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Review

# Potential benefits of using a multicomponent vaccine for prevention of serogroup B meningococcal disease

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ABSTRACT

Meningococcal serogroup B (MenB) has become the main cause of invasive meningococcal disease in industrialized countries in recent years. The diversity of MenB strains and poor immunogenicity of the MenB capsular polysaccharide have made vaccine development challenging. Two MenB vaccines, including factor H binding protein (fHbp) as a major antigenic component, are now licensed for use. In addition to fHbp variant 1, the multicomponent vaccine 4CMenB contains neisserial heparin binding antigen, *Neisseria* adhesin A, and outer membrane vesicles containing porin A. The vast majority of circulating MenB strains contain genes encoding at least one 4CMenB component and many express genes for more than one vaccine antigen. Recent studies have suggested that serum bactericidal activity is enhanced against strains that express two or more vaccine antigens. Bacterial killing may also occur when antibodies to vaccine components are collectively present at levels that would individually be sub-lethal. The evaluation of immune responses to separate vaccine components does not take cooperative activity into account and may underestimate the overall protection. Available data on 4CMenB effectiveness indicate that this multicomponent vaccine affords broad coverage and protection against MenB disease. 4CMenB also has the potential to protect against disease caused by non-MenB meningococci and *Neisseria gonorrhoeae*.


**Contents**



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## Introduction

Invasive meningococcal disease (IMD) remains an important cause of morbidity and mortality worldwide, across all ages. The disease is caused by *Neisseria meningitidis*, a human-specific bacterium, for which 12 serogroups have been identified. These serogroups are classified on the basis of their capsular polysaccharide. Meningococcal serogroups A, B (MenB), C, W, Y, and more recently X, account together for almost all IMD (Borrow et al., 2017). IMD incidence varies by age, being highest in infants and toddlers. In certain populations, a second incidence peak is observed in adolescents and young adults, who are also the main carriers of *N. meningitidis* (Borrow et al., 2017).

MenB is a prominent cause of IMD in industrialized countries, especially where the introduction of monovalent or tetravalent conjugate polysaccharide vaccines has reduced the incidence of serogroups A, C, W, and Y. In Europe, 54% of IMD cases were caused by MenB in 2016 (European Centre for Disease Prevention and Control, 2018). In the USA, nearly 70% of IMD cases among persons aged 16–23 years were caused by MenB in 2017 (Centers for Disease Control and Prevention, 2017).

Two broadly-protective MenB vaccines, MenB-FHbp (Trumenba, Pfizer) (Perez et al., 2018) and 4CMenB (Bexsero, GSK) (O'Ryan et al., 2014), are currently approved for use in several countries worldwide. Despite having been developed independently, both vaccines include factor H binding protein (fHbp) as a major antigenic component. Three distinct variants of fHbp have been described, namely variants 1, 2, and 3, which have been alternatively classified as subfamilies, with subfamily B containing variant 1 and subfamily A containing variants 2 and 3 (Rappuoli et al., 2018). The three variants are immunologically distinct and do not induce cross-protective antibodies, although some low cross-reactivity has been evidenced between variants 2 and 3 (Seib et al., 2011). MenB-FHbp includes two lipidated fHbp components, representing variants 1 and 3 (belonging to subfamilies B and A, respectively). 4CMenB contains fHbp variant 1 (presented as a fusion protein with GNA2091 accessory protein) plus three additional antigenic components: neisserial heparin binding antigen (NHBA) fused with accessory protein GNA1030, *Neisseria* adhesin A (NadA), and outer membrane vesicles (OMV) obtained from the *N. meningitidis* epidemic strain NZ98/254, expressing porin A (PorA) serosubtype P1.4 (O'Ryan et al., 2014). In this paper, we discuss the four antigenic components of 4CMenB and the potential benefits of using this multicomponent vaccine to prevent IMD caused by diverse MenB strains.

## Role and contribution of fHbp

fHbp is a lipoprotein expressed on the surface of the meningococcus that binds human complement regulatory factor H, thus allowing the bacterium to escape complement killing and survive in human blood. fHbp is expressed in vivo during the disease process and can induce bactericidal antibodies. Three major genetic and immunological fHbp variants are distinguished, with limited antigenic cross-reactivity: variant 1 (corresponding to subfamily B according to a different classification) and variants 2 and 3 (both classified in subfamily A). Variant 1 is expressed by the majority of MenB disease-causing isolates worldwide, while genes encoding variants 2 or 3 are present in the remainder (Murphy et al., 2009; Pajon et al., 2010). While fHbp is present in nearly all meningococcal disease-causing strains, its expression can vary greatly among strains (at least 15-fold), with variant 2 and 3 strains expressing significantly less fHbp than variant 1 strains (Biagini et al., 2016). The level of fHbp expression has been found to be a key determinant of bactericidal susceptibility to anti-fHbp antibodies (Jiang et al., 2010). Preclinical studies have indicated that as many as 19% of strains expressing fHbp variant 2 or 3 may not be susceptible to bactericidal killing by MenB-fHbp-induced antibodies because they express insufficient antigen on the cell surface (McNeil et al., 2018). Similarly, protection would not be expected against strains that do not express fHbp. Meningococcal strains that remain virulent despite having a truncated or absent fHbp gene have already been evidenced (Lucidarme et al., 2011), suggesting that fHbp may be expendable for *N. meningitidis*. However, such strains are extremely rare, and there is currently no evidence to suggest that the introduction of protein-based MenB vaccines will exert selective pressure.

## Role and contribution of additional antigens: NadA, NHBA, and PorA

Recognizing that a vaccine containing fHbp variant 1 alone would not provide sufficiently broad strain coverage, three additional components targeting different mechanisms of MenB pathogenesis and survival were selected for inclusion in 4CMenB: the NHBA and NadA proteins and OMV.

NHBA is a surface-exposed lipoprotein expressed by most meningococcal strains (Lucidarme et al., 2010; Tsang et al., 2015; Wang et al., 2011) and by other *Neisseria* species (Muzzi et al., 2013). Binding to heparin has been shown to improve the pathogen's survival in blood and to mediate adhesion to epithelial cells (Serruto et al., 2010; Vacca et al., 2016). NHBA peptide sequence can vary considerably, but cross-protection has been demonstrated across a variety of NHBA variants (Giuliani et al., 2010). 4CMenB includes NHBA variant 1.2.

NadA is an auto-transporter adhesin believed to play an important role in nasopharyngeal colonization and bacterial invasion (Capecchi et al., 2005). Recent data showed that 27% of IMD MenB isolates, collected from 17 different countries between 2000 and 2016, harbored the *NadA* gene (Muzzi et al., 2019). However, this may vary over time and by geographic region. In the UK for example, the percentage of isolates harboring a functional *NadA* gene increased from 5.8% in 2007–2008 to 8.0% in 2014–2015 (Parikh et al., 2017). Among the six variants identified, NadA1, NadA2, and NadA3 have been found to be highly immunogenic and to elicit cross-reactive antibodies with serum bactericidal activity (Bambini et al., 2014; Comanducci et al., 2002 Comanducci et al., 2002). 4CMenB includes NadA subvariant 3.1.

The fourth major component of 4CMenB, OMV derived from a MenB outbreak strain, was previously used to control epidemic disease in New Zealand (Oster et al., 2005). The main reason for including OMV in 4CMenB was to cover sequence type (ST) 41/44 clonal complex strains, especially those expressing the homologous variant P1.4 PorA. However, during early clinical development, the inclusion of OMV in combination with the other antigenic components (NadA, NHBA, and fHbp) was proved to confer broader immunogenic benefits (Bai et al., 2011). This may be due to responses against non-PorA components of OMV, cooperativity between antibodies induced by OMV and other antigenic components, or to the OMV having an adjuvant property (Bai et al., 2011; Giuliani et al., 2010). Other non-PorA components of OMV, such as the outer membrane protein complex, the iron-regulated ferric enterobactin transporter, porin B, and lipo-oligosaccharide might also induce serum bactericidal activity (Holst et al., 2009).

Two accessory antigens fused to fHbp (GNA2091) and NHBA (GNA1030) were included in the final 4CMenB formulation, primarily to improve antigen stability. They have been shown to induce bactericidal antibodies and protection in animal models (Serruto et al., 2012), and may also contribute to the overall immunogenicity of 4CMenB.

## Contribution of individual 4CMenB antigens to the coverage of diverse MenB strains

MenB strains are highly diverse in the sequence and level of expression of their surface proteins. Therefore, an individual MenB strain may express none, some, or all of the antigens targeted by 4CMenB. A MenB strain sufficiently expressing at least one surface protein that is adequately cross-reactive with a vaccine component may be susceptible to killing by vaccine-induced antibodies, and thus predicted to be 'vaccine-covered'. The meningococcal antigen typing system (MATS) assay has been developed to estimate the breadth of coverage of MenB strains by 4CMenB (Medini et al., 2015). MATS estimates the quantity of antigen expressed by a MenB strain and the extent of cross-reactivity with the corresponding vaccine component. A MATS analysis of 442 disease-causing MenB isolates collected in the USA predicted that 91% of strains would be covered by 4CMenB, with coverage varying little year-to-year. NHBA was found to cover the most strains (83%), followed by fHbp (53%), PorA (5.9%), and NadA (2.5%) (Rajam et al., 2017). As expected, the 4CMenB fHbp component contributed strongly to the coverage of strains expressing fHbp variant 1, but provided almost no coverage of strains expressing fHbp variants 2 and 3 (approximately 40% of the panel). Importantly, 83% of these strains were estimated to be covered by non-fHbp components of 4CMenB (Rajam et al., 2017).

MATS-based estimates of 4CMenB coverage range from 68% to 89% in European countries and from 66% to 91% in Australia, Canada, Brazil, and the USA (Abad et al., 2016; Medini et al., 2015; Parikh et al., 2017; Rajam et al., 2017; Simoes et al., 2017; Tzanakaki et al., 2014; Vogel et al., 2013; Wasko et al., 2016), with an overall estimated coverage of 81% calculated for a sample size of 3912 invasive MenB strains, collected from 17 different countries (Muzzi et al., 2019). Antibodies induced by the NHBA and fHbp components of 4CMenB have been consistently observed to make the highest contribution to coverage.

## Contribution of individual 4CMenB antigens to vaccine immunogenicity and antibody persistence

Immunological data have been comprehensively and extensively reviewed elsewhere (Rappuoli et al., 2018; Toneatto et al., 2017; Watson and Turner, 2016). In summary, robust immune responses to each individual component of 4CMenB have been demonstrated in clinical studies across age groups, including in infants, toddlers, and adolescents. Booster vaccination after priming in infancy or adolescence has also been demonstrated to induce robust responses to all four antigens, indicating an anamnestic response.

Antibody persistence has been evaluated up to 36 months following vaccination during infancy. hSBA titers $\geq$5 across vaccine antigens were found to be maintained for 9–97% and 10–90% of children vaccinated according to a 3 + 1 schedule at 2, 4, 6, and 12 months and 2, 3, 4, and 12 months of age, respectively (Iro et al., 2017). A study comparing 2 + 1 (at 3.5, 5, and 11 months or 6, 8, and 11 months of age) and 3 + 1 schedules (at 2.5, 3.5, 5, and 11 months of age) showed that similar percentages of children (38–93% and 36–84%) maintained hSBA titers $\geq$4 at 24–36 month post-vaccination (Martinon-Torres et al., 2018). A consistent observation across studies is that long-term antibody persistence is the highest for NadA and the lowest for PorA. However, the clinical relevance of the poor antibody persistence for PorA remains unclear, especially since the vaccine has demonstrated 82.9% effectiveness against all MenB cases in infants, within 10 months from implementation in the national immunization program in the UK and despite the use of a 2 + 1 schedule instead of the licensed 3 + 1 one (Parikh et al., 2016).

More recent data following the administration of approximately three million doses also indicate that protection lasts from the two-dose primary vaccination up until the booster dose, administered at 12 months of age (Joint Committee on Vaccination and Immunisation (JCVI), 2018). Nevertheless, one-dose effectiveness of 4CMenB over the 10-month period was estimated to be only 22.0% (Parikh et al., 2016). This finding was not unexpected, as the immune responses following administration of a single dose of 4CMenB were observed to be lower than those following two doses. In infants aged 2.5–6 months at first vaccination, hSBA titers $\geq$4 were achieved by 62–82% versus 100% of children for fHbp, 91–95% versus 100% for NadA, 39–43% versus 98–99% for PorA, and 21–36% versus 49–77% for NHBA, at 1 month after a single 4CMenB dose versus a two- or three-dose primary series (Martinon-Torres et al., 2017).

Emerging data from the MenB vaccination program in the UK show that vaccination with 4CMenB according to a 2 + 1 schedule provides protection at least until the end of the second year of life (Joint Committee on Vaccination and Immunisation (JCVI), 2018), covering the period of highest age-based risk of meningococcal disease. Our understanding of the longevity of disease protection in infants will continue to develop as more data become available.

The persistence of antibodies after 4CMenB vaccination has also been evaluated in several clinical studies across different age groups and geographies. Studies in adolescents and young adults showed that although antibody levels declined after 4CMenB vaccination, antibodies against all vaccine antigens were evidenced up to 7.5 years post-primary vaccination, regardless of the vaccination schedule used (Nolan et al., 2018b). As for infants, differences between waning rates of antibodies induced by each component of 4CMenB have also been observed for adolescents and young adults (Nolan et al., 2018a; Santolaya et al., 2013; Snape et al., 2013a,b). Notably, antibodies to NHBA and NadA declined more slowly after primary 4CMenB vaccination than antibodies to fHbp and PorA.

The finding that some individuals maintain circulating NHBA and NadA antibodies at protective levels for several years after primary vaccination highlights the potentially important role that these non-fHbp vaccine components may have in terms of long-term clinical disease protection. Antibodies elicited by any one of the individual vaccine antigens may be sufficient to provide protection against an invasive strain, depending on the type and amount of antigen expressed by the pathogen. Whilst it is desirable for antibodies to each vaccine component to be maintained as long as possible to ensure broad coverage against antigenically diverse endemic strains, sustained protection against specific individual strains may not require high levels of circulating antibodies to all four components.

## Cooperative activity of antibodies induced by 4CMenB antigens

The killing of meningococci by vaccine-induced antibodies requires that the binding of antibodies to the bacterial cell surface is sufficient to activate complement. In this regard, the capacity of 4CMenB to induce antibodies that simultaneously bind multiple targets may be beneficial. While a strain may be susceptible to killing if it expresses only one vaccine-matched antigen, serum bactericidal activity is enhanced against strains that express two or more vaccine antigens. All MenB IMD strains contain genes encoding at least one 4CMenB component; however, most of them express genes for more than one antigen. In itself, the presence of antigen-encoding genes is not directly predictive of a strain's susceptibility to antibody-mediated killing, since this depends critically upon the bacterial antigen being sufficiently expressed and cross-reactive with the vaccine variant. However, the presence of genes encoding several antigens very likely increases the

number of targets for surface-binding by 4CMenB-elicited antibodies (Toneatto et al., 2017).

Notably, among the 442 USA MenB mentioned previously, 42% were simultaneously covered by two vaccine antigens, and 6% were covered by three antigens (Rajam et al., 2017). In a recent study, the evaluation of monoclonal antibodies elicited by 4CMenB vaccination showed that they were cross-reactive against different antigen variants and recognized multiple epitopes on each of the antigens. Antibodies targeting different epitopes demonstrated synergy, enhancing the potency of the bactericidal response (Giuliani et al., 2018). A different, previous study had already postulated that antibodies against fHbp and NHBA, which show no bacterial killing independently, may display cooperative bactericidal activity against meningococcal strains expressing both antigens (Vu et al., 2011). Taken together, these findings indicate that the immune responses to 4CMenB evaluated using antigen-specific test strains potentially underestimate the level of protection provided, since the cooperative effect of multiple antibodies in vivo is not taken into account (Frosi et al., 2013).

## Potential for 4CMenB to offer protection beyond MenB disease

All four antigens contained in 4CMenB are shared with other clinically relevant *N. meningitidis* serogroups (Wang et al., 2011), highlighting the potential for the vaccine to provide broader disease protection. As an example, 4CMenB was shown to induce cross-protective antibodies against serogroup W ST11 strains circulating in England and Wales. Since these strains expressed fHbp and PorA variants that were clearly mismatched with vaccine antigens, the observed cross-protection must be attributed to NHBA and NadA, individually or in combination (Ladhani et al., 2016). Such cross-protection may prove important, as hypervirulent serogroup W ST11 strains have recently emerged in Europe, Australia, and South America. Additional studies of serogroup C, X, and Y strains from various countries have highlighted varying degrees of susceptibility to killing by pooled serum from infants and adolescents vaccinated with 4CMenB (Hong et al., 2013; Tomei et al., 2014). For instance, bactericidal killing was observed against 45–90% of serogroup C, Y, and W strains collected in UK, Germany, France, and Brazil (Tomei et al., 2014).

4CMenB may also offer some degree of protection against diseases caused by other related species, including *Neisseria gonorrhoeae* (Hadad et al., 2012). In New Zealand, a vaccine containing the same OMV component as 4CMenB was used to control a prolonged MenB epidemic between 2004 and 2008 (Arnold et al., 2011). A retrospective case–control study estimated a vaccine effectiveness of 31% in preventing gonorrhea infection among fully vaccinated 15–30-year-olds (Petousis-Harris et al., 2017), showing the potential of OMV vaccines to reduce the incidence of gonorrhea. In addition, other non-OMV components of 4CMenB could further contribute to cross-protection, in particular NHBA, which is highly conserved across gonococcal strains (Comanducci et al., 2002; Hadad et al., 2012; Semchenko et al., 2018). Given growing concerns relating to gonococcal infections and the threat of antimicrobial resistance, any disease reduction attributable to 4CMenB use would be highly desirable from a public health perspective.

## 4CMenB universal mass vaccination—challenges and opportunities

The epidemiology of meningococcal disease is diverse, with important variations from one geographical region to another, across age groups, and over time. The impossibility of designing a highly immunogenic polysaccharide-based vaccine against MenB makes the molecular and serological diversity of MenB strains particularly relevant. The development of 4CMenB by reverse vaccinology to identify potential antigens based on their level of expression and surface localization/secretion constituted an important success in the effort to control and prevent meningococcal disease. The vaccine has already demonstrated broad coverage against clinically relevant MenB strains (Muzzi et al., 2019) and has been implemented in the national immunization program in the UK, Ireland, and Italy. However, as the pathogen continues to evolve, potential changes in the antigen expression of circulating strains are anticipated. Data so far are encouraging, with 4CMenB maintaining consistent coverage worldwide and over time, as predicted by MATS (Muzzi et al., 2019) and confirmed by field effectiveness data from the UK, where a 60% reduction in the estimated number of cases of MenB IMD in infants was observed in the third year of the 4CMenB vaccination program (Joint Committee on Vaccination and Immunisation (JCVI), 2018).

A number of unknowns persist, such as the exact duration of protection afforded against the disease, effectiveness in other age groups, and the impact on carriage, but these knowledge gaps are gradually being addressed as clinical experience increases and evolves. The latest analysis of the UK data showed that protection is afforded up to at least the second year of life following two-dose vaccination in infants (Joint Committee on Vaccination and Immunisation (JCVI), 2018), thus covering the period of highest susceptibility to meningococcal disease. At the moment, evidence is insufficient to support the impact of 4CMenB vaccination on carriage, although a study in adolescents showed a significant reduction in MenB, MenC, MenW, and especially MenY carriage rates following vaccination with a two-dose series (Read et al., 2014). A larger trial, currently ongoing in Australia, will afford further data on the impact of 4CMenB on pharyngeal meningococcal carriage in adolescents (Marshall et al., 2018).

Unless and until a substantial impact of 4CMenB on meningococcal carriage is demonstrated, mass vaccination programs should continue to target the direct protection of higher-risk age groups, i.e., infants and adolescents. A vaccination program targeting infants alone has already proven successful in reducing MenB disease. Future vaccination programs targeting both infants and adolescents, such as the one recently initiated in South Australia, may prove to be even more effective in providing rapid and sustained control of serogroup B meningococcal disease. If 4CMenB is shown to impact pharyngeal carriage, then its use in adolescents may have the additional benefit of interrupting transmission and providing indirect protection to unvaccinated individuals. The widespread use of 4CMenB in adolescents also raises the possibility of a wider public health benefit if the vaccine is effective in preventing infections caused by *N. gonorrhoeae*.

## Conclusions

Data on the effectiveness of 4CMenB continue to accumulate as vaccination programs are implemented across various countries and in different age groups. In individuals 2 months to 20 years of age, 4CMenB vaccination led to a significant reduction in relative disease risk (0.22), at 2 years after the start of a mass vaccination campaign in the Saguenay-Lac-Saint-Jean region of Canada (De Wals et al., 2017). A two-dose vaccine effectiveness of 82.9% was also estimated following the implementation of 4CMenB in the national immunization program in the UK, over 10 months of use in infants (Parikh et al., 2016). Alongside the growing body of clinical evidence, our understanding of how each of the individual vaccine antigens may contribute and cooperate also continues to evolve. Available data suggest this rationally designed multicomponent vaccine offers broad coverage and effective disease protection. Other benefits of this approach may become manifest as usage grows.

## Author contributions

All authors participated in the development and the review of the manuscript and approved the final submitted version.

## Conflict of interest

All authors are employees of and hold shares in the GSK group of companies.

## Trademarks

Bexsero is a trademark owned by or licensed to the GSK group of companies. Trumenba is a trademark of Pfizer Inc.

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