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REVIEW

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Translating meningococcal serogroup B vaccines for healthcare professionals

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ABSTRACT

Introduction: Vaccination is an effective strategy to combat invasive meningococcal disease (IMD). Vaccines against the major disease-causing meningococcal serogroups are available; however, development of vaccines against serogroup B faced particular challenges, including the inability to target traditional meningococcal antigens (i.e. polysaccharide capsule) and limited alternative antigens due to serogroup B strain diversity. Two different recombinant, protein-based, serogroup B (MenB) vaccines that may address these challenges are currently available. These vaccines have been extensively evaluated in pre-licensure safety and immunogenicity trials, and recently in real-world studies on effectiveness, safety, and impact on disease burden.

Areas covered: This review provides healthcare professionals, particularly pediatricians, an overview of currently available MenB vaccines, including development strategies and evaluation of coverage.

Expert opinion: Overall, recombinant MenB vaccines are valuable tools for healthcare professionals to protect patients against IMD. Their development required innovative design approaches that overcame challenging hurdles and identified novel protein antigen targets; however, important distinctions in the approaches used in their development, evaluation, and administration exist and many unanswered questions remain. Healthcare providers frequently prescribing MenB vaccines are challenged to keep abreast of these differences to ensure patient protection against this serious disease.

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Factor H binding protein; MATS; MEASURE; Meningococcal serogroup B; *Neisseria meningitidis*; serum bactericidal assay; vaccines

1. Introduction

Invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* is a serious public health burden because of its rapid progression, severity, and potential epidemic nature [1–4]. Twelve meningococcal serogroups have been characterized, but virtually all globally reported cases of IMD are caused by six serogroups: A, B, C, W, X, and Y [4,5]. Vaccination is an effective measure to prevent IMD, particularly by limiting disease spread and epidemics, as shown by a dramatic decline since 2010 in serogroup A meningococcal disease due to mass preventive immunization campaigns with a conjugate MenA vaccine targeting persons 1 to 29 years of age [6]. As of November 2017, over 280 million individuals have been vaccinated against serogroup A across 21 countries in the African meningitis belt [6].

Invasive meningococcal disease caused by serogroup B is rare yet potentially deadly, representing a serious public health concern [3–5,7,8]. Of all reported IMD cases in the United States and Europe in 2017, 38% and 51%, respectively, were caused by serogroup B, with case fatality rates of 12.0% and 7.0% [8,9]. Disease caused by serogroup B can occur at any age but is most common in infants, young children, and adolescents [8–10].

Monovalent, bivalent, trivalent, and quadrivalent vaccines targeting meningococcal serogroups A, C, W, and Y have been developed by targeting capsular polysaccharides, while a pentavalent conjugate vaccine including serogroup X is under development [1,6,11]. Because capsular polysaccharides are conserved across all strains of a given serogroup, meningococcal polysaccharide vaccines should thereby broadly protect against all strains with capsular serogroups homologous to those contained in the vaccine [12]. However, a similar development strategy was not effective for meningococcal serogroup B owing to the structural similarity of the group B polysaccharide with polysialic acid structures on human neural tissue; this resulted in limited immunogenicity and possible cross-reactivity to molecules in mammalian neurons [13,14]. MenB vaccine development has also been hampered by the diversity of surface antigens [14]. Consequently, the development of safe and effective vaccines against serogroup B required novel strategies, distinct from those utilized to develop vaccines for serogroups A, C, W, and Y.

Using varying approaches to identify vaccine antigens, two protein-based MenB vaccines have been developed: MenB-

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Article highlights

- Globally, invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* remains a significant public health burden; meningococcal serogroup B is a predominant cause of IMD.
- Vaccines targeting meningococcal serogroups that cause the majority of IMD are currently available.
- Vaccines against meningococcal serogroups A, C, W, and Y were developed by targeting capsular polysaccharides; however, the development of vaccines against meningococcal serogroup B required different approaches because the serogroup B capsular polysaccharide was an unsuitable antigen.
- Two compositionally different protein-based serogroup B vaccines (MenB-FHbp [Trumenba®] and MenB-4C [Bexsero®]) were independently generated by separate strategies that focused on identifying novel antigens that were highly immunogenic, surface-exposed proteins expressed across the diversity of disease-causing serogroup B strains.
- The breadth of coverage afforded by both of these new protein-based MenB vaccines was extensively evaluated and demonstrated using surrogate approaches but with important distinctions in the methodologies applied for each vaccine.
- Overall, this review summarizes the differences between MenB-FHbp and MenB-4C, including comparisons of the strategies used in their development and evaluation, to provide guidance to their most frequent prescribers, namely pediatricians.

FHbp (Trumenba® [bivalent rLP2086]; Pfizer Inc, Philadelphia, PA, USA) and MenB-4C (Bexsero® [4CMenB]; GlaxoSmithKline Vaccines, Srl, Siena, Italy). These vaccines are composed of differing recombinant protein variants found on the surface of *N meningitidis* to elicit antibodies against the invading serogroup B strains [15,16]. Both vaccines are licensed in several countries. Currently, MenB-FHbp is approved for use in individuals aged 10 to 25 years in the United States, Canada, and Brazil as well as those aged 10 years and older in a number of other countries [16–18]. MenB-4C is approved from 2 months of age in multiple countries outside the United States; in the United States MenB-4C is only approved for individuals aged 10 to 25 years [15,19–29].

Because pediatricians typically prescribe meningococcal vaccines, it is important they understand the extent of coverage provided by different available vaccine formulations to ensure their patients are optimally protected against circulating meningococcal strains. However, a recent national representative survey conducted among US pediatricians and family physicians revealed that there are significant gaps in knowledge on serogroup B disease incidence rates, as well as MenB vaccines' effectiveness and immunogenicity data, and this appears to be a major driver of the decision not to recommend the vaccines [30]. Existing recommendations by the Advisory Committee on Immunization Practices (ACIP) for quadrivalent MenACWY vaccines, and the fact that MenB vaccine was given a Category B (individual clinical decision-making) as opposed to a Category A (routine) recommendation by ACIP, were also factors in their decision *not* to recommend MenB vaccines [30]. Because MenACWY vaccines do not provide protection against serogroup B, this suggests that some patients may not be sufficiently protected against the spectrum of disease-causing meningococcal strains. This possible misconception, as well as confusion over official vaccination guidelines [30,31], may be tied to the infrequent prescribing of MenB vaccines by US healthcare professionals, with only 22% of 17-year-olds in this region receiving ≥1 dose of the multidose series in 2019 [32]. Therefore, further guidance for healthcare professionals is vital to support a recommendation of MenB vaccine to their patients.

This review aims to clarify the differences between the available MenB vaccines as well as highlight the importance of both MenB and MenACWY vaccination. Hurdles encountered in developing these vaccines, the different approaches taken to overcome these hurdles, as well as the extensive methodologies used to evaluate the vaccines (and their limitations) are examined. With the intent of providing an informative guide for pediatricians and other physicians in the clinic, this review ultimately describes how MenB vaccines are useful and valid tools for use by healthcare professionals to protect their patients against a potentially devastating disease.

2. Strategies for vaccine development against meningococcal serogroups A, C, W, and Y

2.1. Initial meningococcal vaccine formulations

In the first half of the 20th Century, approximately 400,000 people were administered killed whole-cell meningococcal bacteria vaccines, but their use diminished with the availability of antibiotics [33]. Meningococcal vaccines targeting the capsular polysaccharide of serogroups A, C, W, and Y were first developed in the 1960s [14]. However, these plain polysaccharide vaccines were not immunogenic in children <2 years of age and thus were later replaced by polysaccharide conjugate vaccines [14]. Polysaccharide conjugate vaccines contain a protein carrier that is covalently linked to the polysaccharide to elicit more robust immune responses in infants and young children and induce immunologic memory [14]. Furthermore, conjugate vaccines can prevent carriage acquisition [34,35]; carriage prevention promotes indirect protection when administered in high-coverage catch-up programs that include adolescents and young adults [35–37], the age groups experiencing the highest rates of meningococcal carriage [38].

The first meningococcal polysaccharide conjugate vaccine to be used was the monovalent serogroup C (MenC) vaccine, which was introduced into the UK national immunization program in 1999 [14,39]. Through routine immunization and a large catch-up campaign, a dramatic and sustained reduction in serogroup C cases was observed in the targeted age group and also indirectly in unvaccinated individuals in the following years [39–41].

Another monovalent polysaccharide conjugate vaccine targets meningococcal A (MenA) (MenA-TT; MenAfriVac™ [Serum Institute of India Ltd., Hadapsar, India]), which was developed in response to the continuing high levels of serogroup A disease in the meningitis belt in Africa [42,43]. MenAfriVac was introduced in 2010 for individuals aged 1 to 29 years as part of a mass immunization campaign, targeting >200 million people in regions with the highest burden of disease [43]. Since the introduction of this vaccine, there have been significant decreases in the incidence of serogroup A disease and serogroup A carriage in those regions [43,44].

2.2. Development of quadrivalent MenACWY polysaccharide conjugate vaccines

In addition to mono valent polysaccharide conjugate vaccines, higher valent quadrivalent polysaccharide conjugate vaccines targeting serogroups A, C, W, and Y have also been developed and licensed [14]. Currently, there are four licensed MenACWY polysaccharide conjugate vaccines available: MenACWY-D (Menactra®; Sanofi Pasteur, Swiftwater, PA, USA) [45], MenACWY-CRM197 (Menveo®; GlaxoSmithKline, Rixensart, Belgium) [46], MenACWY-TT (Nimenrix®; Pfizer Inc, Sandwich, UK) [47], and MenACYW-TT (MenQuadfi; Sanofi Pasteur, Swiftwater, PA) [48]. An increasing number of countries is now including MenACWY vaccines in national programs, largely in response to shifting meningococcal disease epidemiology [35,49–52]. For example, several countries have recently observed a striking increase in serogroup W and Y meningococcal disease [50,51,53–57] prompting MenACWY vaccination and a switch from the existing monovalent MenC vaccine in many regions [35,49–51,58–76].

3. The development of novel recombinant protein-based MenB vaccines and the challenge of elucidating MenB vaccine antigens

3.1. Initial strategies for MenB vaccine development

Development of a broadly protective MenB vaccine proved challenging, as the approach used for vaccines targeting serogroups A, C, W, and Y was not applicable for MenB vaccines [13,14]. Therefore, MenB vaccine development shifted to focus on alternative surface-expressed serogroup B protein antigens. Initially, MenB vaccines composed of outer membrane vesicles (OMVs) were developed [77]. These OMV vaccines contain surface-expressed components released by the outer membrane of *N meningitidis* [14], with porin A (PorA) being the immunodominant antigen; importantly, PorA is expressed by nearly all meningococcal strains [78]. Unfortunately, however, the protein sequence of PorA is highly variable, limiting the effectiveness of OMV vaccines to those serogroup B strains expressing homologous PorA variants [78–81]. Three monovalent OMV MenB vaccines have been developed and subsequently licensed: VA-MENGOC-BC® (developed in Cuba); MenBvac® (developed in Norway); and MeNZB™ (developed in New Zealand) [82–84]. Although these OMV MenB vaccines are valuable tools for controlling outbreaks caused by a particular serogroup B strain [85,86], they are less appropriate for broad protection against serogroup B disease. In addition, OMV MenB vaccines have been shown to be immunogenic only for the homologous strain in infants [87]. Investigational multivalent OMV vaccines have been trialed but have not progressed beyond clinical testing [88]. Thus, the challenge has been to identify alternative surface-expressed proteins that elicit immunogenic responses to the diversity of serogroup B strains for broader protection.

To develop a MenB vaccine that would be broadly effective against the disease, researchers focused on identifying highly immunogenic, surface-exposed, protein antigens that were largely conserved across numerous disease-causing serogroup B strains. Below we briefly summarize the independent approaches taken to identify MenB vaccine antigens and describe the unique formulations of MenB-4C and MenB-FHbp.

3.2. MenB-FHbp development

For MenB-FHbp development, researchers used a screening approach that combined biochemical and immunologic methodologies [89] to identify factor H binding protein (FHbp) as a suitable vaccine antigen [90,91]. FHbp is a surface-exposed lipoprotein that protects bacteria from the host's defense system by binding human factor H, a downregulator of the complement activation system [92,93]. The protein is expressed by >99% of all invasive serogroup B disease isolates [91], with strains expressing a single FHbp variant from 1 of 2 distinct subfamilies, A and B [94–96]. Importantly, although FHbp sequence identities within subfamilies can range from 83% to 99%, these identities range from only 60% to 75% between subfamilies A and B [94,96]. Immune responses to FHbp are largely subfamily specific, indicating that broad immunologic coverage requires antigens from both FHbp subfamilies [89]. Therefore, MenB-FHbp contains recombinant FHbp antigens from both subfamily A (variant A05) and B (variant B01; Table 1) [16]. In addition, both FHbp variants are lipidated in MenB-FHbp because preclinical studies showed that lipidated forms of the protein induced higher immunologic responses than nonlipidated variants and could cross-protect against FHbp variants not present in the vaccine [89,96].

3.3. MenB-4C development

To develop MenB-4C, researchers used a genome-based reverse vaccinology approach [100–103], through which the most promising candidate antigens were FHbp, neisserial adhesion A (NadA), and neisserial heparin-binding antigen (NHBA) [101]. As stated above, FHbp is an outer membrane protein widely expressed across serogroup B strains. NHBA and NadA are surface-exposed components that play important roles in the bacterial invasion of a human host, and NHBA is involved in the adhesion of the meningococcus to epithelial cells by binding directly to the cell surface [104,105]. NHBA has high sequence variability with low expression in some serogroup B strains [102], and NadA expression is variable and may be absent in some hypervirulent strains [100,106]. MenB-4C was formulated to contain recombinant versions of all 3 identified proteins (FHbp, NadA, and NHBA) as well as an OMV-containing PorA serosubtype P1.4 [15], previously used to control an outbreak of serogroup B in New Zealand (Table 1) [80,107].

It is important to note that although both MenB-4C and MenB-FHbp independently identified FHbp as a suitable vaccine antigen, the recombinant FHbp included in each vaccine is different. MenB-FHbp contains lipidated versions of both subfamily variants (variants A05 and B01) whereas MenB-4C includes only a single nonlipidated FHbp antigen (variant B24). It is also important to note that the antigens contained in the recombinant protein vaccines are not expressed only in

Table 1. Antigens in meningococcal serogroup B vaccines.

Antigen Identity	FHbp	NHBA	NadA	PorA
MenB-FHbp [16,91]	Subfamily A05/variant 3.45 + Subfamily B01/variant 1.55*	NA	NA	NA
MenB-4C [12,15]	Subfamily B24/variant 1.1†	Peptide 2‡	Peptide 8, variant 2/3§	P1.4‖
Protein function [78,97–99,104,105]	Binds and downregulates factor H, an inhibitor of the alternative complement pathway	Binds heparin and involved in adhesion to eukaryotic cells	Binds to epithelial cells and contributes to meningococcus invasion	Outer membrane protein that functions in ion exchange; elicits immune response
Protein expression [12,78,80,90,94,100,101,104–106,122]	Surface-exposed lipoprotein; expressed by nearly all meningococcal isolates, but expression levels vary between strains	Surface-exposed lipoprotein; expression is constitutively low in some strains	Surface-exposed; variable expression level among isolates; not expressed in some hypervirulent meningococcal strains	Surface-exposed; expressed by majority of meningococcal strains, but antigenically diverse

FHbp = factor H binding protein; MenB = *Neisseria meningitides* serogroup B; NA = not applicable; NadA = neisserial adhesion A; NHBA = neisserial heparin-binding antigen; PorA = porin protein A.
*Recombinant lipidated proteins.
†Recombinant fusion protein with *N meningitidis* strain 2996 accessory protein 936.
‡Recombinant fusion protein with *N meningitidis* strain 2996 accessory protein 953.
§Fragment of full-length protein from *N meningitidis* strain 2996.
‖Part of outer membrane vesicle from *N meningitidis* strain NZ98/254.

serogroup B strains, but also on the surface of other serogroups, anticipating that these vaccines may provide protection against other invasive meningococcal serogroups [15,16,91].

4. Approaches for evaluating the immunogenicity of recombinant protein-based MenB vaccines

4.1. Overview

The assessment of meningococcal vaccine efficacy, in general, is challenging; the overall low incidence of IMD [8,9] would require traditional clinical efficacy trials to enroll an inordinately high number of subjects. Because this approach is unfeasible, a surrogate measure of meningococcal vaccine efficacy has been developed: the serum bactericidal antibody (SBA) assay [108]. As described in more detail below, these in vitro assays measure functional antibodies developed in human sera, either from environmental exposure or vaccination, which are able to kill the bacteria [109,110]. The SBA assay is used as a surrogate to predict protection obtained by a vaccine and is globally accepted for licensure [109,111].

Specifically, SBA assays evaluate the ability of serum antibodies to kill meningococci by complement-mediated lysis and are typically performed with human sera, specific meningococcal test strains, and exogenous complement sourced from either humans or baby rabbits [12,109]. Original SBA assay studies using human complement (hSBA) conducted in the 1960s established the accepted correlate of protection for serogroup C disease as an hSBA titer of ≥1:4 [112]. Additional studies using rabbit complement (rSBA), a more readily available reagent with low nonspecific bactericidal activity, similarly established a correlate of protection for serogroup C as an rSBA titer of ≥1:8, but no formal threshold has been established for serogroups A, W, or Y [109,113,114]. Importantly, rSBAs are not appropriate for testing against serogroup B because the use of rabbit complement in conjunction with serogroup B strains causes misleadingly higher rSBA titers compared with hSBA titers [12,115]. Therefore, accurate analysis of MenB vaccine immunogenicity requires the use of SBA assays with human complement [12].

4.2. Challenges to the analysis of MenB vaccine immunogenicity: test strains and breadth of coverage

Analyses of vaccine efficacy against meningococcal serogroups A, C, W, and Y primarily use SBA assays with a single representative test strain for each serogroup; this is sufficient because the serogroup-specific capsular polysaccharide antigen for these vaccines is largely conserved across all strains of the targeted serogroup [12]. Therefore, serum bactericidal activity measured against the representative strain largely correlates with protection against all disease-causing strains of that serogroup. However, SBA assays for protein-based MenB vaccines are more complicated owing to the high diversity of proteins expressed across serogroup B strains [12,116]. Differing approaches were undertaken to evaluate the vaccine-elicited immunogenicity and breadth of coverage afforded by MenB-FHbp and MenB-4C vaccines, thus precluding direct comparison of results.

4.2.1. Evaluating MenB-FHbp vaccine immunogenicity

A rigorous approach to evaluate MenB-FHbp vaccine immunogenicity was taken that accounted for the sequence diversity and expression level differences of the FHbp antigen among serogroup B strains [12]. Immunogenicity was assessed using hSBAs against a diverse panel of serogroup B test strains, including 4 primary and 10 additional test strains, all of which contained FHbps that are heterologous to vaccine antigens [12,117]. The four primary test strains were selected from a large collection of 1263 serogroup B disease–causing isolates from the United States, the United Kingdom, France, Norway, and the Czech Republic [94], and included two subfamily A (A22 and A56) and two subfamily B (B24 and B44) variants, representing the medium to low FHbp expression levels in serogroup B strains [12,117]. Further, 10 additional test strains were randomly selected to support the breadth of coverage provided by MenB-FHbp; collectively, the FHbp variants in these 14 test strains represented those found in approximately 80% of invasive disease-causing serogroup B isolates in Europe and the United States [118]. Therefore,

the ability of MenB-FHbp to induce bactericidal antibodies against these heterologous strains in SBA assays indicates its potential to elicit protective immune responses to the diversity of circulating serogroup B strains [12,117].

Clinical studies assessed the vaccine immunogenicity of MenB-FHbp using these test strains in hSBA assays [12,117]. In these studies, the ability of MenB-FHbp to provide protection against serogroup B disease was defined by five stringent co-primary hSBA endpoints; these included the percentage of subjects that achieved a vaccine-specific response to each test strain (≥fourfold rise in hSBA titer following vaccination) and an hSBA titer that was at least the lower limit of quantification (LLOQ; typically ≥1:8 or ≥1:16, a more conservative threshold than the standard correlate of ≥1:4) for all 4 test strains combined (composite response) [12,117].

Evaluations using the 4 primary and 10 additional serogroup B test strains in hSBAs were performed in 2 pivotal phase 3 clinical studies in subjects 10 to 25 years of age [95]. Following the above-defined endpoints, these studies showed that 1 month after MenB-FHbp vaccination, adolescent and young adult recipients had broadly protective immune responses against the diverse serogroup B test strains [95]. For the primary strains, 79% to 90% of the subjects had a fourfold rise in hSBA titer following 3 doses of the vaccine, and 86%–100% of the recipients achieved hSBA titers ≥LLOQ against each strain. For the composite response, 83% to 85% of the recipients had hSBA titers ≥LLOQ against all 4 primary strains combined. In addition, 72% to 99% of the 3-dose recipients achieved hSBA titers ≥LLOQ against each of the 10 additional serogroup B test strains. Similar results were observed in studies examining immune responses following two doses of MenB-FHbp whereby 90% to 98% and 69% to 70% of the subjects had hSBA titers ≥1:8 for FHbp subfamily A and B strains, respectively, at 1 month after dose 2 [119]. One long-term study showed that antibody responses can persist up to 4 years in adolescents following MenB-FHbp vaccination, whereby 24%–62% of the subjects continue to maintain protective titers (hSBA titer ≥1:4) regardless of whether a 2- or 3-dose primary schedule was administered [120]. Another study in adolescents demonstrated that 20.0%–59.0% of the subjects continued to demonstrate hSBA titers ≥LLOQ against each strain up to 4 years post 3-dose vaccination with MenB-FHbp [121].

To further analyze broad coverage of MenB-FHbp across diverse serogroup B strains, a flow cytometric Meningococcal Antigen Surface Expression (MEASURE) assay was developed to detect and quantify the expression of any FHbp variant from either subfamily on individual serogroup B strains [122]. The MEASURE assay was validated by quantifying the FHbp expression levels of 1814 serogroup B strains [122], and subsequent hSBA assays showed that serogroup B strains with ≥30 pg FHbp/μg could be killed by the antibodies in human serum samples from individuals vaccinated with MenB-FHbp [122]. Of the 1814 strains, 91% expressed a sufficient level of FHbp to be susceptible to bactericidal killing by MenB-FHbp–induced antibodies [122].

MenB-FHbp efficacy against serogroup B outbreak strains has also been investigated to provide further support that the vaccine protects against the diversity of serogroup B strains. Robust protective responses (hSBA titer ≥1:8) against all strains in MenB-FHbp–vaccinated adolescents and young adults after 3 MenB-FHbp doses were observed in an evaluation of 27 serogroup B strains that included 4 US outbreak strains and collectively represented 83% and 80% of the invasive disease-causing strains in the United States and Europe, respectively [123]. Additional analyses on serogroup B outbreak strains showed that 53% to 100% of MenB-FHbp 2- and 3-dose vaccine recipients showed protective responses (hSBA titer ≥1:4) against 4 of 5 serogroup B strains responsible for recent outbreaks at US universities [12]. For the fifth strain, 20% to 40% of 2- and 3-dose recipients, respectively, showed hSBA titers ≥1:4. Another study conducted in France observed that after receiving two doses of MenB-FHbp vaccine, 40% to 93% of the young adolescents showed protective responses (hSBA titer ≥1:4) against 6 serogroup B outbreak strains [124].

4.2.2. Evaluating MenB-4C vaccine immunogenicity

Initial assessments of MenB-4C vaccine immunogenicity were primarily evaluated using three or four serogroup B indicator strains in hSBA assays [100,125]. Importantly, each indicator strain was specific to a single vaccine antigen (either FHbp, NadA, NHBA, or PorA). In the strain selection process, a given indicator strain was chosen if it expressed a homologous or closely related antigen and largely lacked the remaining three protein components [100,125–127]. As such, serum bactericidal activity in hSBA assays with these indicator strains represented immune responses directed at a particular vaccine antigen (Table 1) [100,125].

Long-term clinical studies were necessary to assess the immunogenicity of MenB-4C using these four serogroup B indicator strains. As such, an open-label multicenter study of previously vaccinated adolescents and young adults demonstrated that protective antibody responses (hSBA ≥1:4) persisted in 9% to 84% of Australian and Canadian subjects at 4 years and in 29% to 84% of Chilean subjects at 7.5 years after 2 primary doses of MenB-4C vaccination [128]. Importantly, the percentage of subjects who continue to maintain protective antibody responses (hSBA ≥1:4) varied depending on the serogroup B indicator strains assessed [128], suggesting that the use of indicator strains to measure vaccine immune responses may not capture the true breadth of response to circulating serogroup B strains.

In an effort to overcome limitations associated with the hSBA assay, MenB-4C breadth of coverage against serogroup B disease-causing strains was also evaluated using the novel Meningococcal Antigen Typing System (MATS) [129–131]. This system predicts the strain coverage for each antigen contained in MenB-4C by assessing the expression levels and cross-reactivity of FHbp, NadA, and NHBA antigens via enzyme-linked immunosorbent assays (ELISAs) and identifying the PorA genotype in panels of serogroup B disease isolates [125,131,132]. This method was built on the assumption that a given serogroup B strain is susceptible to vaccine-elicited antibody killing if it expresses a MenB-4C antigen in sufficient amounts [100]. In a MATS-ELISA, each antigen from a test serogroup B strain and reference serogroup B strain is

captured by specific polyclonal antibodies, with the difference in ELISA reactivity between strains defined as the relative potency (RP) of the antigen [131,132]. Coverage against serogroup B strains is then assumed when the RP is above the positive bacterial threshold (PBT) for an antigen, a value originally defined from the bactericidal activity of immunized infant sera in hSBA assays against 57 serogroup B strains [100,131]. Thus, in the MATS assay, an ELISA-defined RP above the PBT for ≥1 of the 3 antigens (FHbp, NadA, or NHBA) or a matched PorA genotype as identified by PCR demonstrates strain coverage [131].

Using the MATS assay, it has been estimated that 78% of approximately 1000 different invasive European serogroup B isolates are susceptible to antibodies induced by the MenB-4C vaccine [19], and evaluations from a European infant immunization program have estimated the vaccine as 64% effective against all serogroup B strains [133]. A study from Brazil tested a panel of 99 strains and demonstrated that the MATS predicted strain coverage at 81% [134]. Another study using a panel of 40 serogroup B strains representing 535 different isolates from England and Wales showed that MATS predicted MenB-4C coverage at 70% in immunized infants and adolescents [135]. Notably, this study showed that when using hSBA, the predicted MenB-4C strain coverage was higher at 88% for the same age groups [135]. Additionally, the study revealed that the MATS assay had a predicted accuracy of 78%; together these data suggest that MATS may underestimate MenB-4C strain coverage [135].

Using hSBA assays, a study in Santa Clara University students vaccinated with two doses of MenB-4C in response to a serogroup B outbreak in 2016 showed that 93% of the students achieved hSBA titers ≥1:4 against the Santa Clara University strain; 53% to 73% of these students had hSBA titers ≥1:4 against serogroup B outbreak strains from 3 different US institutions [136]. Another separate study showed that only 66% of MenB-4C–vaccinated students had protective titers (hSBA titer ≥1:4) against a particular serogroup B outbreak strain, despite MATS predicting higher coverage [137].

Additional real-world experience is provided by MenB-4C implementation in the England, which introduced routine infant vaccination in 2015 at a reduced 2-dose administration schedule. After the program was initiated, early estimates of vaccine coverage for both doses were high at 85% to 89% [138]. Within the first 10 months, the incidence rates of serogroup B disease among the vaccine-eligible cohorts of infants reduced by 50% compared with the 4 previous years [138]. Conversely, there was only an estimated non-significant 14% reduction in serogroup B cases in the unvaccinated cohort. Long-term data from the same study showed a 75% reduction in the number of cases of serogroup B disease in vaccine-eligible cohorts during the first 3 years of the immunization program [139]. Another study from Quebec, Canada, where a mass MenB-4C vaccination program was implemented in 2014 reported the estimated direct vaccine protection 4 years after the program was launched to be 79%, with an 86% overall reduction in IMD risk due to serogroup B at the provincial level [140].

Importantly, recent data using a single outcome measure 12 months after vaccination showed that MenB-4C did not have any effect on the carriage of disease-causing meningococci [141]. The real-world vaccine effectiveness studies described above show that direct protection against serogroup B disease is conferred by MenB-4C vaccine.

5. Recombinant MenB vaccine schedule

5.1. Vaccine posology

Currently, MenB-FHbp and MenB-4C are indicated for use in multiple countries [15–29,142]. Despite the overlap in the age of administration, it should be noted that these vaccines are clinically distinct and must not be given interchangeably (i.e. the same vaccine given initially should be used to complete the vaccination series) [143].

The approved schedules for MenB-FHbp and MenB-4C vary slightly by country, and therefore, healthcare professionals are encouraged to review their country's corresponding prescribing information. In the approved populations, MenB-FHbp can be administered in either a 2- or 3-dose schedule (Table 2) [16]. Generally, MenB-FHbp can be administered in two 0.5-mL doses, one each at 0 and 6 months; however, if more rapid immunity is required during a period of increased risk (i.e. during an outbreak) [143,144], a 3-dose schedule can be administered with ≥1 month between the first and second doses and a third dose ≥4 months after the second dose [17,20–22].

In countries other than the United States where MenB4-C is approved, the vaccine can be administered to infants beginning at 2 months of age (Table 2) [15,19,23–29]. Depending on the country, a 2- or 3-dose schedule is approved for infants aged 2 to 5 months, whereas older infants (aged 6–11 months) should receive 2 doses of MenB-4C; a booster dose is given at 12 to 23 months of age, administered 2–6 months after the

Table 2. General characteristics of immunization schedules for MenB vaccines*.

	Primary Immunization Schedule (Interval Between Doses)	
Age at First Dose	MenB-4C [15,19,23–29]	MenB-FHbp [16,17,20–22,179]
Infants 2–5 mo	3 doses (≥1 mo) or 2 doses (≥2 mo)	Not approved
Infants 6–11 mo	2 doses (≥2 mo)	Not approved
Toddlers 12–23 mo	2 doses (≥2 mo)	Not approved
Children 2–10 y	2 doses (≥1 mo)†	Not approved
Adolescents and adults‡ ≥10 y	2 doses (≥1 mo)	2 doses (6 mo) or 3 doses (≥1 mo between doses 1 and 2; ≥4 mo between doses 2 and 3)

*The approved MenB-4C and MenB-FHbp immunization schedules are dependent on the country. Healthcare professionals are encouraged to view their country's specific prescribing information for exact details.
†Brazil, Chile, Israel, and Uruguay recommend a ≥2-mo interval between doses.
‡In the United States, MenB-4C and MenB-FHbp are currently approved only for adolescents and young adults aged 10–25 years; MenB-4C is approved in a 2-dose (interval, ≥1 mo) schedule, and MenB-FHbp is approved in a 2-dose (0, 6 mo) and 3-dose (0, 1–2, 6 mo) schedule.

primary series depending on age and country in which vaccination is administered [15,19,23–29]. MenB-4C can be administered to toddlers, children, adolescents, and adults outside the United States in a 2-dose schedule; the 2-dose schedule is supported by studies demonstrating that antibody persistence and booster responses are similar between infants receiving a MenB-4C vaccine as 2-dose or 3-dose schedule [146]. In the United States, MenB-4C administered in a 2-dose schedule is approved for individuals aged 10 to 25 years only; in Canada, the vaccine is approved only for patients 2 months to 25 years of age.

5.2. Concomitant administration

The immunogenicity and safety of concomitant administration of MenB vaccines with meningococcal and nonmeningococcal vaccines have been investigated in the approved populations. In adolescents, the coadministration of MenB-FHbp with MenACWY-D (a MenACWY vaccine; see section 2.2) and Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine) met noninferiority criteria for immunogenicity and was considered safe [147]. Similar results were observed for concomitant administration of MenB-FHbp with Tdap and inactivated poliovirus vaccine (Tdap/IPV) and quadrivalent human papillomavirus vaccine (HPV4) [148,149]. No concomitant administration studies for MenB-4C in adolescents or young adults have been published.

Notably, clinical studies of MenB-4C in infants have demonstrated safety and noninferior antibody responses when coadministered with diphtheria-tetanus-acellular pertussis, IPV, and hepatitis B plus *Haemophilus influenzae* type b vaccine (DTaP-IPV-HBV/Hib), seven-valent pneumococcal conjugate vaccine (PCV7), measles-mumps-rubella vaccine, varicella vaccine, MenACWY vaccine, and MenC-CRM vaccine [150–152].

5.3. Safety

Although not the focus of this review, the safety of both the MenB-FHbp and MenB-4C vaccines has been demonstrated. For MenB-FHbp, the most frequently reported local or systemic safety events in individuals aged ≥10 years were injection site pain, headache, and fatigue [95,149,153]; recent studies exploring the safety of MenB-FHbp in children aged 1 to 9 years have been completed, with preliminary analyses suggesting that the vaccine is generally safe and tolerable in this age group [154,155].

Similarly, after MenB-4C vaccination in infants, toddlers, and children, injection site tenderness, pain, and erythema were the most commonly reported local reactions, and irritability was the more frequently reported systemic reaction [151,156–160]. Of note, a systematic review of 14 studies describing adverse events following MenB-4C vaccination showed that fever was reported in 48% of the infants after MenB-4C vaccination [161]. A separate study reported an overall increase in the incidence of fever ≥39°C following concomitant administration of MenB-4C and other routine infant immunizations [162]. However, there is evidence to suggest that fever in infants following MenB-4C immunization can be successfully managed through prophylactic acetaminophen use without any reduction in immune responses to the vaccine [163]. For adolescents and adults, injection site pain, malaise, and headache were the most commonly reported local and systemic events following MenB-4C vaccination [19,164].

6. Discussion

One of the best ways to combat serogroup B disease is large-scale prevention by vaccination, which can curtail the spread and outbreak of infection [6,77]. This review aims to inform pediatricians and others prescribing meningococcal vaccines on how MenB vaccines have been carefully developed and extensively evaluated for prevention against serogroup B disease.

Traditionally, meningococcal vaccines were designed to target the capsular polysaccharide of a particular serogroup [14], a proven strategy to reduce meningococcal disease transmission and incidence [165–167]. However, because the capsular polysaccharide of meningococcal serogroup B strains was not a suitable target for vaccine production [13,14], innovative approaches to identify unique subcapsular protein antigens were thus undertaken to generate 2 different recombinant MenB vaccines, MenB-4C and MenB-FHbp.

The MenB-4C and MenB-FHbp vaccines are both predicted to protect against the significant diversity of circulating serogroup B strains, with real-world experience also providing evidence that these vaccines are valuable tools to combat serogroup B disease. However, despite the utility of MenB vaccines, barriers to their use remain in the clinic. For example, one study in the United Kingdom reported that while most parents recognized meningitis as a life-threatening disease, many were not aware of the MenB vaccine [168]. In the United States, studies have indicated that healthcare providers are not frequent prescribers of MenB vaccines, potentially because of a general lack of knowledge of serogroup B disease and the available vaccines as well as an inability to define official vaccination guidelines [30,31]. In Greece, where MenB vaccination is not included in the national immunization plan, pediatricians may hesitate to recommend vaccination to parents owing to high out-of-pocket costs [169]. In Spain, despite the availability of the MenB vaccine through the private market, the low national healthcare budget dedicated to vaccines may preclude the inclusion of the MenB vaccine into a publicly funded program [170]. The need for more than one dose for primary immunization may also be seen as a disadvantage by healthcare providers.

Existing recommendations for other meningococcal vaccines (such as a MenACWY vaccine, which does not protect against serogroup B) could also play an important role in lowering the likelihood of prescribing MenB vaccines [30]. This gap in providers' knowledge of meningococcal vaccines is notable because they are key liaisons between patients and healthcare systems and are vital in promoting meningococcal vaccination and reducing disease burden. Providing clear vaccination guidelines and informing healthcare professionals of the breadth of coverage afforded by each meningococcal vaccine may help to ensure that patients are fully vaccinated and comprehensively protected against IMD caused by

multiple serogroups. In fact, in South Australia, a statewide MenB vaccination program was recently launched with the goal of immunizing individuals from 6 weeks to 21 years of age [171]. Such a large-scale program is unprecedented within both the Australian and global contexts and could provide a blueprint for MenB vaccination programs to other countries in the future.

Differences in the use of MenB and MenACWY vaccines are evident among US adolescents where vaccine completion rates for MenB vaccines remain low while those for MenACWY vaccines in the same age group are high [32]. Importantly, routine MenACWY use in the United States has helped reduce the incidence of meningococcal disease caused by serogroups A, C, W, and Y [166]. The successful introduction of MenACWY vaccines into the country highlights the importance of meningococcal vaccination and may also provide key insight into how clear guidelines for healthcare providers can translate into effectively ensuring their patients are adequately protected against disease.

Determining ways to improve vaccine coverage/completion rates so populations are protected against all meningococcal serogroups, including serogroup B, remains an unmet need globally. As MenB and MenACWY vaccines cover most disease-causing serogroups [5], guidelines that include concomitant administration of these two vaccines can help protect against the majority of meningococcal disease worldwide and would likely improve compliance by requiring fewer medical visits [172–174]. Alternatively, a single pentavalent MenABCWY vaccine, currently in development [175,176], could potentially simplify existing meningococcal vaccine recommendations and increase the convenience of vaccination to optimize the protection of those at risk [32,177].

7. Conclusion

Two distinct protein-based MenB vaccines are now available in multiple countries to protect against IMD caused by serogroup B, a condition causing serious public health concern worldwide. These vaccines were developed using independent and innovative approaches to ensure protection against the diversity of disease-causing serogroup B strains. This review provides an informative overview of the available MenB vaccines to help guide healthcare practitioners, particularly those treating children and adolescents, to ensure that vulnerable individuals are adequately protected against this debilitating disease.

8. Expert opinion

Although uncommon, IMD is unpredictable, rapidly progressing, and potentially fatal, with up to 20% of the survivors experiencing long-term physical or intellectual impairments [1,3]. An effective strategy to combat IMD is prevention through immunization with meningococcal vaccines that target the major disease-causing serogroups (A, B, C, W, X, and Y) [3,6,77]. Until recently, meningococcal vaccines were limited to targeting serogroups A, C, W, and Y, while the globally prevalent disease-causing serogroup B eluded a suitable vaccination approach [91]. The development and evaluation of two different recombinant protein-based MenB vaccines represent a significant triumph over particularly challenging design hurdles and, when used in conjunction with MenACWY vaccines, provide healthcare professionals with the tools to comprehensively protect their patients against the multiple causes of a potentially devastating disease. However, difficulties remain in increasing awareness of the utility of MenB vaccines to healthcare providers. Providers, especially pediatricians, are integral factors in promoting patient vaccination and prevention of disease. Informing providers of the nuances of meningococcal vaccines and the importance of MenB vaccination will be vital in further reducing the global incidence of IMD.

During the next 5 years, we expect that the large-scale implementation of MenB vaccination will drive population-based surveillance studies that will provide more real-world data on the effectiveness of both MenB vaccines. While MenB vaccine effectiveness against IMD has already been shown in some regions [138–140], we anticipate such studies will show minimal, if any, effect of MenB vaccines on the meningococcal carriage. Specifically, previous studies conducted after MenB vaccination campaigns at US universities experiencing serogroup B outbreaks have indicated that MenB-4C and MenB-FHbp may have limited effects on carriage [178,179]. The most recent study from Australia demonstrated no meaningful differences in serogroup B carriage prevalence between individuals vaccinated with MenB-4C and those who were unvaccinated [141]. Based on these data, it stands to reason that vaccination with MenB-FHbp may not lead to any meaningful reductions in the carriage, although definite conclusions await real-world evidence. These data further suggest that MenB vaccination strategies should focus on the direct protection of individuals against disease.

We also anticipate future clinical studies will further investigate the duration of protection afforded by both MenB vaccines and the optimal use of booster doses to ensure protection throughout an individual's lifetime. Although vaccine-elicited immune responses have been shown to decline following MenB vaccination, studies have shown that immune responses in adolescents can persist up to 4–7.5 years after MenB-4C primary vaccination and up to 4 years following MenB-FHbp vaccination [120,128]; however, it should be noted that results from clinical studies on the antibody persistence of the 2 vaccines cannot be directly compared as the vaccines are compositionally different. Booster doses of either MenB-4C or MenB-FHbp have also been shown to be immunogenic [120,128], and the ability of MenB vaccines to provide sustained protection against disease appears promising.

We also expect that studies in the next 5 years will examine the potential for MenB vaccines to provide protection against additional meningococcal serogroups or perhaps even other *Neisseria* species [107]. Preliminary studies have suggested that both MenB vaccines could elicit immune responses against other meningococcal serogroups, including serogroup X [172,173]. A retrospective study from New Zealand examined whether MenB vaccination could be protective against diseases caused by other *Neisseria* species and found that individuals immunized with an OMV MenB vaccine were significantly less likely to be hospitalized due to *N gonorrhoeae* infection [107]. In addition, as noted above, pentavalent

MenABCWY vaccines are currently in development, which should simultaneously protect individuals against the five common disease-causing serogroups [175,176]. Both MenB-4C and MenB-FHbp contain FHbp, which is found in most IMD strains across serogroups [15,16,91]. Overall, the newly available recombinant protein-based MenB vaccines are promising prophylactic interventions for physicians to combat IMD and potentially diseases caused by other *Neisseria* species.

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Author contribution statement

MAS, FM-T, LS, CB, and JP contributed to the concept of the review. MAS, FM-T, LS, CB, and JP drafted the article. All authors critically revised the article and approved the final version.

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