination against human-papillomavirus (HPV) is a case in point. The National Immunization Survey-Teen has collected vaccination information on adolescents aged 13–17 years in the US since 2006. This study showed that although HPV coverage increased since 2006, in 2012, 54% (52–56%) of adolescent girls had received a single dose, 43% (32–35%) had received 2 doses and only 33% (32–36%) had completed the 3-dose series [27].

3. Use of a multicomponent MenB vaccine in adolescents and young adults

Use of a meningococcal vaccine derived from OMVs has been associated with clinical effectiveness in controlling regional outbreaks of specific strains of MenB as outlined above. Experience in past MenB outbreaks showed that PorA is the immunodominant antigen in OMV [30–32]. However, due to the specificity of the immune response to PorA and the diversity of PorA antigens present in meningococcal serogroup B strains, these tailor-made vaccines, which were effective against the strains that they were designed to combat, were poorly immunogenic against heterologous strains. In order to provide broad protection against MenB,

Table 1
Summary of 4CMenB studies in adolescents and adults.

Study (year)	Study objectives	Location	Participants vaccinated	Reference
Kimura et al. (2011)	Safety, tolerability, and immunogenicity of 3 doses of 4CMenB and 1 dose of MenACWY-CRM in healthy at-risk adults	Germany, Italy	53	[37]
Toneatto et al. (2011)	Safety, tolerability, and immunogenicity of 4CMenB in the first human study	Switzerland	70	[38]
Santolaya et al. (2012)	Immunogenicity and tolerability of 1, 2, or 3 doses of 4CMenB 1–6 months apart	Chile	1631	[39]
Read et al. (2014)	Impact of Men-ACWY or 4CMenB vaccination on meningococcal carriage rates one month after each vaccine course	UK	2954	[40]
Québec Ministry of Health	Provincial vaccination campaign in Saquenay-Lac-Saint-Jean in to all individuals aged 2 months to 20 years	Québec, Canada	43,740	[41,42]
Perrett et al. (2014)	Immunogenicity and safety equivalence of rMenB + OMV NZ lot 1 to rMenB + OMV lot 2, 30 days after vaccination of 2-doses	Canada, Australia	344	[43]
Findlow et al. (2012)	Safety and immunogenicity of 4CMenB and MenACWY-CRM in UK laboratory workers with potential occupational exposure	UK	38	[44]
CDC sponsored	Safety of 4CMenB in university students receiving vaccination during campus outbreak	US (Princeton University)	5471	[45,58]
CDC sponsored	Safety of 4CMenB in university students receiving vaccination during campus outbreak	US (University of California at Santa Barbara)	9067	[45,58]
TOTAL			63,368	

a multi-component protein-based vaccine (4CMenB, Bexsero[®], Novartis Vaccines) was developed containing four major antigenic components: factor H-binding protein (fHbp) fused with GNA2091, *Neisseria* adhesin A (NadA), Neisserial Heparin Binding Antigen (NHBA) fused with GNA1030, and OMV from the New Zealand outbreak strain NZ98/254 (NZ OMV) [33,34]. The OMV component contains PorA serosubtype 1.4 [34]. These components are relevant to the organism's function, virulence, and/or survival and were selected to provide broad coverage against circulating strains of MenB [35]. Interestingly, the vaccine components are also present in meningococcal isolates of other serogroups allowing potential use against meningococcal isolates belonging to non-B serogroups, although this was not the initial intention for this vaccine [36]. Clinical trials have shown 4CMenB to induce bactericidal antibody responses against meningococcal antigens in a high proportion of infants, adolescents, and adults, with an acceptable tolerability profile.

4CMenB is approved for use in 37 countries including EU/EEA countries, Australia, Canada, Chile, Colombia, and Uruguay and is recently approved in the US. A total of 9 studies (5 randomized controlled, 3 open-label single-arm, 1 post-licensure) which enrolled adolescents and adults to receive 4CMenB have been conducted (see Table 1) [37–45]. A total of 63,368 adolescents and young adults received 4CMenB vaccination in studies conducted in the US, Canada, Chile, UK, Germany, Switzerland, Italy and Australia.

4. Immunogenicity

The 4CMenB vaccine has been shown to induce robust bactericidal antibodies against strains expressing the vaccine antigens in studies in infants, adolescents and young adults. In total, six studies included immunogenicity objectives of which the results of four have been published (Table 1) [37–40,43,44]. The four published studies supported a two-dose vaccine schedule in adolescents and adults [37–40]. In each study, the immunogenicity objective was to determine the proportion of subjects with human complement serum bactericidal antibody (hSBA) titers $\geq 1:4$, which is considered to be the surrogate marker of protection. Titers $\geq 1:5$ were also assessed as a more conservative threshold to ensure, with 95% confidence, that subjects with a titer $\geq 1:5$ will have achieved a titer

of at least 1:4. Reference strains (44/76-SL, 5/99, NZ98/254, and M10713) were selected to match each one of the vaccine components, and hSBA assay helped demonstrate responses against the strains to determine immunogenicity of the key vaccine components [46].

4.1. Responses to various vaccination schedules

In adolescents, different two-dose vaccine schedules were assessed with doses administered up to 6 months apart. A phase 2b/3 trial conducted in 1631 Chilean adolescents aged 11–17 years looked at the immunogenicity of 4CMenB after administration of 1, 2, or 3 doses [39]. The results showed that 1 month after the first dose, 92–96% and 99–100% of adolescents had protective titers (hSBA titers $\geq 1:4$) against the 3 indicator strains tested at 1 month after the first dose and 1 month after the second dose, respectively (Fig. 1). Note that the indicator strain for NHBA had not been identified at the time this study was conducted and therefore, NHBA analyses were conducted post hoc at limited time points (Fig. 1). No further benefit was observed after a third dose, as assessed by the percentage of subjects achieving putatively protective titers of hSBA $\geq 1:4$ (hereafter referred to as protective titers). Although higher GMTs were observed in response to a third dose in comparison to a second dose, 99–100% of subjects had already achieved protective titers against the four vaccine components at 1 month after the second dose. Higher GMTs in response to a third dose did not increase the percentage of subjects with hSBA titers $\geq 1:4$ against NadA or fHbp, and it is unclear whether there is any clinical benefit of higher titers in response to the OMV component. Similar results were observed at 1 month after the 2-dose schedule both in the UK among 18–24 year old university students (99–100% achieved hSBA titers $\geq 1:4$ against fHbp, NadA and PorA1.4) [47] and among 11–17 year old adolescents in Canada and Australia (99–100% achieved hSBA titers $\geq 1:5$ against fHbp and NadA; 75% achieved hSBA titers $\geq 1:5$ against PorA1.4) [43]. At two weeks after the second vaccination, 100% of subjects in the Canada and Australia study had hSBA titers $\geq 1:5$ against strains fHbp and NadA; the percentage of subjects with hSBA $\geq 1:5$ against strain NZ OMV at two weeks was higher compared to 1 month after vaccination (84–96%, 64–80%, respectively) [43]. These results support

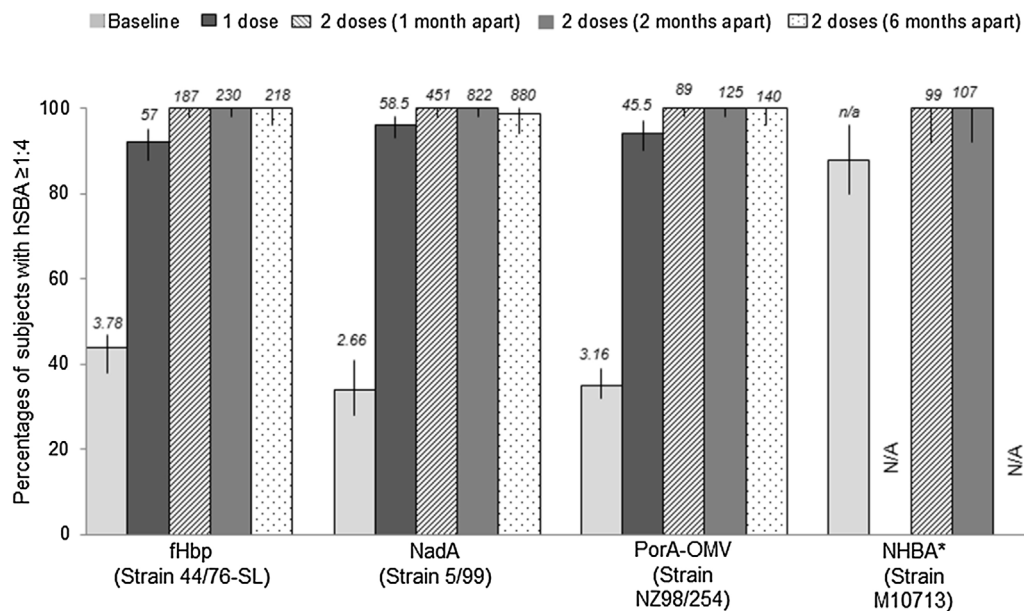


Fig. 1. Percentages of adolescents aged 11–17 years with hSBA titers $\geq 1:4$ and GMTs at one month post vaccination with 4CMenB. Factor H-binding protein (fHbp); Neisseria adhesion A (NadA); Neisserial heparin binding antigen (NHBA); Outer membrane vesicle (OMV). Note: Numbers above bars show geometric mean titers (GMT) of hSBA antibodies against the respective antigen component.

Source: fHbp, NadA, and PorA-OMV adapted from Ref. [39]. Supplementary web appendix: Web Tables 1a–1c. *NHBA adapted from the European Union, Summary of Product Characteristics: Annex 1. <http://ec.europa.eu/health/documents/community-register/2013/20130114125155/anx.125155-en.pdf>.

the use of a 2-dose 4CMenB schedule in adolescents and young adults.

4.2. Antibody persistence 1–2 years post-vaccination

Antibody persistence after 4CMenB vaccination was evaluated in two clinical studies up to two years after the second vaccination in subjects aged 11–25 years at the time of enrollment [47,48]. Persistence of bactericidal antibodies was measured by assessing both the percentage of subjects with hSBA titers $\geq 1:4$ over time, as well as geometric mean titers (GMTs) against the components in the vaccine.

In a study conducted in the UK, university students were administered a two-dose series of 4CMenB and 85–97% of students aged 19–25 years maintained hSBA titers $\geq 1:4$ against each of the four vaccine components for at least 11 months after the second dose [47]. In another study, a subset of adolescents from a phase 2b/3 study in Chile was enrolled in an extension study, along with an additional cohort of 4CMenB-naïve subjects, aged 13–19 years [48]. Of 1625 eligible participants from the original Chilean study, 666 (41%) were followed for antibody persistence along with 151 newly recruited 4CMenB-naïve control subjects. Persistence was measured 18–24 months after the primary 2-dose series, which showed 77–94% of adolescents with putatively protective hSBA titers $\geq 1:4$ (77% PorA1.4; 82% fHbp; 94% NadA). These results confirm that two doses of 4CMenB, administered 1–6 months apart, provide levels of antibodies considered protective against MenB for at least two years.

5. Safety

The safety of 4CMenB has been evaluated in 4697 adolescents and young adults across four pre-licensure Novartis-sponsored studies (Table 2) [37–40]. In addition, safety data on serious adverse events (SAEs) among 14,538 university students and staff were collected under an expanded-use Investigational New Drug (IND) recommendation by the US Centers for Disease Control and

Prevention (CDC) to address two MenB outbreaks at university campuses during 2013 [45–58].

In the four Novartis-sponsored randomized clinical studies, solicited adverse events (AEs) were collected from a majority of subjects and unsolicited medically attended and SAEs were collected from all subjects [37–40]. Overall, these studies showed that 4CMenB was generally well-tolerated with no signals of safety concerns. Fig. 2 compares rates of solicited local and systemic reactions in adolescents aged 11–18 years among vaccine and placebo recipients in the Chilean adolescent study [39]. The most commonly reported local reaction was pain at the injection site, experienced by 86% of 4CMenB subjects versus 60% in the placebo group. The most common systemic reaction was malaise with 51% reported in 4CMenB subjects compared to 30% for placebo. Fever was reported in a low percentage of subjects after first and second vaccinations (0–2% across vaccine groups). None of the subjects reported fever after the third dose and booster vaccinations. Similar results were found in the other three studies (Table 2).

6. Strain coverage of 4CMenB vaccination

The diversity of relevant surface antigens targeted by vaccine-induced antibodies has been a barrier to develop a serogroup B meningococcal vaccine with a meaningful breadth of potential coverage. The aim in utilizing various antigenic components, each targeting antigens which are relatively conserved, is to increase the coverage of a vaccine. Thus, while an OMV vaccine has its limitations in that it is strain-specific, the multi-component vaccine 4CMenB has demonstrated the potential for a wide breadth of coverage [49].

Reverse vaccinology was used to assess the genome of a MenB strain in order to identify genes associated with expression of surface proteins that displayed the ability to induce bactericidal activity against MenB in animal models [50]. The meningococcal antigen typing system (MATS) was developed to predict 4CMenB coverage in a given region by estimating coverage against a panel of strain isolates from that region. MATS combines conventional

Table 2
Summary of key safety findings for 4CMenB studies in adolescents.

Study [Ref]	Age at enrollment	Participants evaluated (countries)	Study design	General safety findings
Kimura et al. Clin Vac Immunol, 2011 [37]	18–50 years	53 adults (Italy, Germany)	Open-label, multi-center, safety, and immunogenicity study in healthy (at-risk) adults	Most common systemic reactions: malaise (4CMenB, ~53%, after three doses) Most common local reaction: injection site pain (4CMenB, 100%, after three doses) Events judged as possibly and probably related to 4CMenB: 7 subjects who experiences at least one adverse event were possibly related to either 4CMenB or MenACWY vaccination
Toneatto et al. Hum Vac, 2011 [38]	18–40 years	70 adults (Switzerland)	Observer blind, single-center, randomized, safety, and immunogenicity study in healthy adults	Most common systemic reactions: myalgia (4CMenB, ~83%; rMenB, ~85%; rMenB + OMVNW ^a , ~71%, after two doses) Most common local reaction: injection site pain (4CMenB, ~100%; rMenB, ~100%; rMenB + OMVNW, ~86%, after two doses) Events judged as possibly and probably related to 4CMenB: 1 case of pruritus
Santolaya et al. Lancet, 2012 [39]	11–17 years	1631 adolescents (Chile)	Observer-blind, multi-center, randomized, controlled, safety, and immunogenicity study in healthy adolescents with various schedules	Most common systemic reactions: malaise (4CMenB, 51%; placebo, 30%) and headache (4CMenB, 42%; placebo, 27%). Most common local reaction: pain (4CMenB, 86%; placebo, 60%). Events judged as possibly and probably related to 4CMenB: 2 cases of juvenile arthritis, assessed as possibly and probably related to 4CMenB reported 170 days and 198 days after the third dose of 4CMenB.
Read et al. Lancet, 2014 [40]	18–24 years	2943 adults (UK)	Observer-blind, multi-center, randomized, controlled, pharyngeal carriage study in young adults	Most common systemic reactions: myalgia (4CMenB, 75%; placebo, 50%) Most common local reaction: injection site pain (4CMenB, 93%; placebo, 48%) Events judged as possibly and probably related to 4CMenB: a case of dyspnea, hand tremors, and acute thyroiditis occurring 2, 18, and 18 days post-vaccination.

^a Recombinant meningococcal serogroup B vaccine (rMenB); outer membrane vesicle (OMV) from the Norwegian (NW) outbreak strain.

Note: Table 2 has fewer studies listed than in Table 1. This is due to safety data not yet published or available for some studies at the time this paper was written.

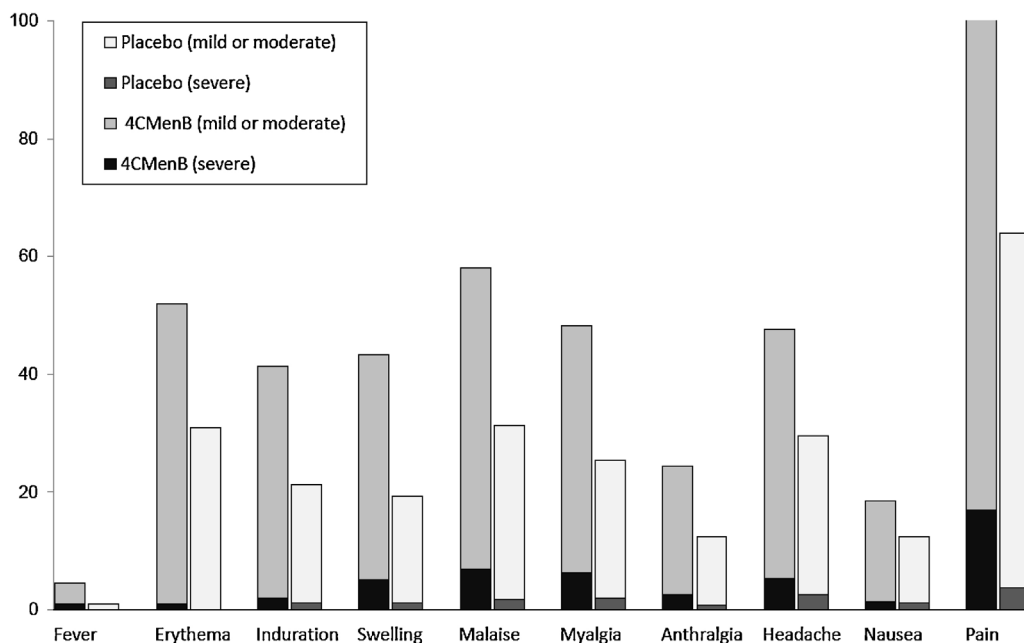


Fig. 2. Reactogenicity to doses of 4CMenB and placebo in adolescents in Chile. Note: 330 doses of 4CMenB, 2739 doses of Placebo.

genotyping for PorA with a specialized sandwich enzyme-linked immunosorbent assay (ELISA) to assess the phenotypic expression and cross-reactivity of the remaining vaccine antigens (fHbp, NadA, and NHBA) on the MenB surface [50]. The 4CMenB coverage estimate is determined by computing the percentage of regional strains that meet a minimum threshold of reactivity in the MATS-ELISA and/or contain the PorA 1.4 antigen. The minimum threshold is an antigen-specific minimum that is predictive of killing in the hSBA. Using this method, it has been estimated that 78% of MenB strains would be covered by vaccination with 4CMenB across Europe [49]. Importantly, a study performed on strains collected from England and Wales from 2007 to 2008 to compare with bactericidal antibody response in infants and adolescents, MATS was shown to produce a conservative estimate of 4CMenB coverage [51]. Globally, 4CMenB coverage has been evaluated in 13 countries on more than 2700 strains with individual country coverage estimates ranging from 66% in Canada to 91% in the US [49,51–57].

7. 4CMenB vaccination effect on nasopharyngeal carriage

4CMenB can be considered not only for its potential for direct protection in adolescents and young adults but also to induce herd protection by limiting acquisition in unvaccinated populations. Christensen et al. carried out a systematic and meta-analysis review of previous observational studies that reported pharyngeal carriage of all meningococcal serogroups [10]. They evaluated studies conducted in 28 countries in Europe, the Americas, and the Caribbean in order to identify age specific patterns in overall carriage; the analyses were not stratified by serogroup or strain. This study showed estimated carriage prevalence of 4.5% in infants to 7.7% in 10-year olds, peaking at 23.7% in 19-year olds, and 7.8% in 50-year olds. This study underscores the potential relevance of a vaccine reducing carriage in adolescent populations.

To better understand whether such a protein-based meningococcal vaccine might impact carriage, a clinical study was performed in 2954 UK university students, randomized to receive 4CMenB, a quadrivalent meningococcal conjugate vaccine (MenACWY-CRM) or a control vaccine [40]. Students were enrolled in the first three months of the academic year. One month after the second dose, there were no significant differences in carriage between those in the 4CMenB and the control group (OR = 1.2, 95% CI: 0.8–1.7). However, three to twelve months after the second dose, the 4CMenB group had significantly lower carriage of capsular groups BCWY, with 26.6% (95% CI: 10.5–39.9) carriage reduction compared to the control group. It is worth noting that 4CMenB was administered in a 2-dose series, but because the highest acquisition was observed between the first two study visits, the study vaccines may have been administered too late to observe a maximal impact. However, over the course of the study, a reduction in meningococcal carriage rates was observed in both the 4CMenB group (1–10 months post vaccination) and the MenACWY-CRM group (1–11 months post vaccination), showing a potential impact on acquisition.

8. Use of 4CMenB to address outbreaks in college settings

Recent outbreaks of serogroup B meningococcal disease originated at Princeton University in March 2013 and at the University of California at Santa Barbara (UCSB) in November 2013, resulting in 13 cases and 1 death [45,58–61]. Since 4CMenB was not approved for use in the US at the time of the outbreaks, the CDC responded by recommending 4CMenB under an expanded-use IND recommendation by the US CDC for use in the student populations at Princeton and UCSB [45,58]. Safety surveillance was conducted by the CDC in cooperation with the universities. The CDC had not

yet published their report on these outbreaks at the time of this writing. However, some information regarding the outbreaks was available on the CDC website. From March to November 2013, eight cases of MenB disease were reported at Princeton University, with an attack rate of 134/100,000 among undergraduates [45,58]. Two of the eight cases were left with serious sequelae (neurocognitive deficit, hearing loss) and there were no fatalities among these eight cases [45]. A total of 5772 individuals were recommended for vaccination and 5502 (95%) individuals at Princeton had received the first dose and 5139 (89%) had received the second dose of 4CMenB as of April 2014. As of February 2014, SAEs were reported at a rate of 2/1000 vaccinees following the first dose and at a rate of 0.2/1000 vaccinees following the second dose; none of these SAEs had been determined to be causally related to the vaccine [45]. A case of MenB disease was reported at Drexel University in March 2014 that resulted in death [61]. This case was found to be caused by the same strain identified in the Princeton outbreak and the student in question had been in close contact with students from Princeton University about a week before becoming ill. Antibiotic prophylaxis was recommended and administered to close contacts of the Drexel University student but widespread vaccination was not undertaken [61].

The outbreak that occurred at UCSB during the same time period was caused by a genetically unrelated MenB strain [45,58]. There were four cases among undergraduates at UCSB from March to November 2013, for an attack rate of 21.1/100,000 [59]. Although these students recovered, one was left with serious sequelae (bilateral foot amputation) [45]. Approximately 17,000 students at UCSB had been vaccinated as of February 2014 [59]. No information regarding AEs was available at the time of this writing. These university outbreaks of meningococcal serogroup B underscored the need for a MenB vaccine to be approved in the US. Subsequently, the submission for a biologics license application (BLA) for 4CMenB was filed and has now been approved in the US for use in adolescents and young adults, 10–25 years of age.

9. Post-licensure experience with 4CMenB in Saguenay-Lac-Saint-Jean, Québec

In Québec, Canada, following introduction of the MCCV, although there was reduction in serogroup C disease, there was an increase in serogroup B incidence across all age groups, particularly in young children and adolescents [18]. Therefore, shortly after approval of 4CMenB, the Committee on Immunization Québec (CIQ) under the Institute National Public Health (Institut National de Santé Publique du Québec (INSPQ)) decided to implement a vaccination campaign in Saguenay-Lac-Saint-Jean in May 2014 in all individuals aged 2 months to 20 years [41,42]. This represents the first public program to provide 4CMenB to a broad population. 43,740 children, adolescents, and young adults had received at least the first dose as of June 2014 [42]. The Ministry of Health in Québec also undertook active safety surveillance based on parent-completed diary cards. Of the 43,740 vaccinees, electronic questionnaires were completed for 12,332. Fever within 48 h post-vaccination was reported by 9% of respondents and 1.9% reported fever within 3–7 days. Fever incidence was higher in children <2 years (14–15%) than in children 2–4 years and 5 years and older (12% and 6–8%, respectively). Antipyretic prophylaxis reduced the probability of fever within 48 h post-vaccination in children <2 years by approximately 50%. The most frequently reported health problems were malaise (56%), local reactions (49%), gastrointestinal (34%), or respiratory problems (24%). Open-ended written comments were provided by 20% of respondents, of whom 83% cited injection site pain. One case of febrile seizure was identified and no hospitalizations related to the vaccine were reported. This

large-scale safety surveillance study did not reveal any serious or unusual health problems associated with 4CMenB.

10. Discussion

Adolescents and young adults constitute a high-risk age group for IMD and the majority of cases could be vaccine-preventable. The incidence of IMD due to specific serogroups, including serogroup B, varies over geographic regions and over time [1,4–9]. Despite rapid, high quality medical care, meningococcal disease can be fatal and is associated with long-term sequelae such as loss of limbs, cognitive impairment, deafness, and deficit in physical functions. Furthermore, adolescents typically have higher rates of carriage than other age groups and thus could serve as a source of transmission to other at-risk groups [40].

Two recent outbreaks at Princeton University and UCSB highlighted the need for a meningococcal B vaccine in US adolescents and young adults. Although two vaccines against MenB disease have recently been licensed for use in the US [Trumenba® (rLP2086, Pfizer), Bexsero® (4CMenB, Novartis)], neither had been approved at the time of these outbreaks. The occurrences at both Princeton University and UCSB resulted in 13 cases, 1 death, and serious sequelae. The emergency vaccination against MenB disease at both universities with 4CMenB appeared to have been successful in controlling the outbreaks [45,58]. The economic and social costs of the response to the outbreaks have not been quantified for MenB, but previous analyses on the burden of MenC outbreaks have been estimated on a range of \$13–28 million in health care costs [62]. While vaccine use in outbreak situations is promising, due to the sporadic and rapid nature of outbreaks, intervention is oftentimes unable to prevent secondary cases. Thus, implementation of a national immunization program for vaccinating adolescents and young adults against MenB is currently a strategy to consider in the US to address this unmet medical need [63].

The adolescent population is known for non-optimal compliance when it comes to completing scheduled vaccinations [64]. In response, some countries have successfully implemented school-based vaccination programs or mandatory school and/or college entry requirements. Particularly in countries that do not (universally) have such programs, a shorter dose schedule, with as few doses as possible, typically helps to improve schedule compliance. Two and 3-dose vaccination schedules were investigated in the 4CMenB development program. The two-dose schedule resulted in nearly all (99–100%) participants with protective titers at one month post-second-dose, indeed even after only one dose 92–96% of adolescents had protective hSBA titers. Furthermore, 85% of participants maintained protective antibodies against MenB for at least two years. These results support the administration of a 2- rather than 3-dose series. In addition, post-licensure studies are required to determine vaccine effectiveness as well as persistence in adolescents and young adults. As more data is gathered from post-licensure studies, the suitability of a 2-dose schedule could be made clearer. Fewer doses may help to improve compliance in this population known for poor compliance and partial protection could be expected even after the first dose.

4CMenB has been designed to provide broad coverage against the diverse strains of meningococcal B. As a result of the demonstrated effectiveness of OMV-based vaccines to control regional outbreaks of specific MenB strains, the OMV component PorA 1.4 was selected for inclusion in 4CMenB. However, the effectiveness of an OMV-based vaccine is limited to strains that contain the same PorA protein (particularly in young children). Therefore, reverse vaccinology was used to perform a complete analysis of the genetic sequence of a MenB strain in order to

systematically identify surface-exposed proteins [50]. These were then screened for their ability to induce bactericidal activity against MenB, and the most promising of these, fHbp, NadA, and NHBA, were included in the formulation of 4CMenB. Based on an assessment performed on a large panel of 442 representative meningococcal B strains from the US, MATS showed that 91% of these strains are predicted to be covered by 4CMenB-elicited immune sera.

4CMenB elicits robust immune responses in adolescents and adults, as well as in infants and older children [37,39,65–68]. Clinical studies have shown that the vaccine has an acceptable safety profile. In adolescents and adults, rates of solicited AEs, especially injection site pain, occurred more frequently in 4CMenB recipients than in the control/placebo groups. However, most reactions were mild or moderate in severity and of limited duration. Finally, while preliminary safety data looks promising, post-licensure safety data is expected shortly from studies conducted in large populations during the vaccination campaigns at Princeton University, UCSB, and Québec. As for all new vaccines, larger phase IV studies after more widespread use will be required to evaluate possible rarer AEs.

Unexpected outbreaks of MenB disease at various institutions in the US, provinces in Canada, and other world regions highlight the need for an effective and preventative intervention on a national level. The vast majority of IMD is caused by serogroups A, B, C, W, and Y. In addition to currently available MenACWY vaccines, the utilization of a well-tolerated and highly immunogenic vaccine against MenB offers the possibility to help prevent most IMD.

Conflicts of interest

This review was funded by Novartis Vaccines and Diagnostics. James Wassil and Véronique Abitbol are employees of Novartis Vaccines and Diagnostics. Peter Dull was an employee of Novartis Vaccines and Diagnostics at the time the manuscript was written and is currently at the Bill and Melinda Gates Foundation. Terry Nolan and Miguel O’Ryan did not receive any monetary incentives from the sponsor with respect to this manuscript. Both their institutions have received research contracts from Novartis to carry out clinical studies of MenB vaccine. The authors have no financial relationships relevant to this review article to disclose.

Contributors’ Statement

James Wassil and Véronique Abitbol carried out the initial concept and design of the manuscript outline, had significant input in providing critical reviews of the contents, and reviewed and revised the manuscript. Terry Nolan and Miguel O’Ryan contributed to the analysis and interpretation of the studies reviewed in the manuscript, and critically reviewed and revised the manuscript. Peter Dull contributed to the conceptualization of the manuscript, had significant input in providing critical reviews of the contents, and participated in critical revisions of the manuscript.

All authors listed were responsible for the drafting and revising of the manuscript. All authors provided critical reviews of the content of the manuscript, and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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