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REVIEW

Immunogenicity and safety of meningococcal vaccines, MenACWY-CRM and 4CMenB, in groups at increased risk for meningococcal disease

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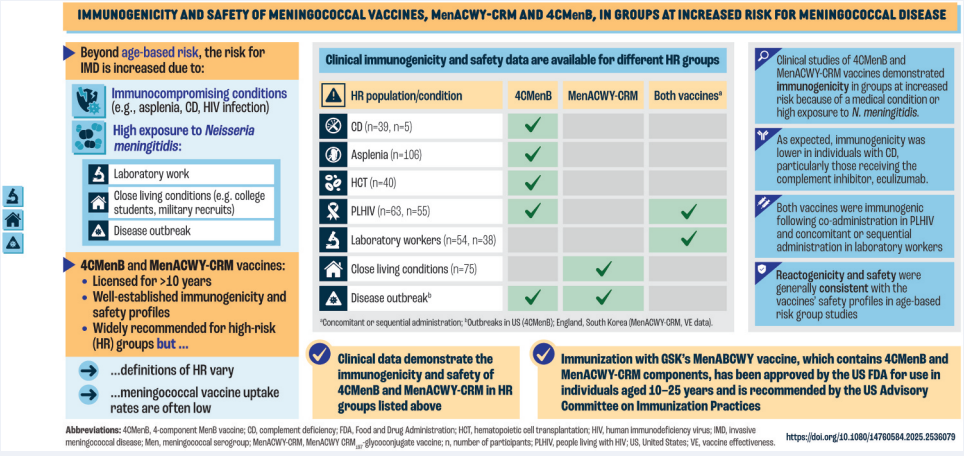
ABSTRACT

Introduction: Individuals with immunocompromising conditions (e.g. asplenia, complement deficiency, HIV infection) or with high exposure to *Neisseria meningitidis* (e.g. laboratory workers, those in outbreak settings) have an increased risk of meningococcal disease. Immunization with meningococcal serogroups ACWY (MenACWY) and serogroup B (MenB) vaccines is recommended for high-risk groups in many countries, although definitions of high-risk vary. There are not yet clinical data for the pentavalent meningococcal serogroups ABCWY (MenABCWY) vaccines in high-risk populations.

Areas covered: This review examines studies conducted in high-risk groups with the component vaccines of GSK's MenABCWY vaccine, the 4-component MenB vaccine (4CMenB) and quadrivalent MenACWY CRM_{197}-glycoconjugate vaccine (MenACWY-CRM). These component vaccines have been licensed for more than 10 years and are recommended in groups categorized as high risk.

Expert opinion: The component vaccines of GSK's MenABCWY vaccine, 4CMenB and MenACWY-CRM, have demonstrated immunogenicity and safety in high-risk groups, including with concomitant or sequential vaccine administration. As expected, immunogenicity was reduced in patients with complement deficiencies, particularly those receiving eculizumab. Further data are required on meningococcal vaccination in high-risk groups for the future refinement of national and regional recommendations and to support proactive approaches to improve vaccine uptake in high-risk groups.



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1. Introduction

Six *Neisseria meningitidis* serogroups (A, B, C, W, X, and Y) are responsible for almost all invasive meningococcal disease (IMD) cases [1]. Most cases occur in infants, children aged 1–4 years, and adolescents/young adults [2,3], and an increasing incidence in older adults has been reported in some countries [2,4]. The risk for IMD is also raised in association with certain medical conditions, with an increased risk compared with the general population ranging from 2.5- to 13-fold for people living with human immunodeficiency virus (HIV) [5–11] to up to 10,000-fold for those with persistent complement component deficiencies [12] (Figure 1). Additionally, an increased risk for IMD occurs following high exposure to *N. meningitidis*. This can occur due to a person's occupation, such as microbiologists routinely exposed to *N. meningitidis* isolates, or travel to hyperendemic or epidemic countries, and certain groups, including military recruits and college students, have an increased risk of IMD outbreaks because of close living conditions and social activities [13–15].

Meningococcal vaccines are recommended for high-risk groups in many countries, but there are national and regional

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Article highlights

- Data from the last decade show 4CMenB and MenACWY-CRM vaccines are immunogenic and well tolerated in groups at increased risk because of a medical condition or high Neisseria meningitidis exposure.
- Immunogenicity was reduced in patients with complement deficiencies, particularly those receiving eculizumab, although some increase in bactericidal antibody titers was observed.
- Evidence supports concomitant or sequential 4CMenB and MenACWY-CRM vaccine administration in high-risk groups.
- In general, the vaccines' safety profiles were consistent with those established from studies of age-based risk groups.
- A new MenABCWY vaccine containing 4CMenB and MenACWY-CRM as components has been approved by the US FDA for use in individuals aged 10–25 years and is recommended by the US Advisory Committee on Immunization Practices.

differences in specific populations defined as being at increased risk [16]. This might be due to various factors, but a major contributor is likely to be the lack of evidence for the immunogenicity and safety of meningococcal vaccines in populations other than those with an age-based increased risk [13]. In this article, we focus on the available evidence for the multicomponent meningococcal serogroup B vaccine (4CMenB; *Bexsero*, GSK) and the quadrivalent MenACWY CRM_{197}-glycoconjugate vaccine (MenACWY-CRM; *Menveo*, GSK), in view of the recent approval by the United States (US) Food and Drug Administration (FDA) of the pentavalent MenABCWY vaccine (*Penmenvy*, GSK) that contains both vaccine components [17,18]. Another pentavalent vaccine (*Penbraya*, Pfizer) contains components of the bivalent MenB vaccine, MenB-FHbp (*Trumenba*, Pfizer), and MenACWY

Figure 1. Groups at increased risk for invasive meningococcal disease (IMD) in association with certain medical conditions or high exposure to *N. meningitidis* [5–13,56–59,68].

HIV, human immunodeficiency virus; US, United States.

tetanus toxoid conjugate vaccine (MenACWY-TT; *Nimenrix*, Pfizer) [19]. MenB-FHbp has been used in response to college outbreaks in the US [20] but there are no published data on its immunogenicity against outbreak strains in vaccinated students. Results from a trial of MenB-FHbp in participants with anatomic or functional asplenia or complement deficiencies are available (ClinicalTrials.gov: NCT04893811) but not yet published in a peer-reviewed journal. There are published results for MenACWY-TT in high-risk groups, including those living with HIV [21], immune deficiencies [22], and impaired splenic activity [23], and an immunization program for adolescents, who received MenACWY-CRM or MenACWY-TT, successfully controlled a national MenW outbreak in England [24].

Over 82 million doses of MenACWY-CRM have been distributed (up to December 2022; GSK data) since the licensure in 2010 [25]. 4CMenB was licensed in 2013 and has been approved in more than 50 countries [26], with over 110 million doses distributed (up to June 2024; GSK data). 4CMenB contains as antigenic components factor H binding protein (fHbp), *Neisseria* adhesin A (NadA), Neisserial Heparin-Binding Antigen (NHBA), and outer membrane vesicles (OMV) containing Porin A (PorA) protein as the immunodominant antigen [27]. Extensive immunogenicity and safety data are available for both vaccines [25,28] and evidence is available of real-world effectiveness across all age groups and in different global regions [25,26].

In this narrative review, we provide an overview of MenACWY and MenB immunization recommendations in high-risk populations and discuss clinical immunogenicity and safety data for 4CMenB and MenACWY-CRM that are available for groups categorized as being at increased risk of IMD because of a medical condition or high exposure to *N. meningitidis*.

2. Meningococcal vaccination recommendations for at-risk populations

There are differences among countries in terms of specific populations that are recommended for MenACWY and MenB vaccination, as reviewed previously [16] and illustrated in the listing of 21 countries in Table 1 [13,29–54]. The US Advisory Committee on Immunization Practices (ACIP) recommends MenACWY and MenB vaccination from the age of, respectively, 2 months and 10 years for individuals at high risk, specified as persons with complement component deficiencies, asplenia, persons using complement inhibitor treatment, microbiologists with routine exposure to *N. meningitidis* isolates, and persons at increased risk during an outbreak [13]. MenACWY is recommended for additional groups: those living with HIV, travelers to an area where meningococcal disease is hyperendemic or epidemic, first-year college students living in residence halls, and military recruits.

Other countries have different recommendations (Table 1). For example, in Belgium [31], Italy [44–46], and Portugal [50], no specific vaccination recommendations exist for laboratory workers routinely exposed to *N. meningitidis*. Also, some countries have no vaccination recommendations for IMD epidemic/outbreak settings or for travelers to endemic or epidemic areas. Reasons for differences in recommendations among countries may include a lack of robust surveillance data for at-risk populations and insufficient awareness of IMD and prevention, as well as reasons related to vaccine licensure, prioritization, and cost-effectiveness [16]. Another reason could be a lack of meningococcal vaccination data for at-risk populations.

3. Immunogenicity of 4CMenB and MenACWY-CRM in at-risk populations

The immunogenicity of 4CMenB vaccination has been assessed in individuals with complement deficiency (CD), asplenia, and after hematopoietic cell transplantation (HCT), in people living with HIV, and when administered in response to outbreaks. Immune responses following MenACWY-CRM have been evaluated in military recruits, and following the sequential or concomitant administration of both vaccines in people living with HIV and laboratory workers. The available data for these population groups are discussed below.

3.1. Complement deficiency and asplenia

People with persistent complement component deficiencies are at increased risk for meningococcal disease [12] because an effective immune response to IMD and, ultimately, bacterial lysis requires complement system activation via various pathways [55]. Similarly, complement inhibitor recipients are at increased risk; the use of the terminal complement inhibitor, eculizumab, is associated with a 1,000–2,000-fold increased incidence of IMD [56]. There is also evidence that individuals with anatomic or functional asplenia have an increased risk and a higher mortality rate from the disease [13,57–59]. *N. meningitidis* has increased virulence in sickle cell disease due to hyposplenism, but the prevalence of meningococcal infection in association with this disease is unclear [60,61].

Two clinical studies have examined 4CMenB vaccination in children with CD [62,63], one of which also included children with defects in splenic function [62]. A phase 3 study included children aged 2–17 years, of whom 40 had CD (nine due to eculizumab treatment, four due to terminal CD, 27 had other causes), and 112 had asplenia or splenic dysfunction [62]. Two 4CMenB doses were given 2 months apart, and complement-mediated killing of 4CMenB antigen test strains (fHbp, NadA, PorA, and NHBA) was measured by human complement serum bactericidal antibody (hSBA) assay [64]. Percentages were calculated of participants with hSBA titers above the cutoff of 4 or 5, regarded as indicative of seroprotection [65,66].

One month after the second 4CMenB dose, percentages of complement-deficient children with hSBA titers ≥1:5 were 87% for fHbp, 95% for NadA, 68% for PorA, and 73% for NHBA, compared with 98%, 99%, 83%, and 99%, respectively, in healthy controls [62] (Table 2). This study also included an exploratory analysis using endogenous complement from each participant's serum rather than exogenously sourced complement. As expected, this analysis showed that the percentages of participants with protective hSBA titers against each MenB antigen were lower than with the exogenous complement hSBA assay (Table 2). For children with defects in splenic function, immune responses were similar to those in healthy children with hSBA assay using exogenous complement or endogenous complement (Table 2). Of eight children

Table 1. Meningococcal serogroup B (B) and serogroup ACWY (ACWY) vaccine recommendations for groups at increased risk for meningococcal disease in selected countries.

		Persons at risk due to medical condition				Persons at risk due to high exposure to *Neisseria meningitidis*				
Country	Ref	Functional/anatomical asplenia/splenectomy	Complement deficiency[a]	HIV	Other[b]	Lab personnel working with *N. meningitidis*	Other occupation[c]	IMD epidemic/ outbreak settings	Close contacts of IMD or high risk cases[d]	Travelers to endemic or epidemic areas
Australia	[29]	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY		B, ACWY	ACWY
Austria	[30]	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY		B, ACWY	B, ACWY
Belgium	[31]		B, ACWY	B, ACWY	B, ACWY					
Brazil	[32–35]	B, ACWY	B, ACWY	ACWY	B, ACWY	B, ACWY				B, ACWY
Canada	[36]	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY
Czechia	[37]	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY
Finland	[38]	B, ACWY	B, ACWY				B, ACWY		B, ACWY	
France	[39]	B, ACWY	B, ACWY	ACWY	B, ACWY	B, ACWY		B, ACWY	B, ACWY	ACWY
Germany	[40]	B, ACWY	B, ACWY		B, ACWY	B, ACWY		B, ACWY	B, ACWY	B, ACWY
Greece	[41]	B, ACWY	B, ACWY	B, ACWY		B, ACWY		ACWY		ACWY
Ireland	[42]	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY		B, ACWY	B, ACWY	
Israel	[43]	B, ACWY	B, ACWY	B, ACWY		B, ACWY		B, ACWY	B, ACWY	
Italy	[44–46]	B, ACWY	B, ACWY	B, ACWY	B, ACWY				B, ACWY	B, ACWY
New Zealand	[47]	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY		B, ACWY	B, ACWY
Norway	[48]	B, ACWY	B, ACWY	B, ACWY		B, ACWY			B, ACWY	B, ACWY
Poland	[49]	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B, ACWY		B, ACWY	B, ACWY	B, ACWY
Portugal	[50]	B, ACWY	B, ACWY		ACWY			ACWY		ACWY
Spain	[51]	B, ACWY	B, ACWY	B, ACWY	B, ACWY	B		B, ACWY	ACWY	ACWY
Türkiye	[52,53]	ACWY	ACWY	ACWY		ACWY	ACWY	ACWY		ACWY
UK	[54]	B, ACWY	B, ACWY							
US	[13]	B, ACWY	B, ACWY	ACWY		B, ACWY	ACWY	B, ACWY		ACWY

[a]Including deficiency due to use of complement inhibitors, such as eculizumab.
[b]Other medical conditions may include hematopoietic stem cell transplantation; congenital (e.g. hypogammaglobulinemia) or acquired immunosuppression (e.g. organ transplantation, antineoplastic therapy or high-dose systemic corticosteroid therapy), sickle cell disease, type 1 diabetes mellitus, chronic renal/adrenal insufficiency, severe chronic liver diseases, cancer, cerebrospinal fluid leak, cochlear impact.
[c]Other occupations may include healthcare workers providing care to IMD patients, firefighters, police officers, people who travel frequently for work, aid workers, professional athletes, military (recruits or before foreign missions), ambulance workers.
[d]Including those living in large collectives.
HIV, human immunodeficiency virus; IMD, invasive meningococcal disease; UK, United Kingdom; US, United States.

Table 2. Summary of immunogenicity results following 4CMenB vaccination in populations at increased risk of meningococcal disease due to complement deficiency, asplenia or splenic dysfunction, or hematopoietic cell transplantation.

Study design; 4CMenB vaccine schedule	Ref	Population Immunogenicity assessment[a]	MenB test strain fHbp	 NadA	 PorA	 NHBA
Open-label; 0–2 mo	[62]	**Complement deficiency** ($n = 39$)				
		Exogenous complement, percentage participants hSBA titers ≥1:5, baseline/post-dose 2	0%/87%	0%/95%	0%/68%	56%/73%
		Endogenous complement, percentage participants hSBA titers ≥1:4, baseline/post-dose 2	3%/68%	6%/60%	0%/41%	47%/60%
		Asplenia/splenic dysfunction ($n = 106$)				
		Exogenous complement, percentage participants hSBA titers ≥1:5, baseline/post-dose 2	7%/97%	12%/100%	4%/86%	79%/94%
		Endogenous complement, percentage participants hSBA titers ≥1:4, baseline/post-dose 2	11%/100%	35%/100%	5%/88%	95%/100%
		Healthy controls ($n = 85$)				
		Exogenous complement, percentage participants hSBA titers ≥1:5, baseline/post-dose 2	6%/98%	6%/99%	2%/83%	78%/99%
		Endogenous complement, percentage participants hSBA titers ≥1:4, baseline/post-dose 2	5%/98%	14%/100%	3%/85%	97%/100%
Open-label; 0, 1–2 mo	[63]	**Complement deficiency, alternative pathway** ($n = 2$)				
		Exogenous complement, number of participants hSBA titers ≥1:4 post-dose 2/total	2/2	2/2	1/2	NA
		Endogenous complement, number of participants hSBA titers ≥1:4 post-dose 2/total	2/2	2/2	2/2	NA
		Opsonophagocytic killing, bacterial survival <1% post-dose 2/total	2/2	2/2	0/2	NA
		Complement deficiency, late terminal pathway ($n = 3$)				
		Exogenous complement, number of participants hSBA titers ≥1:4 post-dose 2/total	2/3	3/3	2/3	NA
		Endogenous complement, number of participants hSBA titers ≥1:4 post-dose 2/total	1/3	0/3	0/3	NA
		Opsonophagocytic killing, bacterial survival <1% post-dose 2/total	3/3	3/3	2/3	NA
		Healthy controls ($n = 3$)				
		Exogenous complement, number of participants hSBA titers ≥1:4 post-dose 2/total	3/3	3/3	2/3	NA
		Endogenous complement, number of participants hSBA titers ≥1:4 post-dose 2/total	3/3	3/3	2/3	NA
		Opsonophagocytic killing, bacterial survival <1% post-dose 2/total	1/3	3/3	1/3	NA
Open-label; 0–2 mo	[68]	**Hematopoietic cell transplantation** ($n = 40$)				
		Exogenous complement, percentage participants hSBA titers ≥1:4, baseline/post-dose 2	8%/58%	5%/63%	10%/78%	0%/15%

[a]Post-dose 2 assessment, 1 month after second vaccine dose.

fHbp, factor H binding protein; hSBA, human serum bactericidal antibody; MenB, meningococcal serogroup B; 4CMenB, 4-component MenB vaccine; mo, study months; n, number of participants; NA, not analyzed; NadA, Neisseria adhesin A; NHBA, Neisserial Heparin-Binding Antigen; PorA, Porin A.

with CD due to eculizumab treatment, protective hSBA titers were detected against fHbp, NadA, PorA, and NHBA in, respectively, four (50%), six (75%), two (25%), and one (12.5%), while all four children with terminal CD had protective titers against each antigen. Therefore, as expected, the immune response to 4CMenB was particularly low in patients receiving eculizumab treatment, although some increase in hSBA titers was still observed in this subgroup [62]. Overall, bactericidal activity increased from baseline for most children in this study, including those with defects in complement function, and with exogenous or endogenous complement measurement.

In another study, hSBA titers were also measured using the exogenous complement and endogenous complement [63]. Children with CD in the alternative pathway (two children) or late terminal pathway (LTP; three children) were vaccinated with 4CMenB and compared with three vaccinated healthy adults. Protective hSBA titers were induced against fHbp, NadA, and PorA in most children in the exogenous complement hSBA assay, while fewer children in the LTP group achieved hSBA titers ≥1:4 using the endogenous complement assay (Table 2). In the analysis of opsonophagocytic killing, bacterial survival of <1% was reported for all children with CD for the fHbp and NadA test strains (Table 2).

3.2. Hematopoietic cell transplantation recipients

HCT recipients have an estimated 30-fold increased risk for IMD compared with non-transplanted individuals [67]. An open-label study evaluated the immunogenicity of two doses of 4CMenB administered 2 months apart in 40 allogeneic HCT recipients who were vaccinated at least 6 months after transplantation [68]. Vaccine response against at least one vaccine antigen was defined as hSBA titers ≥1:4 post-vaccination for patients with hSBA titer <4 at baseline or four-fold increases in hSBA titer post-vaccination for patients with hSBA titer ≥ 4 at baseline. Vaccine response against at least one vaccine antigen was achieved by 90% patients a month after vaccination and by 62% 10 months after the vaccination schedule. Proportions of patients with hSBA titers ≥1:4 1-month post-vaccination were 58% for fHbp, 63% for NadA, 78% for PorA, and 15% for the NHBA test strain (Table 2). Ten months after two doses, these percentages were 27%, 51%, 27%, and 11%, respectively. Overall, antibody titers against each MenB test strain increased after vaccination and then declined over 12 months but remained above baseline for three of the four antigens [68].

3.3. People living with HIV

For people living with HIV, there is an increased risk for meningococcal disease, particularly for those with a low CD4 count or high viral load [8]. The immunogenicity of 4CMenB was evaluated in people living with HIV in two phase 4 studies; in one, participants were co-administered MenACWY-CRM [69–71].

The first study recruited 63 individuals with perinatally acquired HIV and, 3 weeks after the 0–2 months vaccine schedule, all had hSBA titers ≥1:4 against antigens fHbp, NadA, and NHBA [69]. The second included 55 people living with HIV aged 20–45 years administered two doses of 4CMenB and MenACWY-CRM concomitantly 1 month apart [70]. Bactericidal immune responses were evaluated by baby rabbit complement SBA (rSBA) assay for serogroups A, C, W, and Y, and by hSBA assay for MenB antigens fHbp, NadA, and PorA. One month post-vaccination, hSBA titers ≥1:4 were achieved against fHbp in 98% of participants and against NadA and PorA in all participants, while rSBA titers ≥1:8 were detected against MenC in 94% of participants and against MenA, MenW, and MenY in all participants (Figure 2). In a follow-up study of 38 participants 18 months after primary vaccination [71], percentages of participants with hSBA titers ≥1:4 were 92% for fHbp, 68% for NadA, and 76% for PorA, while percentages with rSBA titers ≥1:8 ranged from 58% for MenC to 87% for MenA (Figure 2). After 30 months (32 participants), the percentages were 88%, 88%, and 75%, for fHbp, NadA, and PorA, respectively, and 88%, 47%, 78%, and 88%, for serogroups A, C, W, and Y, respectively (Figure 2).

3.4. Groups at increased risk due to outbreak or living conditions

Historically, young adults living in crowded conditions, such as students living in residence halls and military recruits, have been identified as being at increased risk for meningococcal disease [16]. Immunization programs with 4CMenB and MenB-FHbp have been implemented to end outbreaks of MenB disease in US universities [20,72]. In two of these outbreaks, in which students were vaccinated with 4CMenB, immune responses were evaluated against the outbreak strains [73,74]. Approximately 2 months after two doses administered 10 weeks apart, 66% of 499 students had hSBA titers ≥1:4 against the outbreak strain compared with 21% of 19 unvaccinated students (Figure 3) [73]. Among the students who received two doses, hSBA titers ≥ 1:4 against NadA were present in 99%, and against fHbp in 95% [73]. At the second university, students received two 4CMenB doses 6–8 weeks apart [74]. After the second dose, hSBA titers ≥1:4 against the outbreak strain were present in 93% of 237 students versus 37% of 52 unvaccinated students (Figure 3). Percentages of students with hSBA titers ≥ 1:16 against the outbreak strain were 62% for those who received two doses, and 12% for unvaccinated students [74]. In both universities, no further IMD cases were identified among vaccinated students [73,74].

For MenACWY-CRM, while published data on immunogenicity against outbreak strains are not available, results from an immunization program of adolescents in England in 2015–2018 [24] and of military recruits in South Korea in 2013–2016 [75] showed vaccine effectiveness of 94% and 88%, respectively. The program in South Korea followed an immunogenicity study of 75 military recruits that showed 97–100% achieved rSBA titers ≥1:8 against serogroups A, C, W, and Y 3 weeks after immunization with one MenACWY-CRM dose [76].

3.5. Occupational exposure to meningococci

Since *N. meningitidis* is an airborne respiratory pathogen, laboratory workers handling live meningococcal cultures have a potential occupational exposure risk. The immunogenicity of sequential or concomitant administration of 4CMenB and MenACWY-CRM in healthy laboratory staff routinely exposed to *N. meningitidis* was assessed in two phase 2 trials [77,78].

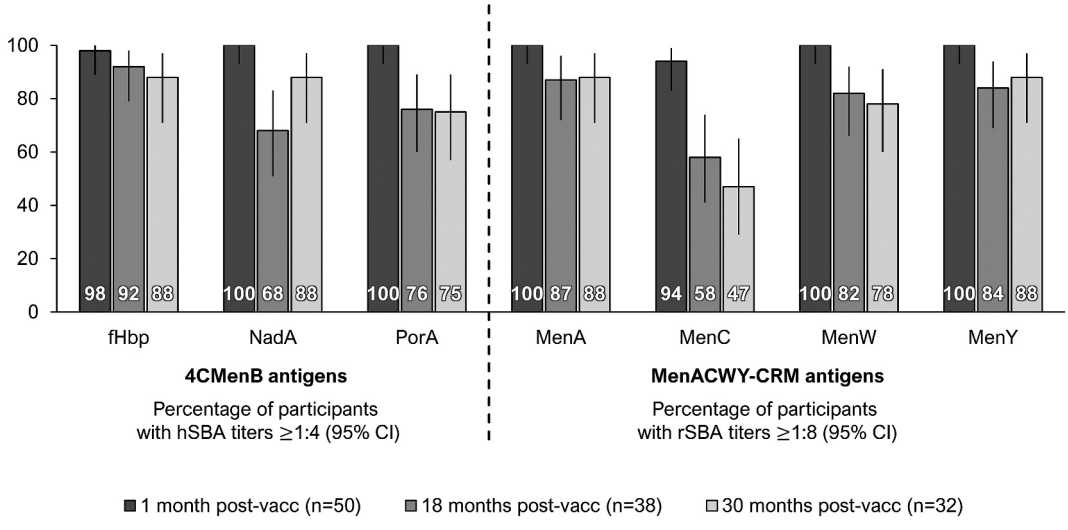

Figure 2. Percentages of participants living with HIV with protective SBA titers against each vaccine antigen following two doses of 4CMenB and MenACWY-CRM co-administered 1 month apart [70,71].

CI, confidence interval; fHbp, factor H binding protein; HIV, human immunodeficiency virus; hSBA, human complement SBA; Men, meningococcal serogroup; n, number of participants; NadA, *Neisseria* adhesin A; PorA, Porin A; post-vacc, after 2-dose schedule; rSBA, rabbit complement SBA; SBA, serum bactericidal antibody.

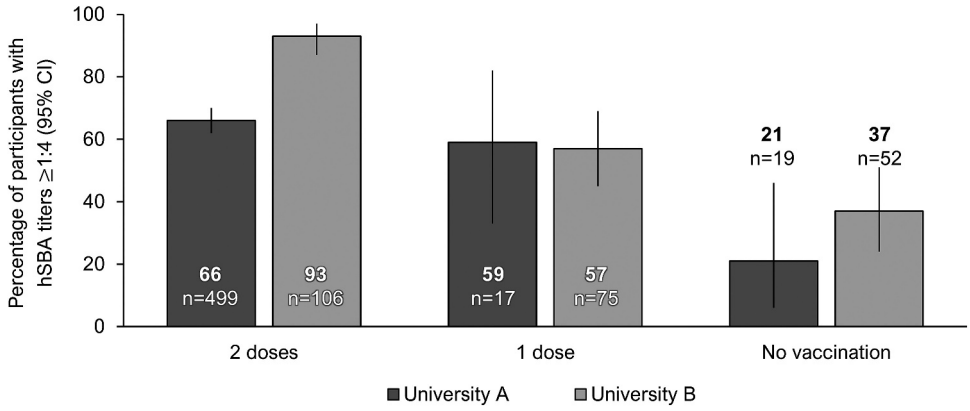

Figure 3. Percentages of participants with hSBA titers ≥ 1:4 against MenB outbreak strains following 4CMenB vaccination program in two US universities [73,74]. CI, confidence interval; hSBA, human serum bactericidal antibody; Men, meningococcal serogroup; n, number of participants; US, United States.

In the first study, 41 adults received 4CMenB at 0, 2, and 6 months, followed by a single dose of MenACWY-CRM 1 month later [77]. The percentages of participants with hSBA titers ≥1:4 increased from 37% at baseline to 97% 1-month post-vaccination for fHbp, from 37% to 100% for NadA, and from 22% to 92% for PorA. One month after MenACWY-CRM, hSBA titers ≥ 1:4 were detected in 96% of participants for MenA, 100% for MenC and MenW, and 83% for MenY.

In the second study, 32 adults received one dose of 4CMenB and MenACWY-CRM concomitantly followed by two further doses of 4CMenB 2 and 6 months after the first [78]. One month after vaccination, protective hSBA titers (≥1:4) against seven MenB strains, including fHbp, NadA, and PorA strains and four wild-type strains, were detected in 90–100% of participants. Almost all the participants had rSBA titers ≥ 1:8 (93–100%) and titers ≥1:128 (90–100%) against the MenACWY strains post-vaccination.

4. Safety of 4CMenB and MenACWY-CRM in at-risk populations

The safety of 4CMenB was assessed in children with defects in complement and splenic function [62], in HCT recipients [68], and in combination with MenACWY-CRM in people living with HIV [70] and laboratory workers [77,78]. In general, where reported, incidences of solicited and unsolicited adverse events (AEs) are consistent with the vaccines' safety profiles established from studies of age-based risk groups conducted over the last decade [25,28], with no safety concerns. Any increase in reactogenicity (such as fever) associated with 4CMenB versus MenACWY-CRM was in line with the known safety profile of 4CMenB [28].

Additional safety results are available from a study of data from 16,974 students who received at least one 4CMenB dose (31,313 doses in total) during two US university outbreaks [79]. Overall, 8% of vaccinated students reported an AE, of which 96% were not serious and consistent with 4CMenB safety in clinical trials. Fifty-four (0.3%) students reported serious AEs, of which six (rhabdomyolysis and anaphylaxis in one participant each; fever, myalgia, malaise, and neck stiffness in one participant) were suspected of being related to vaccination [79].

Another study assessed the safety of MenACWY-CRM in 138 infants and toddlers, of whom 42% had a high-risk medical condition (54 with anatomic or functional asplenia, four with DiGeorge syndrome) [80]. Post-vaccination electronic health records were analyzed for children who received at least one dose of MenACWY-CRM. During 6 months after vaccination, 40 children experienced an AE-related emergency department visit or hospitalization, 39 of whom had a high-risk condition. The researchers felt this did not suggest a safety concern associated with MenACWY-CRM. Thirteen serious AEs were reported, but all but one (febrile convulsions) occurred over 30 days after dose administration so a causal link with vaccination was considered unlikely.

5. Conclusions

Meningococcal vaccination of high-risk groups is recommended in many countries but population categories that are included vary and vaccination schedules are inconsistent. Clinical studies of 4CMenB and MenACWY-CRM vaccines in groups at increased risk because of a medical condition or high exposure to *N. meningitidis* have demonstrated immunogenicity and safety of these vaccines. As expected, immunogenicity was lower in individuals with CD, particularly those receiving the complement inhibitor, eculizumab, although some increase in hSBA titers was observed. This may suggest that serological monitoring of individual immune responses and further doses may be a strategy to explore in specific populations.

Evidence supports concomitant administration of 4CMenB and MenACWY-CRM in healthy individuals and certain high-risk groups. The new MenABCWY vaccine containing 4CMenB and MenACWY-CRM as components has been approved by the US FDA for use in individuals aged 10–25 years and is recommended by the US Advisory Committee on Immunization Practices [81], as is the vaccine containing MenACWY-TT/MenB-FHbp components [82]. While no data exists on the immunogenicity and safety of the MenABCWY vaccines in high-risk populations, a pentavalent vaccine could potentially simplify meningococcal vaccination schedules, thereby possibly increasing vaccine uptake rates in high-risk populations.

6. Expert opinion

Although immunization with MenACWY and MenB vaccines is recommended widely for high-risk groups, there is no standardized approach among national meningococcal immunization programs. This includes differences in specific high-risk groups that are prioritized for vaccination. Moreover, there is disparity in terms of recommendations regarding booster doses for groups at persistent high risk of IMD or who become at-risk [13,29–54]. This can be illustrated by the recommendations in three selected countries: the UK, the US, and Australia. In the UK, booster doses are not recommended, with the rationale that the need for, and timing of, a booster dose has not yet been determined in at-risk individuals [54,83]. In the US, the MenACWY booster-dose interval is variable, and the MenB booster administration is recommended 1 year after primary series completion and every 2–3 years thereafter [13]. In Australia, 3- or 5-year intervals are recommended before the booster dose, depending on the age group and whether MenACWY or MenB is administered [29]. Clarity is therefore required in guidelines on meningococcal vaccination, with standardized definitions of populations who are at high risk and a consensus on appropriate-dose schedules, combined with improved surveillance of IMD for continued assessments.

Another key area for improvement is the rate of meningococcal vaccine uptake, which has been shown to be poor in high-risk populations [16]. Much of the data on vaccine uptake among patients at increased risk because of an immunocompromising condition are from the US [84–86]. A retrospective database study of patients within 3 years of a CD diagnosis found that only 4.6% had received MenACWY vaccination from 2010, when a two-dose series was first recommended by the ACIP, up to 2018 [84]. Only 2.2% of patients received MenB vaccination from 2015, when the ACIP recommendation for MenB vaccines was introduced. Meningococcal vaccination rates were also low in the same time periods among patients with a new asplenia diagnosis; among 2,273 and 741 patients eligible for MenACWY and MenB vaccination, respectively, 28.1% and 9.7% were actually vaccinated [85]. Another database study found that, among people living with HIV, only 16.3% had a first dose of MenACWY vaccine in the 2 years after HIV diagnosis [86].

There is also evidence of low meningococcal vaccination rates among people at risk of high exposure to *N. meningitidis*, as shown by data from college and university students in the US and the UK [87,88]. A survey of US college student health centers in 2017–2018 found that 54% stocked and administered MenACWY, while 37% offered the MenB vaccine [89]. In most cases, the MenB coverage rate was estimated to be 10% at most, or no estimate could be provided [89]. Similarly, there is evidence of suboptimal vaccination among healthcare workers at increased risk of meningococcal disease [90].

This suggests a more proactive approach is required by medical departments or health centers to ensure better vaccine coverage of at-risk groups. Uptake may be increased with improved awareness of vaccination recommendations among healthcare practitioners and patients or parents of at-risk children [16]. The financial cost of meningococcal vaccination may also need to be addressed [89]. Additionally, co-administration can improve vaccine uptake rates but, while well established in children and travelers, this is not a routine practice in adolescents and adults [91]. The safety and immunogenicity of 4CMenB and MenACWY-CRM co-administration have been demonstrated in clinical studies of healthy children and adults, with co-administration approved in some childhood or adolescent immunization programs [92], as well as in healthy laboratory workers [78] and people living with HIV [70]. The availability of a pentavalent vaccine also has the potential to improve vaccine uptake rates through a simplified immunization schedule that provides broad protection against IMD caused by five meningococcal serogroups in one vaccine [17].

While no clinical data are available for the pentavalent MenABCWY vaccines in high-risk populations, phase 3 clinical studies of healthy adolescents and young adults demonstrated that GSK's MenABCWY vaccine (two doses) was non-inferior to 4CMenB (two doses) and MenACWY-CRM (one dose), with a safety profile comparable to that of 4CMenB [93], and that Pfizer's pentavalent vaccine (two doses) showed non-inferiority to MenB-FHbp (two doses) and MenACWY-CRM (single dose) [19]. Additional clinical trial data or real-world evidence are needed on vaccine co-administration and the protection offered by pentavalent meningococcal vaccines for at-risk populations to further refine national and regional recommendations on the optimal meningococcal vaccine schedules for high-risk groups in the future.

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Declaration of interests

Shravani Bobde and Chiranjiwi Bhusal are employed by GSK and hold financial equities in GSK. Woo-Yun Sohn was employed by GSK at the time of the study, and is now employed by Moderna. Catherine Cosgrove declares having received grant/research support from GSK, Novavax, and Moderna. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or material discussed in the manuscript apart from those disclosed.

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Author contributions

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