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Peer reviewed version

Link to published version (if available):
10.1080/21645515.2018.1458175

Link to publication record in Explore Bristol Research
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Global epidemiology of serogroup B meningococcal disease and opportunities for prevention with novel recombinant protein vaccines

Running title: Meningococcus serogroup B epidemiology and vaccines

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Disclosure of potential conflicts of interest

RV: has received grants to support research projects from GSK

M.A.P.S. has received grants to support research projects and consultancy fee from GSK, Pfizer and Sanofi Pasteur.

A.F. is an investigator in vaccine research projects funded by GSK, Pfizer and Sanofi Pasteur (funding paid to his employers).

MO: has received grants to support research projects from GSK

JPT and MTV do not report any conflicts of interest

Abstract

Background: Meningococcal disease (MD) is a major cause of meningitis and sepsis worldwide, with a high case fatality rate and frequent sequelae. *Neisseria meningitidis* serogroups A, B, C, W, X and Y are responsible for most of these life-threatening infections, and its unpredictable epidemiology can cause outbreaks in communities, with significant health, social and economic impact. Currently, serogroup B is the main cause of MD in Europe and North America and one of the most prevalent serogroups in Latin America. Mass vaccination strategies using polysaccharide vaccines have been deployed since the 1970s and the use of conjugate vaccines has controlled endemic and epidemic disease caused by serogroups A, C, W and Y and more recently serogroup B using geographically-specific outer membrane vesicle based vaccines. Two novel protein-based vaccines are a significant addition to our armamentarium against *N. meningitidis* as they provide broad coverage against highly diverse strains in serogroup B and other groups. Early safety, effectiveness and impact data of these vaccines are encouraging. These novel serogroup B vaccines should be actively considered for individuals at increased risk of disease and to control serogroup B outbreaks occurring in institutions or specific regions, as they are likely to save lives and prevent severe sequelae. Incorporation into national programs will require thorough country-specific analysis.

Key words: *Neisseria meningitidis*, epidemiology, meningococcal serogroup B, meningococcal vaccines, outbreaks

Brief overview of meningococcal infection/disease

Meningococcal disease (MD) is a major public health problem and remains a leading cause of meningitis and sepsis in many countries[1,2] Case fatality rates (CFR) reach 10-20% despite aggressive treatment, 10-20% of survivors will develop major long-term sequelae, including deafness, neurological deficit, seizures, limb amputation, and up to 36% of survivors may have one or more deficits in physical, cognitive, and psychological functioning[1–3]. MD occurs in all age groups, although incidence rates are highest in young children and teenagers. MD is mostly sporadic with seasonal variations, with occasional epidemics in large regions or smaller outbreaks in specific settings, which occur at rather unpredictable intervals. During these epidemics an increased number of cases usually occurs among adolescents and young adults [4,5].

Neisseria meningitidis (*N. meningitidis*) is a Gram-negative, aerobic, encapsulated, non-mobile diplococcus, belonging to the *Neisseriaceae* family. The antigenic composition of the polysaccharide capsule defines 12 serogroups: A, B, C, H, I, K, L, W, X, Y, Z and E[6]. Currently, six serogroups, A, B, C, Y, W and X, are responsible for virtually all cases of disease reported worldwide[1,2,4,5]. Meningococci are also classified into serotypes and serosubtypes according to the antigenic composition of the outer membrane proteins (OMP) PorB and PorA, respectively. Meningococci can exchange genetic material encoding for capsule synthesis, modifying the capsular antigenic composition of a specific strain. Antigenically distinct strains due to allelic replacement of the *siaD* gene can lead to outbreaks[7–10]. Genetic multilocus sequence typing targeting polymorphisms within multiple genes, polymerase chain reaction, and whole-genome sequencing are currently the most widely used methods to detect and characterize meningococcal strains[5,6].

Meningococci infect only humans and are transmitted from person to person by aerosolized or direct contact with respiratory secretions or saliva. Acquisition of meningococci can lead to transient carriage, persistent colonization, or result in invasive disease. Most carriers will remain asymptomatic with the microorganism in their nasopharynx throughout their lifetime; invasive MD is a rare outcome of meningococcal infection. For most individuals, carriage is an immunizing process eliciting protective antibodies[11,12].

Asymptomatic nasopharyngeal carriage of *N. meningitidis* is common, with a population prevalence of approximately 5-10% in non-epidemic settings. Carriage prevalence varies with age, being low during the first years of life, increasing in teenagers and young adults when rates of up to 20-50% are reported, followed by a decline during adulthood[11–13]. Major differences in meningococci phenotypic and genotypic distribution between invasive and carriage strains are usually observed, with only a small proportion of carriage strains representing hyper invasive lineages. Carriage rates of meningococci can be considerably higher in outbreak situations, household contacts of people with MD and in closed institutional settings, particularly in military personnel[11,12]. Most carriers have relatively few organisms detectable with a minority having much larger numbers at any one time[14].

Several host-, organism- and environmental-factors have been associated with an increased risk for MD. Deficiencies in the common complement pathway (e.g., C3, properdin, Factor D, Factor H, or C5–C9), eculizumab therapy, functional or anatomic asplenia (including sickle cell disease), chronic underlying illness, infection with the human immunodeficiency virus[12], preceding viral infections (particularly influenza), household crowding, men who have sex with men, microbiology profession, active and passive smoking, and bar attendance, are all risk factors for meningococcal disease[12,15].

Criteria used for case definition of MD vary from one place to another, limiting the reliability of comparisons of incidence rates among different regions. The European Centre for Disease Prevention and Control (ECDC) surveillance network considers a case of invasive meningococcal disease confirmed when at least one of the following criteria is met: isolation of/or detection of *N meningitidis* nucleic acid in a normally sterile site; *N meningitidis* detection in cerebrospinal fluid (CSF) by antigen detection test; or visualization of a Gram negative diplococci in CSF[16]. In the United States of America (USA), as well as in South Africa, a case is confirmed if the bacteria is isolated from a specimen obtained from a normally sterile site[17,18]. In Australia and Canada the criteria includes nucleic acid amplification from a usually sterile site[19,20]. In Latin America, despite the lack of uniform criteria across countries, the Pan American Health Organization includes confirmed cases (either detection of bacterial antigen(s) in CSF or positive culture laboratory proven), probable (suspected case plus turbid CSF or link to a confirmed case), and suspected cases (sudden onset of fever plus meningeal sign or petechial or purpuric rash)[21].

MD occurs worldwide, but there are marked geographical differences in incidence and serogroup distribution[22]. In North America, serogroups B (MenB), C (MenC) and more recently Y (MenY) have been the main serogroups causing MD, whereas in Africa, serogroup A was the main cause of epidemics until 15 years ago when serogroups C, W and X emerged[22,23]. In Europe, serogroups B and Y, and more recently W (MenW) in some areas have predominated, although serogroup C remains prevalent in some countries lacking meningococcal C conjugate (MCC) vaccination programs[22,24]. In Latin America MenB, MenC and, during the past decade, MenW are currently responsible for the majority

of reported MD cases[21]. Serogroups A, B, C, Y, and W have all been present, without apparent particular predominance in Asia. In Australia and New Zealand MenB has predominated during the last decades. However, in 2016, MenW became the predominant meningococcal serogroup in Australia[25–27].

Despite the availability of safe and effective meningococcal conjugate vaccines against serogroups A, C, W and Y for several years, only recently two serogroup B recombinant protein meningococcal vaccines were licensed and recommended for prevention of serogroup B meningococcal disease (B-MD) across different age groups in several countries. The aim of this article is to describe the global burden of B-MD, briefly review the data on vaccines development, and "real world" experience with these vaccines, including the first estimates of effectiveness, safety and impact data based on the as to yet rather limited use of these vaccines in routine immunization programs and for outbreak control.

Serogroup B meningococcal disease, an ever changing, unpredictable epidemiology

Incidence rates (IR) of B-MD have declined during the past years, in the absence of any vaccine intervention. A recently published systematic review reports an average rate ranging from 0.01 to 4.26 per 100,000 population, with a decreasing overall trend, particularly in countries where data collection is more consistently collected data (figure 1)[28]. From 2000 to 2015, only two countries, New Zealand and Ireland, reported mean annual IR of B-MD disease above 2/100,000 habitants per year. Australia, Iceland, Netherlands and UK report IR from 1-2/100,000, while the remaining countries report rates

< 1/100,000. Case -fatality ratios ranged from 3% to 10% in most countries. Three major hyper-invasive genotypes (clonal complex (cc) 32, cc41/44, and cc269) were responsible for most endemic B-MD cases globally[28]. In 2014, 2,760 confirmed cases of invasive MD were reported in Europe, with highest IR in infants (10.1 cases per 100,000). Serogroup B was responsible for most reported cases (64%), while MenC was more prominent in countries that had not implemented MCC vaccination[22,24]. In the USA, 375 cases of MD (IR 0.12/100,000) and 60 deaths (CFR 16%) were reported in 2015, with serogroup B responsible for approximately 60% of the cases among children younger than 5 years of age[29]. In Canada, serogroup B remains as the predominant serogroup, particularly at younger ages. However, increased incidence of serogroup W has been reported recently[30]. In Latin America, incidence rates of MD have varied widely during past years, from < 0.1 cases per 100,000 in Mexico, Peru, Paraguay and Bolivia, to 2/100,000 in Brazil, with the highest incidence rates observed in infants. Misnotification and poor surveillance in some countries of the region, especially in those with low IR, are issues that introduce some bias in the analysis of these data. Regarding serogroup distribution, serogroups B and C are responsible for the majority of cases reported in the region, with an increased number of serogroup W cases associated with the cc ST-11, reported in Argentina and Chile. The highest incidence rates of B-MD disease in the region are reported in Argentina, Brazil, Chile, Colombia and Uruguay[31]. In New Zealand, during the 2000s a serogroup B epidemic occurred with incidence rates reaching 17.4 per 100,000 total inhabitants in 2003. A tailor-made, strain-specific serogroup B vaccine using outer membrane vesicles (OMV) from cc ST-41/44 (MeNZB®, Norwegian Institute of Public Health and Novartis Vaccines) was introduced in 2004. A significant decrease in incidence rates of the B-MD epidemic

strain during the first years after program implementation was observed, leading to discontinuation of vaccination[32].

In Asia, although the true burden of MD is unknown, reported IR are low in all countries although B-MD has been reported causing sporadic cases in Bangladesh, China, India, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan, and Thailand[28]. However, the degree of underreporting has not been fully evaluated in this and to some extent also in other regions. Few studies and low numbers of publications, poorly implemented surveillance programs, lack of guidelines and standard case definitions, and inappropriate laboratory methods are significant issues in Asia, with some notable exceptions[22,33,34].

In Africa, endemic B-MD disease has been reported only in Ghana and South Africa, with almost no B-MD cases reported from the remaining countries. In the 26 countries of the sub-Saharan meningitis belt the incidence of serogroup A decreased dramatically after MenAfriVac® introduction; serogroup W and more recently C have become predominant[35].

Outbreaks of B-MD Disease

A small fraction of reported MD cases occur within the context of meningococcal outbreaks. They are unpredictable and associated with severe outcomes, which can be emotionally devastating within affected communities or institutions. According to the USA Centers for Disease Control and Prevention (CDC), an outbreak is defined by the occurrence of at least three confirmed or probable primary cases of MD caused by the same serogroup in ≤3 months, with a resulting primary attack rate of ≥10 cases per 100,000 population[36]. This definition is used primarily to guide vaccination and antibiotic intervention recommendations. However, in organization-based outbreaks, such as those that occur in universities, schools, daycare centers, occupational training centers, or

correctional facilities, with three or even just two cases of disease, rates may reach >10 cases/100,000 population. In such situations, public health officials may also consider vaccination after only two primary cases are identified. In figure 2, we depict outbreaks reported to the World Health Organization (WHO) from 2012 to 2017; most were caused by serogroup B, affecting high schools, colleges and universities.

Group B Meningococcal Vaccines

The first attempts to prevent MD by vaccination occurred at the beginning of the twentieth century with whole cell formulations, which were used until sulfa chemoprophylaxis became available[37]. Development of polysaccharide vaccines began in the 1960s with the hallmark finding that susceptibility to invasive disease was associated with low levels of serum bactericidal antibodies (SBA) to meningococci[38]. Due to the relatively low incidence of endemic meningococcal disease, vaccine efficacy studies would require hundreds of thousands of subjects. Accordingly, the WHO has accepted an SBA titer using exogenous human complement (hSBA) $\geq$ 1:4 as correlate of protection[39,40]. Meningococcal A, C, W and Y conjugated polysaccharide vaccines have been developed and licensed, in mono, bivalent and multivalent formulations since the year 2000[40]. The capsular polysaccharide of serogroup B strains is poorly immunogenic due to its antigenic structure, which resembles glycosylated neural cell adhesion molecule which is expressed in the developing human brain; as well as immunological tolerance, this antigenic mimicry with human tissue raises the potential for the induction of autoimmunity[34]. For this reason, serogroup B vaccine antigen selection strategy moved towards OMPs, mainly porA and porB, which can elicit strain-specific protective antibodies measurable in human sera. These OMPs were first obtained from OMVs generated in laboratory conditions and shed during the growth process of *N. meningitidis.* They mimic the structure of the outer membrane of the specific meningococcal B strain, are soluble and induce a robust immune response by presenting proteins in their native structural conformation[34,40–43]. OMV vaccines were successfully used in specific clonal outbreaks in Cuba, Norway and New Zealand[34,39,40,43,44]. However, monovalent OMV vaccines elicit highly specific immune

responses to the PorA subtype, and these subtypes are highly variable among different isolates of *N. meningitidis* circulating worldwide.

Studies showed disparity in population immunogenicity, effectiveness and persistence between OMVs, mainly in infants and toddlers[39,40,44]. Multivalent PorA candidates were evaluated, but SBA responses and direct bactericidal activity against strains varied depending on the PorA type[40]. Thus a universal OMV vaccine was not deemed feasible[34,39,40]. Using genomic based approaches, specific OMPs have been synthesized and used with the aim of broadening strain coverage as they should be functionally relevant, immunogenic, and more conserved among geographically diverse strains, compared to OMVs[34]. For MenB, the antigenic variability and level of surface expression of OMPs presents a challenge for determining vaccine coverage against the myriad of circulating strains[34,45,46]. These novel B-MD vaccines, denominated 4CMenB (Bexsero®, *GlaxoSmithKline (GSK)*) and bivalent rLP2086 (Trumenba®, *Pfizer*) are now licensed in the USA, Canada and Europe as well as in other countries.

The multicomponent vaccine 4CMenB has three primary recombinant antigens obtained using an approach denominated "reverse vaccinology", based on DNA sequence data from serogroup B strains which identified surface-exposed proteins, with capacity to induce bactericidal antibodies in animal models[42,47]: factor H binding protein (fHbp), subfamily B/v1, neisserial adhesin A (NadA), and Neisseria heparin binding antigen (NHBA). In addition it includes the OMV expressing PorA from the New Zealand strain, NZ PorA P1.4. Native OMVs have a potential advantage, as detergent extraction solubilizes phospholipids and membrane-associated lipoproteins that enhance the immune response[48]. The selection of the OMV-NZ strain was based on the experience from the OMV-based vaccine MeNZB®, which proved to be safe and efficacious in the control of the clonal

MenB epidemic in New Zealand[42], in combination with immunogenicity results from a study performed in healthy adults[49]. The latter provided evidence that the addition of OMV-NZ to the other three antigens (fHbp, NadA and NHBA) enhanced the coverage against ST-41/44 complex/lineage III strains. Pivotal phase II/III studies are summarized in table 1. The vaccine has been demonstrated to provide a robust priming and anamnestic immune response in all age groups against four laboratory serogroup B reference strains chosen to measure responses against each antigen included in the vaccine, even using a reduced vaccine schedule in young infants[50], and allows concomitant administration with other routine vaccines. Concomitant administration of MCC-CRM vaccine with 4CMenB was performed in Brazilian infants at 3 and 5 months with a booster at 12 months of age. Although the geometric mean titers against meningococcal serogroup C were lower among subjects that received 4CMenB, the proportion that achieved seroconversion was identical, and considered sufficient to MenB, after primary and booster vaccination. Reactogenicity was higher for concomitant vaccines administration, but no safety concerns were identified[51]. The safety profile of 4CMenB has been considered acceptable, although it is reactogenic. Injection site pain/tenderness and fever in infants, and injection site pain, malaise, and headache in adolescents are relatively common[52-54]. Among infants, side effects can become a cause for emergency room visits, hospitalizations, and increase antimicrobial misuse[55,56]. The European Medicines Agency (EMA) approved 4CMenB in 2013 for infants from 2 months of age, as a three-dose primary schedule followed by a booster in the second year of life, and a two-dose schedule in children, adolescents and adults[57]. The USA Food and Drug Administration (FDA) approved the vaccine in 2015 as a two-dose schedule for use in individuals aged 10 through 25 years of age[58]. This vaccine was introduced into the United Kingdom (UK) universal immunization schedule at 2, 4 and

12 months of age in 2015[59,60]. Other countries with approval include Australia, Canada, Chile, Brazil, and Argentina.

The bivalent rLP2086 includes two variants of the surface-exposed fHbp protein. This protein segregates into two genetically and immunologically distinct subfamilies, A (A05) and B (B01), which have been found to be expressed in nearly all strains isolated from invasive disease caused by serogroup B in reference laboratories in Europe and USA[41]. Clinical studies included more than 15,000 subjects aged 10 through 25 years of age in 11 clinical studies conducted in the US, Europe, Canada, Chile, and Australia. These studies demonstrated that the bivalent rLP2086 elicits SBA capable of killing serogroup B strains expressing fHbps that are homologous and heterologous to vaccine components. In phase II trials, two doses of rLP2086 provided robust immunogenicity in healthy adolescents which increased after a third dose[61–64] (Table 1). The vaccine can be administered to adolescents concomitantly with other licensed vaccines, including ACWY meningococcal (MenACWY) conjugate vaccine, quadrivalent human papillomavirus vaccine (HPV), reduced diphtheria toxoid, tetanus toxoid, acellular pertussis and inactivated polio virus vaccine (TdaP-IPV) and tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap)[64-66]. The vaccine has been reported to be well tolerated in clinical trials, although mild to moderate adverse reactions such as pain, redness and swelling at the site of injection are common, followed by headache, fatigue and fever as systemic reactions[62,64,67,68]. The vaccine was approved by the FDA in 2014 for use in adolescents and young adults aged 10–25 years in a three-dose schedule, 0, 1-2 and 6 months or a two-dose schedule, 0 and 6 months, depending on the risk of exposure and the patient's susceptibility to meningococcal serogroup B disease[65]. EMA approved the vaccine in 2017 for subjects aged 10 years and older, in a two-dose schedule administered at a 0 and 6

months interval, or in a three-dose schedule, 0,1-2 and 6 months. At the time of writing, the vaccine had not been submitted for use in children below 10 years of age. A booster dose should be considered following either dosing regimen for individuals at continuing risk of invasive MD[66].

4CMenB in infants is associated with higher rates of local and systemic reactions when given with other routine infant vaccinations, with a significantly increased the risk of serious adverse events (SAEs) compared with control vaccines (odds ratio 4.36 [95% CI 1.05–18.1]; p=0.043), but the incidence of potentially vaccine-related acute SAEs in individuals receiving 4CMenB was low (5.4 per 1,000 individuals)[69]. Fever, local tenderness, erythema and pain have been the most commonly reported adverse effects across the studies. Fever was seen up to 41%, usually on day 1, returning to normal by day 3. Prophylactic administration of paracetamol before and 4–6 hours after vaccination significantly reduces post vaccination fever without affecting immunological responses[70]. Severe erythema, swelling, or induration were seen in < 1%, with a peak on day 1, with a steep decrease on day 2 and lower incidence after booster (table 1). The most commonly reported SAE were febrile convulsions, Kawasaki disease and arthritis. Seven cases of febrile seizures occurred after vaccination with 4CMenB, with a rate of 0.1 events/1,000 vaccination visits in the 4CMenB study arms, mainly during primary infant series, on the day of or day following vaccination[69,71]. Arthritis was reported in 4 subjects, three of them after 4CMenB vaccination[69]. Finally, Kawasaki disease was reported in 7 subjects (1 in the control group and 6 in the 4CMenB groups) in the pre-licensure studies. The onset varied from 1 day to 5.5 months after vaccination and all cases were adjudicated by a panel of outside experts and estimated annual incidence post-vaccination was 72 (95 % CI 23–169) per 100,000 subject-years after 4CMenB versus 56 (95 % CI 1–311) after control vaccines,

which were similar to rates of other rare adverse events observed in other pre-licensure clinical programs[46,57,58,69,71], however, post-licensure safety surveillance will be of paramount importance. In phase 1/2 study in infants, rLP2086 was considered not acceptable due to the high fever rate experienced (64-90%) in the 20 and 60 μg groups so formulation were discontinued[72].

In adolescents headache and fatigue were the most common systemic events for both vaccines. Fever was as infrequent as 4%. Local and systemic reaction rates were similar after each injection and did not increase with subsequent doses, but remained higher than placebo. Pain was most frequently reported in pre-licensure studies with 4CMenB than rLP2086 recipients (86% versus 9,9%), however, an observational study of adverse events during a college outbreak after a campaign vaccination with rLP2086 published recently, reported that the most commonly event following vaccination was injection site pain, reaching 77,6% after the first dose, but only 4% was considered severe[54,57,58,62,65-68,73,74].

Persistence of bactericidal antibodies among infants vaccinated with 4CMenB wanes at 12 months of age although remaining higher than baseline; the magnitude of waning varied for each antigen being less for NadA and fHbp[75,76]. Actually, at 12 months of age, after three priming doses and before the booster dose, the proportions with hSBA titers ≥ 1:5 for fHbp was 57%-85%, ≥ 96% for NadA and between 18-35% for PorA. Following a 12-month booster-dose ≥ 95% of previously immunized participants had titers ≥1:5 for all strains, independent of the priming schedule interval[75]. Similar results were observed in a study that assessed the persistence of immune responses after one year in participants vaccinated as infants, and responses in vaccine-naïve children. Antibodies waned over 12 months, particularly against strain NZ98/254 (PorA), although higher GMTs were observed

compared to the unvaccinated control group[76]. Even in children vaccinated with 5 doses, at 2, 4, 6, 12 and 40 months of age, waning of immunity was observed by 5 years of age, with protective antibodies ranging from 44% to 88% against matched strains and from 13% to 81% against mismatched strains[77]. In children vaccinated between 12 and 24 months of age waning of hSBA titers was also observed by 4 years of age, with a robust response after a booster dose at 40 months of age[78]. For adolescents, protective hSBA titers 18-24 months after completing a two-dose vaccine schedule with the 4CmenB vaccine were detected in 64% for all vaccine-related antigens and in 85% for two of the three target antigens; a third dose did not provide additional benefit[79].

Antibody persistence after the bivalent rLP2086 vaccine was assessed in an open-label, follow-up study of subjects previously enrolled in a primary study. The decline in antibody levels among individuals 11 to 18 years of age, 4 years after a primary series on a 2 or 3-dose schedules, follows a similar pattern. A decrease in response was evident for all test strains from month 6 to month 12, followed by a plateau thereafter up to month 48. Subjects achieving protective hSBA titers for four fHbp variants strains combined ranged from 15.7% to 18.2%. Taking into account the importance of circulating serum antibodies to maintain protection against invasive meningococcal disease, the persistence data suggest that booster doses would be required to maintain long-term protection. All subjects showed a robust immune response one month after a booster dose for different fHbp variants [66,74,80]

The capacity of these protein based vaccines to prevent acquisition of serogroup B carriage, or otherwise to interrupt transmission and thus provide herd protection, once targeting the age groups responsible for carriage, is currently unclear. In UK university students no significant difference in serogroup B carriage prevalence was detected between the

4CMenB vaccinated and non-vaccinated control groups one month after the second dose, however three to twelve months after vaccination, meningococcal carriage prevalence was reduced for all *N meningitidis* and capsular groups BCWY in vaccinated individuals, although to a lower extent compared to carriage reduction conferred by ACWY conjugated vaccines[81]. Another meningococcal carriage study was performed in 3,082 students at the Oregon University following a meningococcal B vaccination campaign with both novel B-MD vaccines, in response to an outbreak in 2015. After 4 carriage surveys over a period of 11 months, no impact on meningococcal carriage was shown, suggesting that novel B-MD vaccines may not provide herd protection in the context of an outbreak response[82]. Similar experience was seen in Rhode Island after a mass vaccination campaign in a college with rLP2086, reinforcing the need for high vaccination coverage to protect vaccinated individuals and chemoprophylaxis for close contacts during outbreaks[83]. A recent study performed in Spain found that the potential impact of the 4CMenB vaccine on Spanish asymptomatic carrier strains appears to be due to the NHBA antigen[84].

Effectiveness of the protein-based vaccines will depend on strain coverage, which can be estimated from hSBA responses performed with a panel of serogroup B strains representative of antigenically and epidemiologically diverse invasive disease isolates. However, the logistical limitations associated with the use of hSBA led to the development of alternative nonfunctional assays to infer vaccine breadth of coverage, such as the meningococcal antigen typing system (MATS) and/or the meningococcal antigen surface expression (MEASURE) flow cytometry-monoclonal antibody based method. 4CMenB is conservatively estimated to provide 66–91% coverage against serogroup B strains worldwide[46,85] based on analysis of pooled sera from vaccinated infants that meet a

minimum threshold of reactivity in the MATS ELISA and/or contain the PorA 1.4 antigen. For the bivalent rLP2086, MEASURE uses immune sera specific to a surface-expressed epitope common to variants within both fHbp subfamilies included in the bivalent vaccine[50]; at the time of writing, testing of strains had not yet been published. For rLP2086, pairwise identity analysis between a test strain and fHbp sequences from the same subgroup indicate high sequence conservation, estimating a coverage from 84.8% to 88.5%[86]. In the future, these types of analysis may provide temporal and regional data for serogroup B vaccine policy related decisions. The meningococcal antigen typing system (MATS) could potentially underestimate coverage, as it was shown in a study when MenB isolates from England and Wales were assessed, reaching a 73% to 88% coverage[45–48]. Another study performed in the United Kingdom (UK) following 4CMenB introduction in infants showed >80% vaccine-mediated protection against all current MenB strains circulating in the country[87,88]. This could be explained by the existence of cross-protective epitope on fHbp variant 1.1 that elicit bactericidal neutralizing antibodies to antigen-binding fragment 1A12 which is cross-reactive and targets an epitope highly conserved across the repertoire of three naturally occurring fHbp variants[89]

These vaccines may prove to be effective against non-serogroup B strains due to cross-protection provided by the highly conserved antigenic proteins included in the vaccines[85,90], as has been reported in the UK in relation with the hyper virulent *Neisseria meningitidis* serogroup W strain circulating, especially in infants. The technique to predict non-MenB vaccine strain coverage using MATS positive bactericidal threshold has not yet been validated. Therefore to evaluate the impact that 4CMenB vaccination may have on non-serogroup B disease SBA activity of sera from vaccinated subjects to kill meningococcal strains belonging to serogroups C, Y, and W isolates have been used, provided by the

reference laboratories in UK, Germany, France and Brazil. An overall proportion of serogroups C, Y and W strains killed at hSBA titers ≥8 ranged from near 45% to 90% [91]. Another study, performed by Gorla et al, with strains representing the total MD cases occurring during 2012 in Brazil showed differences between adolescents and infants coverage with a 100% coverage for MenW and MenY, but no coverage for MenC strains tested with pooled infant immune sera and 100% for MenC, 86% for MenW, and 67% for MenY using adolescent immune sera[92]. Regarding serogroup X, the same analysis was performed for strains from Niger, Chad, Burkina Faso and France, suggesting coverage for african isolates but not for X isolates from France which expressed unrelated fHbp sub variants belonging to variants 2 and 3[93]. The universal presence of full-length NadA genes within currently circulating MenW cc 11 clones, English/Welsh strain, indicates that 4CMenB may afford protection. Tested invasive MenW:cc11 isolates from patients 4 months to 91 years old in England and Wales during 2011–2012 with pooled sera from vaccinated children showed that hSBA titers were high (>1:32) against all MenW isolates[8,90]. In addition, 4CMenB variants for NadA and NHBA, unless different from these alleles peptides in MenW English/Welsh strain, can induce cross-protection, and collaborate in the complement-mediated bactericidal killing[90].

Considering the commonly accepted threshold of €50,000 per QALY, novel MenB vaccines are not expected to be cost-effective in a National Immunization Program (NIP) unless a considerable increase in MenB incidence occurs or new information that clarify its role in herd protection or persistence of immune protection becomes available. Infant vaccination could further reduce the burden of disease and prevent more deaths as compared to adolescent schedules, but at a substantially higher cost; so cost- effectiveness and feasibility of introducing a novel MenB vaccine into a NIP needs to be based on

country-specific assessments[94–100]. This issue requires further analysis and studies, which should be obtained and complemented from the UK experience.

Regarding vaccines comparison, 4CMenB and rLP2086 are both proteins based vaccines, developed using different strategies, aiming to provide broad strain coverage. 4CMenB includes three antigens (including only one subtype of fHbp) in addition to OMV while rLP2086 includes the two main subtypes of fHbp. Comparisons of potential strengths and weaknesses have to be made with caution as different techniques have been used to evaluate these vaccines. Face to face efficacy studies are not available and thus vaccines cannot be fairly compared. Immunogenicity studies use different antigens and criteria and thus for are not comparable. For rLP2086 vaccines protective antibody titers surpass 73% and 80% after two or three doses respectively in adolescents[74] and for 4CMenB, protective levels ranged from 99% to 100% for PorA, fHbp, and NadA antigens[54]. Only the 4CMenB vaccine was licensed in infants with composite antibody levels reaching 85–95 % after the primary series with three doses[57]. Studies of antibody persistence revealed a bactericidal activity lasting 18-24 months in over 64% of adolescents for all three tested 4CMenB vaccine-related antigens[79] and a sharp decline for antigens expressing fHbp subfamilies A and B ranging from near 25% to 60% in the percentage of subjects with protective antibodies since 12 to 48 months after priming with rLP2086[80]; indicating that immunity wanes for both vaccines. In children, a recently published meta-analysis assessed 4CMenB persistence of immunogenicity against the four reference strains finding that it remained high 6 months after the booster dose just for NadA and NHBA reference strains and then decreased till values obtained before booster dose[69,75,78]

The potential for cross-protection against non-B meningococcal strains has been described for 4CMenB, specifically for C, W, Y and X strains, but not yet for rLP2086. For both vaccines, the impact of vaccination on nasopharyngeal carriage is uncertain. 4CMenB has demonstrated a reduction only in one study performed in UK from 3 months after dose two, of 18.2% on any meningococcal strain and 26.6% for capsular groups BCWY, with a reduction in prevalence of carriage observed over 1 year of follow-up[81]. For rLP2086 no impact on carriage has been demonstrated, regardless the number of doses administrated during outbreaks in American universities and colleges[82,83]. Both vaccines can be coadministered with other childhood or adolescent vaccinations. 4CmenB can be coadministered with monovalent or combination vaccines including: diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, heptavalent pneumococcal conjugate, measles, mumps, rubella, varicella, and MCC-CRM vaccine in infants and children; coadministration studies are not available for adolescents[57,58]. For rLP2086 the following vaccines can be given concomitantly in adolescents, TdaP-IPV, quadrivalent HPV, MenACWY conjugate vaccine and tetanus toxoid, Tdap. Bivalent rLP2086 vaccine is not approved for infants[65,66]. Both vaccines are relatively reactogenic as has been described above, causing pain at the site of injection in adolescents and infants, and fever in infants; it is unclear if one vaccine is more reactogenic than the other as no head to head studies are available. 4CmenB has been included in five NIPs[59,60,101-104] and has been used in regional programs and to control specific outbreaks[105–110], especially in colleges, while rLP2086 has not yet been incorporated into a NIP, but has been used in college outbreaks[110–112]. Finally, both vaccines are currently of relatively high cost[97,98,100].

For the investigational vaccine against serogroups A, B, C, W and Y (MenABCWY), phase 2 studies performed in adolescents have showed that two or three doses are able to elicit a robust immune response against ACWY serogroups, at least comparable with those after one dose of MenACWY-CRM vaccine, and for serogroup B test strains with an acceptable reactogenicity and safety profile, similar to 4CMenB. In addition, MenABCWY vaccine may be suitable for booster doses after priming with MenABCWY vaccine or 4CMenB vaccine[113-116]. Further clinical development is necessary but promising to give us the opportunity to control MD.

Consideration for use of the serogroup B protein based vaccines for N. meningitidis outbreaks

Massive vaccination campaigns can be implemented for outbreak control. Importantly, vaccination does not replace recommended chemoprophylaxis[36,105,117]. Before vaccine implementation, appropriate surveillance systems including follow-up of close contacts should be available. Ideally, the infecting strain should be characterized, but, this should not delay the decision regarding vaccine introduction during outbreaks[36]. There is no current preference for one of the two available vaccines according to CDC recommendations and vaccine interchangeability cannot currently be endorsed[118].

Effectiveness and safety of serogroup B protein-based vaccines from "early adopter" countries/regions

The UK experience

For the last several decades capsular group B endemic meningococcal disease has predominated in the British Isles at incidence rates that are higher than those seen elsewhere in Europe[33]. Numerous clonal types of group B causing invasive disease have circulated[119]. This is in contrast to some other capsular groups, notably group C in the 1990s and group W in the second decade of the twenty first century, each of which showed rapid rises in incidence associated with spread of single hyper invasive clones[8]. While these latter problems were, respectively, solved[120] and, at the time of writing, are being tackled by widespread deployment of conjugate vaccines in the adolescent age group[121], who are most commonly carriers and thus onwards transmitters of meningococci in the population, this option does not currently exist for group B.

Accordingly, in the context of recognition that efforts to improve early diagnosis and to improve outcomes through more aggressive or novel adjunctive therapy were unlikely further to reduce case fatality rates or the frequency and severity of long term morbidity and buoyed by strong public and political support for action, the pediatric academic community in Europe engaged actively with the company developing 4CMenB and contributed to advancing the pre-licensure development program[122].

Following European licensure, initial evaluation of the cost effectiveness of using the vaccine, based on estimates of likely coverage of UK invasive strains[122], cast doubt as to whether it would meet the stringent criteria set by the UK government for introduction of healthcare interventions within the National Health Service in the country[60]. However, after further evidence was gathered, it became clear that the threshold could be met if a slightly modified schedule from the one specified in the product license was used and the vaccine was introduced for infants in September 2015[59]. Infants receive 2 doses at 2 and 4

months of age alongside other primary schedule vaccines and receive a third dose at 12-13 months. The uptake reported from August to December of 2017 in UK, reached 95.9% for one dose and 88.4% for two doses by six months of age and 87.4% for the booster dose[123]. Advice concerning routine antipyretic-analgesic use was modified to advise that paracetamol should be given at the time of the first two doses.

Early ecological data comparing changes in rates of meningococcal group B disease over time in the immunized cohort with those in older age groups indicate that the vaccine induces protection more effectively than was predicted pre-implementation[87]. The rates of uptake of the vaccine have been consistently high but concerns that its tendency to cause fever in many infants when given with other vaccines would lead to increases in rates of hospital attendance have been confirmed, reinforcing the importance of paracetamol prophylaxis[56].

Whether deployment of the vaccine in adolescents would reduce carriage and result in herd protection as seen following conjugate vaccine programs remains an unanswered question at the time of writing. If 4CMenB and/or the more recently licensed bivalent fHbp vaccine can do this will determine whether cost-benefit thresholds can be met for their use in this age group. An on-going study in South Australia (Marshall et al., manuscript submitted for publication) and a planned study in the UK may provide the answer.

The Saguenay-Lac-Saint-Jean experience in Canada

The Saguenay-Lac-Saint-Jean (SLSJ) region was affected by a 269 (ST-269) serogroup B clone with an average incidence rate of 3.4 per 100,000 person-years from 2006 to 2013,

which surpassed Canadian average rates by more than 10-fold (0.3/100,000). Cases were concentrated among individuals ≤ 20 years of age. To control the spread of this clone, a massive vaccination campaign using 4CMenB according to its locally approved schedule, was undertaken, targeting more than 50,000 people between the ages of 2 months and 20 years residing in, or attending an educational institution in the region[109]. The vaccine uptake rate for one dose was 82%, but only 70% for at least two doses, mainly due to low uptake in older adolescents and young adults. The vaccination campaign was estimated to have reduced disease incidence by 77% and new serogroup B cases have not been reported among vaccinees, with two cases observed among non-vaccinated adults. An enhanced surveillance system was also implemented to monitor the onset of adverse events following immunization in real time[109,124]. Fever was reported in 12% of vaccinees and was more frequent in young children. Antipyretic prophylaxis (paracetamol mainly) was 50% effective in preventing the occurrence of fever in children less than 5 years of age but not in older age groups. There was no death and no major adverse event with or without sequelae associated with vaccination. During the two-year period following the immunization campaign in SLSJ, no IMD case was recorded among unvaccinated individuals, including infants, thus it seems that at least some herd effect may be occurring[109].

Vaccine use for control of university outbreaks in the USA

From 2009 to 2014 five serogroup B outbreaks on college campuses were reported to CDC. In 2013, 4CMenB vaccination campaigns were implemented in response to ongoing serogroup B outbreaks at the Universities of Princeton and Santa Barbara, due to sustained transmission during 2 academic years. The FDA approved the use of 4CMenB before

national licensure under an expanded access investigational new drug protocol in December 2013[106,108]. The attack rate in Princeton was 134/100,000 among undergraduates living in dorms, with individual cases occurring 2 to 4 weeks apart. The strain isolated expressed two of the 4 antigens (fHbp and NHBA) in sufficient quantities to suggest that 4CMenB might be protective[108]. Vaccine was offered to nearly 5,800 individuals including undergraduate students, faculty, staff and graduate students at increased risk of meningococcal disease, and spouses and caregivers of graduate and undergraduate students living in a dormitory with students. Uptake was very high, reaching 95% for the first dose and 89% for the second dose, with approximately 5,200 individuals who received al least one dose[106]. The rate of reported SAEs was near 2.0/1,000 vaccinees following the first dose and 0.2/1,000 following the second dose, with no causality related to 4CMenB observed[108]. In the University of California at Santa Barbara outbreak, the attack rate was 21.1/100,000; despite the fact that the strain was different from the Princeton strain, protection was expected from 4CMenB based on killing properties of pooled post-immunization sera. The target groups were similar to Princeton with nearly 20,000 subjects eligible and nearly 17,000 vaccinated with no cases occurring in vaccinated students[34,108,117]. Parallel to this immunization campaign, an immunogenicity study was performed in a subset of 607 subjects showing that 66.1% had hSBA protective titers against the outbreak strain[125]. This result was lower than that predicted by the MATS test, suggesting that hSBA underestimates protective immunity. The bivalent rLP2086 vaccine was administered to 3,525 subjects in Providence College and to nearly 22,0000 students in the University of Oregon during outbreaks occurring in 2015, achieving a 94% first dose uptake among eligible students. College-associated cases were not identified during the 4 months follow up period[82,83,107,126].

Despite the success achieved after the widespread vaccination campaigns to control outbreaks of serogroup B-MD, with no further cases reported among vaccinated subjects, the long-term duration and breadth of protection, as well as the impact of these vaccines on prevention of carriage remains to be determined.

Conclusions

Rates of invasive B-MD have been declining worldwide, although in certain geographical areas and populations incidence rates can be particularly high. In addition, outbreaks of B-MD occur in an unpredictable manner in a number of settings where people gather, especially universities. Although several possibilities were raised to explain the declining trend in B-MD incidence observed during the last decades, including declining smoking rates, changes in population immunity, bacterial virulence and a natural cyclical pattern of meningococcal serogroup distribution [25], reasons remain unclear. The high CFR and the significant sequelae in surviving individuals, as well as its potential epidemic nature are the main reasons for primary prevention, for which vaccination is the only effective tool. Age groups at highest risk are young children, especially infants under one year of age, followed by adolescents in areas where close contact is frequent such as university dorms in the USA. Meningococcal vaccines against non-serogroup B strains have been based on protein conjugated capsular polysaccharides targeting specific serogroups (A, C, W and Y) with great success. The rapid and sustained reduction in serogroup C disease rates in the UK and other countries after vaccine implementation into national immunization programs has been a significant achievement. Flexible vaccine schedules focusing not only on direct protection, targeting the age groups with the highest incidence rates of disease (usually infants), but also vaccinating the age groups that act as the reservoir for infection (usually

adolescents and young adults) and thus reducing carriage rates and interrupting transmission in the community, have proven effective for serogroups susceptible to be prevented by this vaccine strategy.

The antigenic mimicry between serogroup B polysaccharide and human neural tissue antigens curtailed development of polysaccharide-based vaccines against this pathogen, and left it unprevented for decades. The solution was found in targeting outer membrane proteins, first in the form of OMVs, which are a laboratory-obtained simile of the outer membrane (of which porins are the main antigenic target). This vaccine proved to be immunogenic, protective, and effective in controlling regional outbreaks, with the caveat that the immune response, based on the induction of SBA, was highly strain-specific for the porin within the OMV. The significant variability of porins among strains circulating worldwide precluded this strategy for universal vaccination. But the proof of concept that protein antigen vaccines can be highly protective had been established. Second generation protein-based vaccine candidates aimed to identify antigens expressed in as many serogroup B strains as possible in order to provide "broad strain" protection. These candidates are now licensed vaccines although in a stage of post-licensing "field evaluation" as they were approved based on safety and immunogenicity studies and their use is currently limited to only one country in a routine national program, to some regions, and a few outbreak situations. The fact that in all the experiences to date results have been encouraging is promising. The 4 component vaccine targeting four different proteins from GSK (developed by Novartis vaccines) and the two component vaccine targeting the two subfamilies of one relevant protein, from Pfizer, elicit serum bactericidal antibodies although in variable quantities depending on the antigen. It seems that antibodies to any of

the protein antigens in the vaccine may be sufficient to protect, but this is uncertain. The exact protective effectiveness for each vaccine is thus currently unknown although for 4CMenB it seems to surpass 85% for the first year after the primary series. Antibodies wane and because MD is fulminant, depending on memory cells is not sufficient to avoid severe disease if a vaccinated individual is exposed several years after vaccination. Thus, booster doses are likely to be needed to provide sustained individual protection. In addition, the breadth of strain coverage, which seems quite inclusive based on MATS testing for 4CMenB (over 60% of strains) and probably also for rLP2086, will require persistent strain surveillance over time. One limitation associated with both vaccines is their high reactogenicity profile both local and systemic, especially among infants. Only one of the two vaccines, 4CmenB, has been licensed for use in infants, and increased medical visits and even hospitalization due to febrile episodes have been reported. Importantly though, this reactogenicity profile has not been associated with severe outcomes to date, and hopefully will be adequately dealt with through parental education, as we gain more experience with both vaccines.

The two-serogroup B vaccines are a significant addition to our armamentarium against highly significant pathogens for humans. The vaccines should certainly be considered for persons at increased risk for MD and when dealing with serogroup B outbreaks occurring in institutions or specific regions, as they will most likely save lives and prevent severe sequelae. Incorporation into national programs will require thorough analysis such as has been done in the UK; the world is once again watching closely the vaccine experience of this country (a post licensure field experiment) which will be of significant help to other

countries with relatively high prevalence rates, who may be considering the incorporation of a serogroup B vaccine for the benefit of their populations.

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Figures legends

Figure 1. Annual incidence per 100,000 people of serogroup B invasive meningococcal disease worldwide from Jan 1, 2000, to March 1, 2015 (28).

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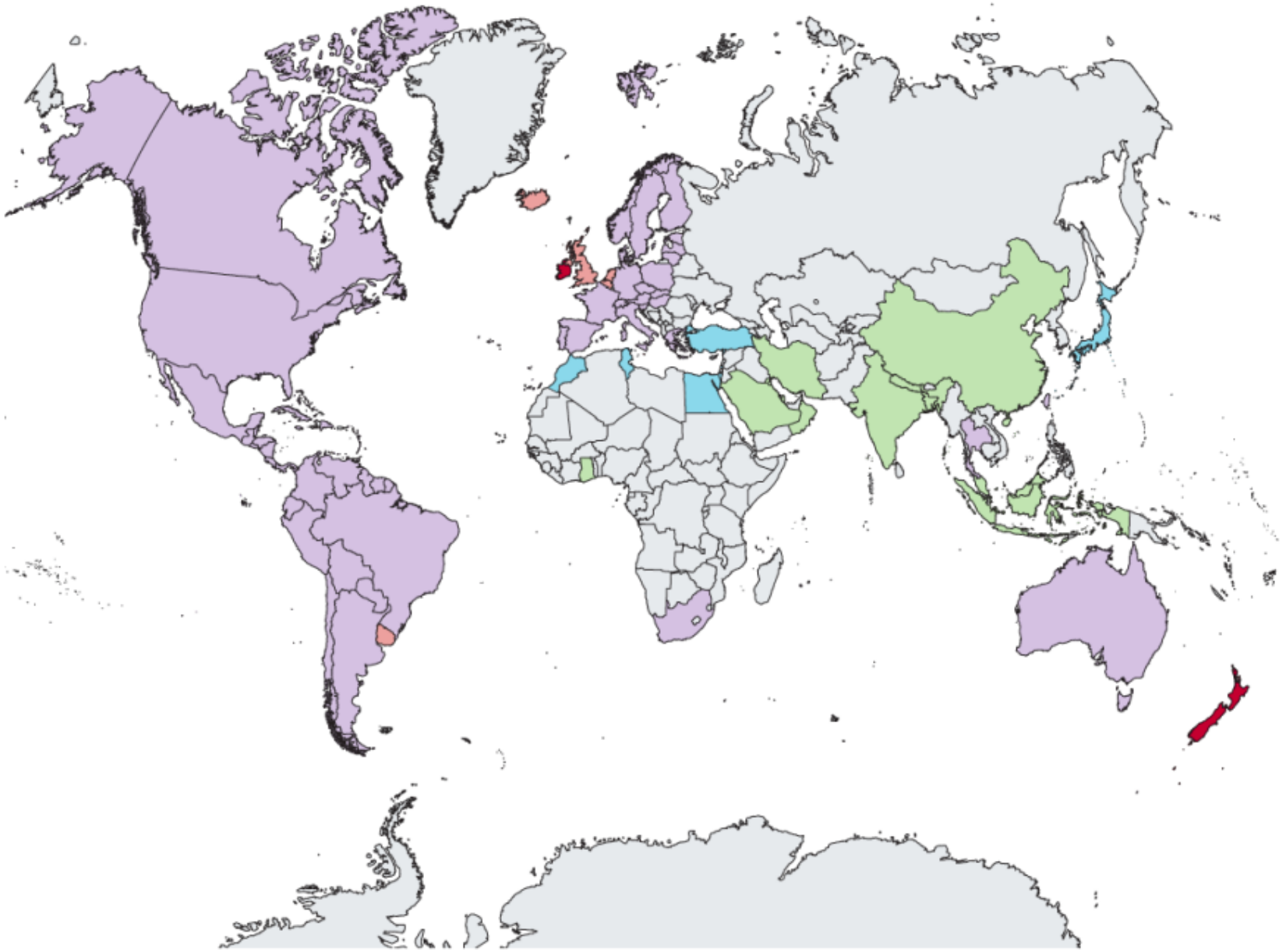
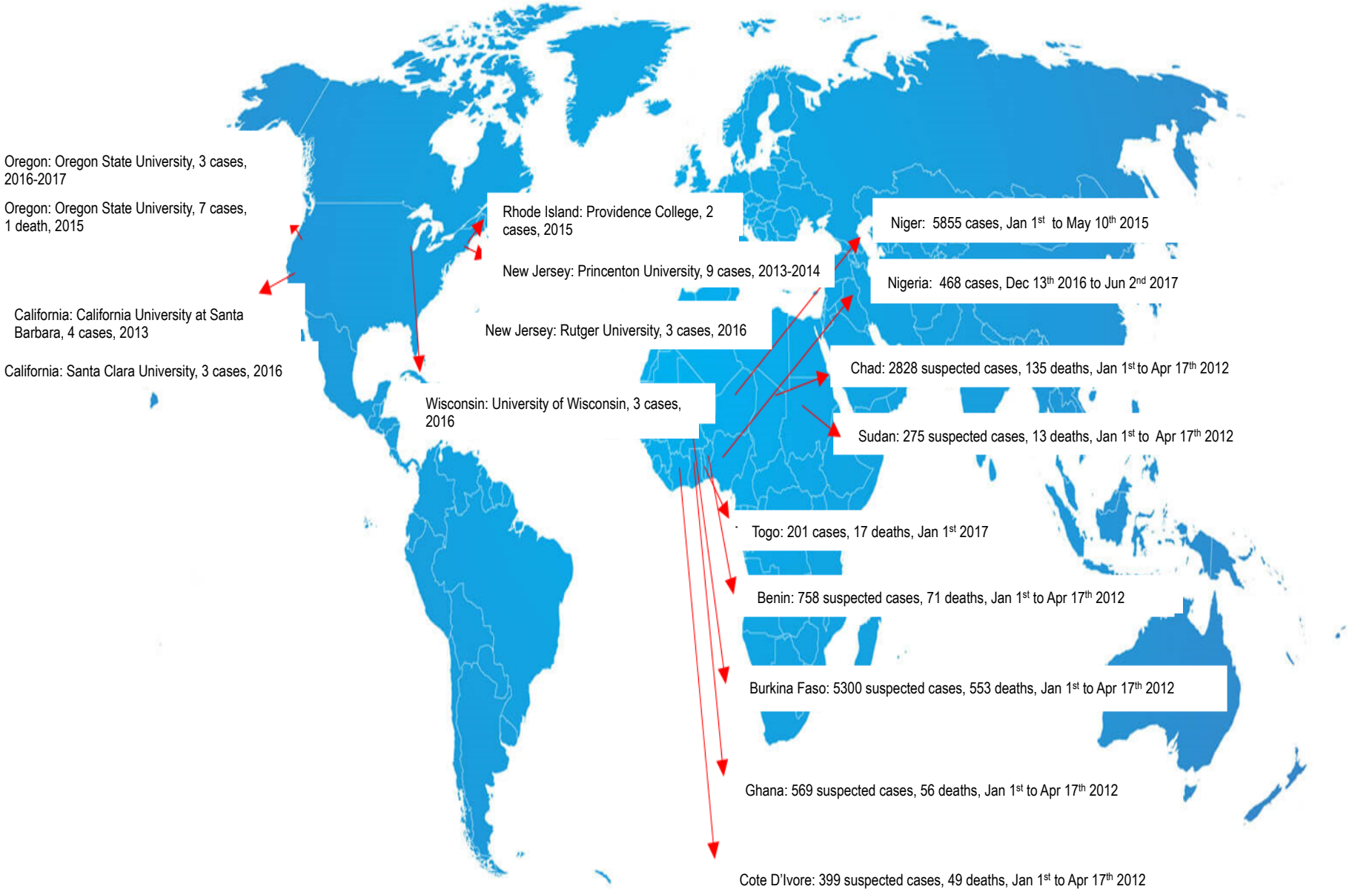
Figure 2. Meningococcal Outbreaks reported to the WHO from 2012 to 2017.

Figure 3. Timeline of some relevant moments in meningococcal disease control and prevention


>2
1·0–2·0
0·01–0·99
Countries where incidence is not reported but serogroup B forms >20% of IMD isolates
At least one NmB isolated during study period but no incidence data or proportion of IMD isolates due to serogroup B <20%
No NmB isolated during the study period or no NmB data identified


Oregon: Oregon State University, 3 cases, 2016-2017
Oregon: Oregon State University, 7 cases, 1 death, 2015
California: California University at Santa Barbara, 4 cases, 2013
California: Santa Clara University, 3 cases, 2016
Rhode Island: Providence College, 2 cases, 2015
New Jersey: Princenton University, 9 cases, 2013-2014
New Jersey: Rutger University, 3 cases, 2016
Wisconsin: University of Wisconsin, 3 cases, 2016
Niger: 5855 cases, Jan 1st to May 10th 2015
Nigeria: 468 cases, Dec 13th 2016 to Jun 2nd 2017
Chad: 2828 suspected cases, 135 deaths, Jan 1st to Apr 17th 2012
Sudan: 275 suspected cases, 13 deaths, Jan 1st to Apr 17th 2012
Togo: 201 cases, 17 deaths, Jan 1st 2017
Benin: 758 suspected cases, 71 deaths, Jan 1st to Apr 17th 2012
Burkina Faso: 5300 suspected cases, 553 deaths, Jan 1st to Apr 17th 2012
Ghana: 569 suspected cases, 56 deaths, Jan 1st to Apr 17th 2012
Cote D'Ivore: 399 suspected cases, 49 deaths, Jan 1st to Apr 17th 2012

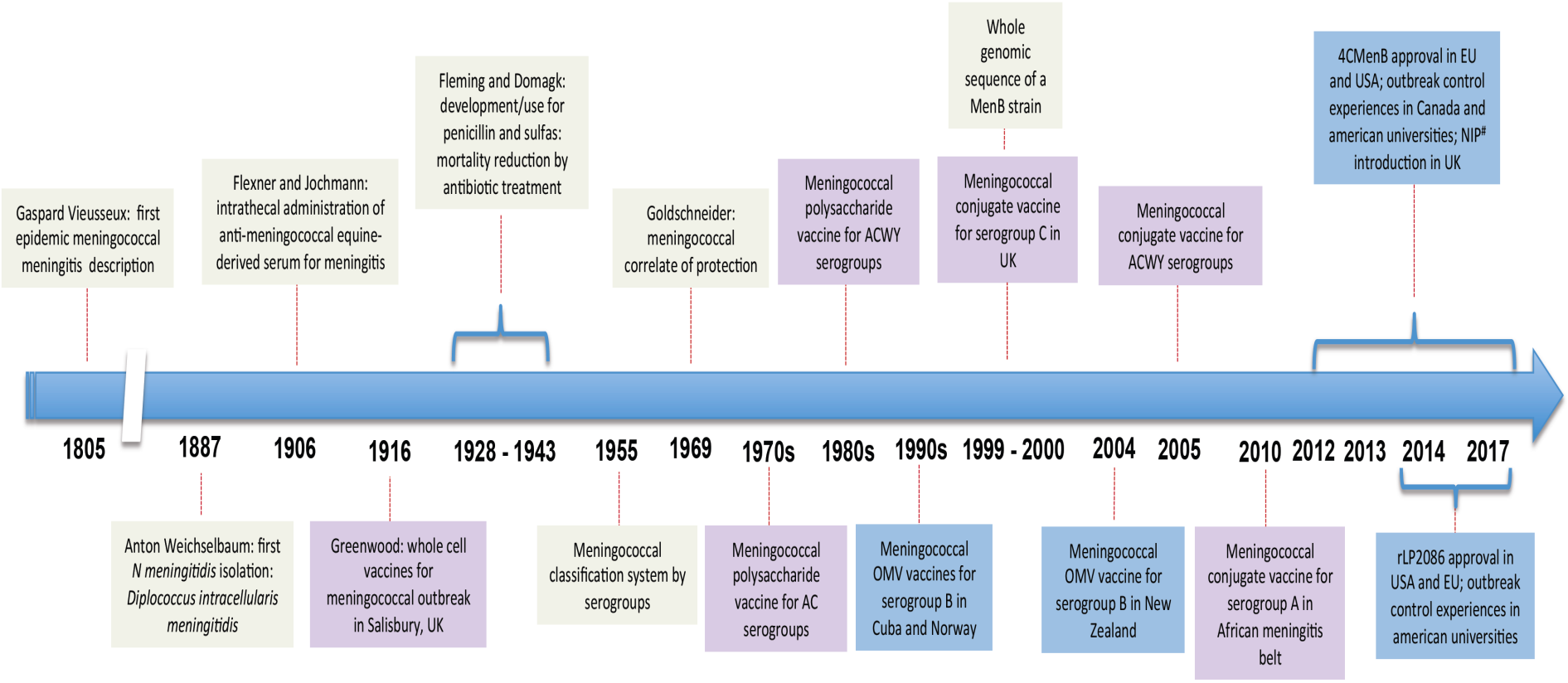

1805
Gaspard Vieusseux: first epidemic meningococcal meningitis description
1887
Anton Weichselbaum: first *N meningitidis* isolation: *Diplococcus intracellularis meningitidis*
1906
Flexner and Jochmann: intrathecal administration of anti-meningococcal equine-derived serum for meningitis
1916
Greenwood: whole cell vaccines for meningococcal outbreak in Salisbury, UK
1928 - 1943
Fleming and Domagk: development/use for penicillin and sulfas: mortality reduction by antibiotic treatment
1955
Meningococcal classification system by serogroups
1969
Goldschneider: meningococcal correlate of protection
1970s
Meningococcal polysaccharide vaccine for AC serogroups
1980s
Meningococcal polysaccharide vaccine for ACWY serogroups
1990s
Meningococcal OMV vaccines for serogroup B in Cuba and Norway
1999 - 2000
Whole genomic sequence of a MenB strain
Meningococcal conjugate vaccine for serogroup C in UK
2004
Meningococcal OMV vaccine for serogroup B in New Zealand
2005
Meningococcal conjugate vaccine for ACWY serogroups
2010
Meningococcal conjugate vaccine for serogroup A in African meningitis belt
2012
2013
2014
2017
4CMenB approval in EU and USA; outbreak control experiences in Canada and american universities; NIP# introduction in UK
rLP2086 approval in USA and EU; outbreak control experiences in american universities

Table 1. Immunogenicity and safety data from pivotal phase II/III studies for novel recombinant B-MD vaccines

Author, vaccine, study design	Immunogenicity	Safety	Concomitant vaccines
Gossger N, et al. 4CMenB [53] Phase IIb, multicenter, open-label, parallel group, randomized controlled trial; infants 2 months of age including two different 3 +1 schedules (sole or co-administered with routine vaccines); N=1,885	After priming ≥ 99% reached protective titers (hSBA ≥ 5) against Nad A, fHbp; and 79 - 86,1% for PorA tests strains. Immune responses were non-inferior by concomitant vaccination; and its immunogenicity was non-inferior to routine vaccines alone for all antigens. Sole administration elicited higher hSBA GMTs for all strains compared to coadministration with routine vaccines; 2,4, and 6-month schedule, rather than an accelerated 2-, 3-, and 4-month schedule, resulted in higher hSBA GMTs for the Nad A test strain.	Fever was more frequent after 4CMenBdoses (26%-41%) compared with routine vaccines (23%-36%); severe erythema, swelling, or induration were seen in ≤ 1%; severe pain was registered in 16% in the accelerated groups.	PCV7 and DTaP-HBV-IPV/Hib No evidence of immune interference, except for pertactin and pneumococcal serotype 6B, of unlikely clinical significance. Increase in reactogenicity in the coadministration group, mainly fever (51%-61%) and severe pain at the injection site (12%).
Vesikari T, et al, 4CMenB [52] Phase III, multicenter, randomized, open label for immunogenicity and observer blind for safety; infants 2 – 12 months of age; 3 +1 schedule N= 3,360	After priming 100% reached hSBA ≥ 5 against fHbp and Nad A, and 84% for New Zealand OMV and NHBA tests strains. After booster dose: 95−100% of children had hSBA ≥ 5 for all antigens.	Fever, injection-site reactions and tenderness were the most frequent adverse events reported Fever: usually on day 1, returning to normal by day 3. Injection-site reactions: peaked on day 1, with a steep decrease on day 2 and lower incidence after booster.	PCV7 and DTaP-HBV-IPV/Hib; MMRV No evidence of immune interference, except for poliovirus type 2 responses, with unknown clinical significance. Increase in reactogenicity in the coadministration group; mainly fever (77% vs. 45%).

Martinón-Torres F, et al, 4CMenB [50] Phase IIIb, multicenter, randomized, open-label; healthy subjects from 2 ½ months to 10 years old, divided in four groups: Group 1: doses at 2½, 3½, and 5 + 11 months of age; Group 2: doses at 3½ and 5 + 11 months of age; Group 3: dose at 6 and 8 + 11 months of age. Group 4: 2-dose-catch-up series, administered 2 months apart. N= 754 infants and 404 children	After priming for groups 1 to 3, and after the catch up series for group 4 100% and 99% reached hSBA ≥ 4 against fHbp and Nad A; After primary/catch-up series hSBA ≥ 4 against Por A was reached in groups 1,3 and 4 in 99% and in 98% for group 2. NHBA 1 month after primary/catch-up series reached 59% for group 1, 49% for group 2, 77% for group 3, and 95% for group 4 After booster response (measured in groups 1,2 and 3) 100% reached hSBA titers ≥ 4 for fHbp and Nad A, ≥99% for Por A NHBA reached hSBA titers > 4 in 84%, 88% and 87% in groups 1, 2 and 3 respectively.	In infants local tenderness, erythema and pain were the most commonly reported adverse effects Rates of systemic adverse reactions in infants were similar across the 3 groups and highest after the first vaccination. Across all groups, no increased reactogenicity was observed following subsequent vaccinations	None
Santolaya ME, et al., 4CMenB [54] Phase IIb/III, multicenter, randomized, observer-blind, placebo-controlled study; adolescents from 11 to 17 years old; 1, 2 or 3 dosing schedule with 1,2 and/or 6 month intervals; N= 1,631	After 1 dose: 92–97% had hSBA titers ≥ 4 against test strains After 2 or 3 doses: 99–100% had hSBA titers ≥ 4 against test strains; reaching seroresponse rates of 99–100% for each strain at 6 months. A third dose had a small incremental effect on geometric mean titers, especially when given at 6 months, but did not increase the	Local and systemic reaction rates were similar after each injection and did not increase with subsequent doses, but remained higher than placebo. Pain was reported in 86% of which 17% was severe, most resolving at day 3; malaise: 51%; headache: 42% and fever: 4%; all the above were statistically significant compared to placebo. No vaccine-related SAEs were	None

	proportion of participants achieving protective titers	reported and no significant safety signals were identified.	
Vesikari T, el al. rLP2086 [63] Phase II, randomized, multicenter, single-blind study; adolescents from 11 – <19 years old; 2- or 3-dose schedules (0,1,6-month; 0,2,6-month; 0,2-month; 0,4-month; 0,6-month); N= 1,713	Participants whom elicited hSBA titers ≥1: 8 for serogroup B test strains expressing vaccine-heterologous fHbp variants A22, A56, B24, and B44: After 2 doses: 90-93%, 98-100%, 69-81%, and 70-77% . After 3 doses: 92-95%, 98-99%, 88-89%, and 86-88% . GMTs were similar between the 2- and 3-dose regimens.	Pain at the injection site, redness and swelling were the most common reactions and were mild to moderate. Severe pain was reported by 9.9% of subjects Headache and fatigue were the most common systemic symptoms and were mild or moderate in severity. Fever was infrequent (1.7%–4.3%). There were no differences in the incidence of SAEs between bivalent rLP2086 and saline recipients.	None
Muse D, et al.; rLP2086 [64] Phase II, multicenter, randomized, active-controlled, observer-blinded study; adolescents from 10 to <13 years old; concomitant or standalone schedule: 0,2 and 6 months; N=2,648	Immune responses to MCV4 + Tdap + rLP2086 were non-inferior to MCV4 + Tdap or rLP2086 alone. Seroprotective hSBA (>1:4) were documented for 62.3%–68.0% and 87.5%–90% of MCV4 + Tdap + bivalent rLP2086 recipients after doses 2 and 3, respectively. A ≥4-fold rise in hSBA titers from baseline was achieved by 56.3% – 64.3% and 84.0%–85.7% of subjects after doses 2 and 3, respectively. Bivalent rLP2086 alone induced similar responses.	Concomitant administration did not substantially increase reactogenicity compared with rLP2086 alone.	MCV4 and Tdap Bivalent rLP2086 concomitantly with MCV4 + Tdap met all noninferiority immunogenicity criteria without an increase in reactogenicity.
Ostergaard L, et al.; rLP2086 [67] Phase III, multicenter,	Immunogenicity data were not collected	SAEs: 1.6% of rLP2086 recipients Medically attended AEs were similar	None

randomized, active-controlled, observer-blind study; adolescents and young adults ≥ 10 - <26 years old; 3 doses schedule (0, 2, and 6 months); N=5,712		between rLP2086 and hepatitis A vaccine/placebo group (5,5% - 7%) and decreased after each consecutive dosing Subjects reporting ≥ 1 AE were greater in the rLP2086 vaccine group.	
Ostergaard L, et al.; rLP2086 [68] Phase III, multicenter, randomized, controlled, observer-blinded, adolescents from 10 – 18 years old and from 18 to 25 years old; 3 doses (0,2 and 6 months) N= 3596 adolescents (10 to 18 years of age); 3304 young adults (18 to 25 years of age)	After 2 doses hSBA titer ≥ 4 against each primary strain ranged from 56.0 to 85.3% in subjects 10 – 18 years old and from 78.8 to 90.2% after dose 3 Young adults with hSBA titers ≥ 4 ranged from 54.6 to 85.6% and 78.9 to 89.7%, after doses 2 and 3, respectively Composite responses after doses 2 and 3 in adolescents were 53.7% and 82.7%, respectively, and those in young adults were 63.3% and 84.5%, respectively	Pain was the most common reaction in the two trial groups, mainly after dose 1, and ≤1.1% reported increased severity of reaction with subsequent doses Headache and fatigue were the most common systemic events among both adolescents and young adults	None

4CB-MD: Bexsero®; fHbp: factor H binding protein; Nad A: neisserial adhesin A; neisseria heparin binding antigen: NHBA; OMV: outer-membrane vesicle; hSBA: human complement serum bactericidal activity; GMTs: geometric mean titres; SAE: serious adverse events; AE: adverse event; SBA: serum bactericidal assays; hSBA: serum bactericidal assays using human complement; PCV7: heptavalent pneumococcal conjugate vaccine; DTaP-HBV-IPV/Hib: diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B vaccine; MMRV: measles, mumps, rubella, varicella; MCV4: meningococcal ACWY conjugate vaccine; Tdap: tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed