



Sex, Age, and Race Effects on Immunogenicity of MenB-FHbp, A Bivalent Meningococcal B Vaccine: Pooled Evaluation of Clinical Trial Data

Johannes Beeslaar · Paula Peyrani · Judith Absalon · Jason Maguire · Joseph Eiden · Paul Balmer · Roger Maansson · John L. Perez

Received: April 8, 2020 / Published online: July 17, 2020
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ABSTRACT

Introduction: An extensive clinical development program showed that the meningococcal serogroup B-factor H binding protein (MenB-FHbp) vaccine affords protection against MenB disease for adolescents and adults. Data were pooled from multiple studies within the program to examine whether MenB-FHbp immunogenicity was influenced by sex, age, or race.

Methods: Immunogenicity was assessed in subjects from seven studies who received 120 µg MenB-FHbp (at 0, 2, 6 months) and had evaluated immune responses against four representative test strains via serum bactericidal assays

using human complement (hSBAs). Immune responses were presented by sex (male, female), age group (10–14, 15–18, 19–25, 10–25 years), and race (white, black, Asian, other).

Results: Among 8026 subjects aged 10–25 years included in this analysis, MenB-FHbp elicited robust immune responses in a high percentage of subjects regardless of demographic characteristics. Across all test strains and demographic subsets, a ≥ 4 -fold rise in titer from baseline was achieved in 76.7–95.0% of subjects, with no major differences by sex, age groups assessed, or races evaluated. Corresponding percentages achieving titers \geq the lower limit of quantification (LLOQ) against all four strains combined were 79.7–87.3% (sex), 81.6–85.5% (age), and 80.0–88.1% (race). Minor differences were observed for geometric mean titers and percentages of subjects achieving titers \geq LLOQ against each strain based on demographics.

Conclusion: These data suggested no clinically meaningful differences in MenB-FHbp immunogenicity when administered as a three-dose schedule based on sex, ages assessed, or races evaluated. This analysis supports the continued recommended use of MenB-FHbp to prevent MenB disease in adolescents and young adults.

Trial Registration: ClinicalTrials.gov identifiers, NCT00808028, NCT01830855, NCT01323270, NCT01461993, NCT01461980, NCT01352845, and NCT01299480.

Digital Features To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.12504986>.

J. Beeslaar (✉)
Pfizer Vaccine Clinical Research and Development,
Hurley, UK
e-mail: johannes.beeslaar@pfizer.com

P. Peyrani · R. Maansson · J. L. Perez
Pfizer Vaccine Clinical Research and Development,
Collegeville, PA, USA

J. Absalon · J. Maguire · J. Eiden
Pfizer Vaccine Clinical Research and Development,
Pearl River, NY, USA

P. Balmer
Pfizer Vaccine Medical Development, Scientific and
Clinical Affairs, Collegeville, PA, USA

Keywords: Clinical trial; Immunogenicity; Invasive meningococcal disease; Serogroup B; Vaccines

Key Summary Points

Why carry out this study?

MenB-FHbp is a vaccine for the prevention of meningococcal disease caused by meningococcal serogroup B (MenB), which predominates in many global regions.

Although an extensive clinical program supported MenB-FHbp immunogenicity, influences of demographic characteristics on immune responses have not been evaluated.

Effects of sex, age, and race on immune responses induced by MenB-FHbp were evaluated using pooled data from seven randomized clinical studies in which adolescents or young adults received 120 µg MenB-FHbp on a 0-, 2-, and 6-month schedule.

What was learned from the study?

MenB-FHbp was associated with robust immune responses against four diverse, vaccine-heterologous MenB test strains, with no clinically meaningful differences observed across demographic subgroups.

These findings confirm a three-dose MenB-FHbp schedule can be used in adolescents and young adults regardless of sex, ages assessed, or races evaluated.

manifests as meningitis or bacteremia, with case fatality rates from 10% to 20% and debilitating long-term sequelae in up to 20% of survivors [1]. In several regions worldwide, meningococcal serogroup B (MenB) accounts for more cases of IMD than any other serogroup, causing 38% of cases in the USA and 51% of cases in the European Union in 2017 [2, 3]. Vaccination is the most effective method for large-scale prevention of IMD [4].

MenB-FHbp (Trumenba[®], bivalent rLP2086; Pfizer Inc, Philadelphia, PA, USA), which consists of two recombinant factor H binding protein (FHbp) variants from each subfamily [subfamily A (variant A05) and subfamily B (variant B01)], is one of two vaccines licensed to prevent MenB disease [5, 6]. Because individual MenB strains generally express a single subfamily variant [7, 8], the MenB-FHbp formulation is predicted to broadly protect against diverse MenB disease-causing strains [7]. An extensive clinical development program has been completed for MenB-FHbp [9], but the impact of sex, age, and race on MenB-FHbp immunogenicity has not been systematically assessed.

Variability in vaccine responses based on age [10–14], sex [15–19], and race [20–23] has been observed for other vaccines. Therefore, it is important for public health authorities and medical practitioners to understand whether differences in vaccine efficacy occur in various populations in order to maximize vaccine benefit [15, 16, 18, 24]. Moreover, understanding the challenges to effective vaccination in specific populations can inform vaccine clinical trial design and vaccine uptake after licensure [18, 20].

MenB-FHbp was shown to elicit robust immune responses and to have an acceptable safety profile during an extensive clinical development program, including studies enrolling 20,803 adolescents and adults [9]. Although data analyzed by demographic subsets have not been published, differences in point estimates of immunogenicity end points based on sex and race were observed in some of the individual studies [8]. However, there were too few participants within each study to provide a comprehensive assessment of the impact of

INTRODUCTION

Invasive meningococcal disease (IMD) is a rare but life-threatening condition caused by *Neisseria meningitidis* and is most commonly diagnosed in children aged < 1 year, adolescents, and young adults [1]. Disease typically

demographics on immunogenicity. Therefore, the current analysis pooled data from studies across the MenB-FHbp clinical development program to generate a larger sample size for evaluating whether sex, age, or race affected MenB-FHbp immunogenicity.

METHODS

Data Sources

The MenB-FHbp clinical development program consisted of 11 clinical studies enrolling adults and adolescents [9]. Seven of these 11 clinical studies (Table 1) [8, 25–29] in which subjects who received 120 µg of MenB-FHbp on a 0-, 2-, and 6-month schedule and had available immunogenicity results for some or all of the four primary test strains (described below) were included in this subgroup analysis. All seven studies had randomized designs, and six of the seven studies included comparator groups receiving either saline or another vaccine.

The data in this article were derived from previously conducted studies; as such, this article does not describe any new studies with human participants or animals and no new ethical approvals were needed.

Immunogenicity Evaluation

Immune responses were evaluated by serum bactericidal assays using human complement (hSBA) against the four primary test strains used in each study [9]. These included two strains expressing FHbp subfamily A variants (PMB80 expressing variant A22, PMB2001 expressing variant A56) and two strains expressing FHbp subfamily B variants (PMB2948 expressing variant B24, PMB2707 expressing variant B44) [9], hereafter referred to as test strains A22, A56, B24, and B44. The five coprimary end points assessing responses 1 month after dose 3 were:

- Percentage of subjects achieving a ≥ 4 -fold rise in titer from baseline against each of the four test strains (criteria for a ≥ 4 -fold rise in titer have been previously described [8, 30]).

- Percentage of subjects achieving titers \geq the lower limit of quantification (LLOQ) against all four primary test strains combined (i.e., composite response; $\geq 1:8$ for the test strains expressing variants A56, B24, and B44 and $\geq 1:16$ for the test strain expressing variant A22)

Additional end points evaluated included:

- Percentage of subjects achieving titers \geq LLOQ against each test strain
- Geometric mean titers (GMTs) against each test strain
- Percentage of subjects achieving titers $\geq 1:4$ (the established correlate of protection [31, 32]) against each test strain

Statistical Analyses

Descriptive statistics are provided for all end points; no hypothesis testing was performed. Percentages are expressed with 95% CIs calculated using the Clopper-Pearson method, and GMTs are expressed as back transformations of the mean logarithm of hSBA titers along with 95% CIs based on Student's *t*-test distributions. Results were presented by sex (male or female), age group [10–25 (total), 10–14, 15–18, 19–25, or 19–25 years], and race (white, black, Asian, or other) for all end points. Analysis by ethnicity (non-Hispanic/non-Latino, Hispanic/Latino, or unknown) was not conducted because data by ethnicity were not collected in all studies.

RESULTS

Demographics

The evaluable immunogenicity population included 8026 subjects aged 10–25 years who were randomly assigned to receive 120 µg MenB-FHbp on a 0-, 2-, and 6-month schedule; demographic characteristics are summarized in Table 2. Percentages of males and females included in the evaluable immunogenicity population were similar. Most subjects (80.7%) were adolescents aged 10–18 years at the time of study entry, and 53.5% of subjects were aged

Table 1 Summary of MenB-FHbp clinical studies contributing to the pooled evaluable immunogenicity population

Study NCT	Published reference	Study design	Study location	Age range, years	Vaccine dose/schedule	Comparator	Strains (FHbp variants) tested	Primary immunogenicity end points	Subjects receiving ≥ 1 dose, <i>n</i>
NCT00808028	Richmond, <i>Lancet Infect Dis</i> , 2012 [26]	Phase 2, randomized, single-blind, placebo-controlled study	EU/Australia	11–18	60, 120, or 200 μ g MenB-FHbp at 0, 2, and 6 mo	200 μ g saline at 0, 2, and 6 mo	PMB1321 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44), PMB17 (B02), PMB1745 (A05), PMB3302 (A04), PMB1256 (B03)	Percentage of subjects achieving ≥ 4 -fold increase in hSBA titers against strains PMB1745 and PMB17	415
NCT01830855	Ostergaard, <i>N Engl J Med</i> , 2017 [8]	Phase 3, randomized, active-controlled, observer-blinded study	USA/Global	10–18	120 μ g MenB-FHbp (lot 1, 2, or 3) at 0, 2, 6 mo	HAV at 0 and 6 mo, saline at 2 mo	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Percentage of subjects achieving ≥ 4 -fold increase in hSBA titers against the 4 primary strains (PMB80, PMB2001, PMB2948, and PMB2707) from baseline to 1 mo postdose 3; percentage of subjects achieving hSBA titers \geq LLOQ against all 4 primary strains (composite response) 1 mo postdose 3	2693
NCT01323270	Vesikari, <i>J Pediatr Infect Dis Soc</i> , 2016 [29]	Phase 2, randomized, placebo-controlled, single-blind study	EU	11–18	120 μ g MenB-FHbp + dTaP/IPV at 0 mo, MenB-FHbp at 2 and 6 mo	Saline + dTaP/IPV at 0 mo, saline at 2 and 6 mo	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Percentage of subjects achieving prespecified antibody titers against DTaP/IPV antigens 1 mo postdose	374
NCT01461993	Senders, <i>Pediatr Infect Dis J</i> , 2016 [27]	Phase 2, randomized, active-controlled, observer-blinded study	USA	11–17	120 μ g MenB-FHbp + HPV or MenB-FHbp + saline at 0, 2, and 6 mo	Saline + HPV at 0, 2, and 6 mo	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	GMTs against HPV-4 antigens when HPV-4 is administered alone vs. with MenB-FHbp; GMTs against 4 primary FHbp strains (PMB80, PMB2001, PMB2948, and PMB2707) when MenB-FHbp is administered alone vs. with HPV-4	1982

Table 1 continued

Study NCT	Published reference	Study design	Study location	Age range, years	Vaccine dose/schedule	Comparator	Strains (FHbp variants) tested	Primary immunogenicity end points	Subjects receiving ≥ 1 dose, n
NCT01461980	Muse, <i>Pediatr Infect Dis J.</i> 2016 [25]	Phase 2, randomized, active-controlled, observer-blinded study	USA	10–12	120 µg MenB-FHbp at 0, 2, 6 mo + MCV4 + Tdap at 0 mo, or 120 µg MenB-FHbp + saline at 0, 2, 6 mo and MCV4 + Tdap at 7 mo	Saline + MCV4 + Tdap at 0 mo	PMB80 (A22) PMB2948 (B24)	GMTs against MCV4 and Tdap antigens when MCV4 and Tdap are administered alone vs. with MenB-FHbp; GMTs against 2 FHbp strains (PMB80 and PMB2948) when MenB-FHbp is administered alone vs. with MCV4 and Tdap	1758
NCT01352845	Ostergaard, <i>N Engl J Med.</i> 2017 [8]	Phase 3, randomized, placebo-controlled, observer-blinded study	USA/ Global	18–25	120 µg MenB-FHbp at 0, 2, and 6 mo	Saline at 0, 2, and 6 mo	PMB80 (A22), PMB2001 (A56) PMB2948 (B24), PMB2707 (B44)	Percentage of subjects achieving ≥ 4-fold increase in hSBA titers against the 4 primary strains (PMB80, PMB2001, PMB2948, and PMB2707) from baseline to 1 mo postdose 3; percentage of subjects achieving hSBA titers ≥ LLOQ against all 4 primary strains (composite response) 1 mo postdose 3	2471
NCT01299480	Vesikari, <i>J Pediatr Infect Dis Soc.</i> 2016 [28]	Phase 2, randomized, single-blind study	EU	11–18	120 µg MenB-FHbp at 0, 1, and 6 mo; 0, 2, and 6 mo; 0 and 6 mo; 0 and 2 mo; or 0 and 4 mo	None	PMB80 (A22), PMB2001 (A56) PMB2948 (B24), PMB2707 (B44)	Percentage of subjects receiving 3 doses of MenB-FHbp achieving hSBA titers ≥ 1:8 against each of the 4 primary strains (PMB80, PMB2001, PMB2948, and PMB2707) 1 mo postdose 3	1696

dTdap/IPV diphtheria, tetanus, acellular pertussis/inactivated poliomyelitis virus vaccine, adsorbed (Repevax[®], Sanofi Pasteur, Lyon, France), *FHbp* factor H binding protein, *GMT* geometric mean titer, *HAI*/hepatitis A virus vaccine (Havrix[®], GlaxoSmithKline, Research Triangle Park, NC, USA), *HPV* human papillomavirus vaccine (Gardasil[®], Merck Sharp & Dohme, Whitehouse Station, NJ, USA), *hSBA* serum bactericidal assay using human complement, *LLOQ* lower limit of quantification, *MCV4* meningococcal (serogroups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (Menaetra[®], Sanofi Pasteur, Swiftwater, PA, USA), *MenB-FHbp* meningococcal serogroup B-factor H binding protein vaccine (Trumenba[®]), *Tdap* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed (Adacel[®], Sanofi Pasteur, Ltd, Swiftwater, PA, USA)

Table 2 Subject demographics in the pooled evaluable immunogenicity population

Total, <i>N</i>	8026
Sex, <i>n</i> (%)	
Male	4153 (51.7)
Female	3873 (48.3)
Age group at first dose, years (%)	
10–18	6474 (80.7)
10–14	4290 (53.5)
15–18	2184 (27.2)
19–25	1552 (19.3)
Age at first dose, years	
Mean ± SD	15.0 ± 4.2
Median (range)	14 (10–25)
Race, <i>n</i> (%)	
White	6982 (87.0)
Black	745 (9.3)
Asian	61 (0.8)
Other	238 (3.0)

10–14 years. Most subjects (87.0%) were white, with the remainder identifying as black (9.3%), Asian (0.8%), or other (3.0%).

Immunogenicity

The percentage of subjects achieving a ≥ 4 -fold rise from baseline for each of the four test strains and percentages of subjects achieving a composite response 1 month after dose 3 are shown in Table 3. Regardless of demographics, high percentages of subjects achieved either a ≥ 4 -fold rise in titer from baseline for each test strain or a composite response.

For sex, the observed differences between percentages of males and females achieving a ≥ 4 -fold rise in titer from baseline were $< 5\%$ for test strains A22, A56, and B24, with males showing a greater response. For test strain B44,

the percentage of males achieving a ≥ 4 -fold rise in titer was 8.3% higher compared with females (85.1% vs. 76.8%, respectively). For the composite response, a higher percentage of males achieved titers \geq LLOQ for all four test strains combined (7.6% higher than in females).

Comparisons across age subgroups indicated no major differences between groups for a ≥ 4 -fold rise in titers from baseline. A higher percentage of subjects aged 10–14 years achieved a ≥ 4 -fold rise in titer compared with subjects aged 15–18 and 19–25 years for strains A22, A56, and B24 (Table 3), and the 95% CIs suggest that younger adolescents may have slightly increased hSBA responses compared with young adults. Specifically, 1.7–5.9% more subjects aged 10–14 years showed a ≥ 4 -fold rise in titer from baseline than those aged 15–18 and 19–25 years, which was not considered clinically significant. In addition, subjects aged 10–18 years showed slightly greater responses against test strains A22 and A56 than those aged 19–25 years, with 4.1% and 3.0% more subjects responding, respectively. For test strain B44, observed differences in the percentage of subjects responding were $< 2.4\%$ across age subgroups, with overlapping 95% CIs. For composite responses, the greatest difference between subgroups was observed between subjects aged 15–18 and 19–25 years (3.9%); however, it should be noted that CIs overlapped across all subgroups.

With regard to race, percentages of subjects achieving a ≥ 4 -fold rise in titers from baseline were generally consistent among white, black, Asian, and other subgroups (Table 3). The greatest percentage difference was observed between whites and Asians for test strain B24, for which 12.4% more Asian subjects achieved a ≥ 4 -fold rise in titer from baseline compared with white subjects. However, it should be noted that these analyses are limited by the very low number of Asian subjects included ($n = 42$ –58 per strain).

The percentage of subjects achieving titers \geq LLOQ for each of the four test strains at 1 month after dose 3 is shown in Table 4. Notably, percentages of subjects achieving titers \geq LLOQ were high across all demographic groups, with only minor differences observed

Table 3 Percentage of subjects in the evaluable immunogenicity population achieving a ≥ 4 -fold rise in hSBA titer from baseline and composite response 1 month after dose 3 according to subgroup

Subjects achieving a ≥ 4 -fold rise										
	A22		A56		B24		B44		Composite response ^a	
	N^b	% (95% CI)	N^b	% (95% CI)	N^b	% (95% CI)	N^b	% (95% CI)	N^b	% (95% CI)
Total	7429	84.1 (83.3, 85.0)	4761	92.1 (91.3, 92.8)	7373	81.4 (80.5, 82.3)	5011	81.1 (79.9, 82.1)		83.6 (82.5, 84.7)
Sex										
Male	3834	85.7 (84.5, 86.7)	2469	94.3 (93.3, 95.2)	3818	83.4 (82.2, 84.6)	2586	85.1 (83.6, 86.4)		87.3 (85.9, 88.6)
Female	3595	82.5 (81.2, 83.7)	2292	89.7 (88.3, 90.9)	3555	79.2 (77.8, 80.5)	2425	76.8 (75.1, 78.5)		79.7 (77.9, 81.3)
Age group, years										
10–18	5904	85.0 (84.0, 85.9)	3281	93.0 (92.1, 93.8)	5862	81.9 (80.9, 82.8)	3485	81.6 (80.3, 82.9)		82.7 (81.4, 84.0)
10–14	3943	86.8 (85.7, 87.9)	1875	93.7 (92.5, 94.8)	3924	83.3 (82.1, 84.4)	2012	82.3 (80.6, 84.0)		83.5 (81.8, 85.2)
15–18	1961	81.2 (79.4, 82.9)	1406	92.0 (90.5, 93.4)	1939	79.0 (77.1, 80.8)	1473	80.6 (78.5, 82.6)		81.6 (79.5, 83.6)
19–25	1525	80.9 (78.8, 82.8)	1480	90.0 (88.4, 91.5)	1511	79.5 (77.4, 81.5)	1526	79.9 (77.8, 81.9)		85.5 (83.6, 87.3)
Race										
White	6418	84.2 (83.3, 85.1)	4084	91.7 (90.8, 92.6)	6370	80.6 (79.6, 81.6)	4308	80.7 (79.5, 81.9)		83.9 (82.7, 85.0)
Black	721	82.5 (79.6, 85.2)	504	95.0 (92.8, 96.8)	722	85.3 (82.5, 87.8)	523	82.8 (79.3, 85.9)		80.0 (76.3, 83.4)
Asian	58	91.4 (81.0, 97.1)	42	90.5 (77.4, 97.3)	57	93.0 (83.0, 98.1)	43	76.7 (61.4, 88.2)		82.9 (67.9, 92.8)
Other	232	85.8 (80.6, 90.0)	131	91.6 (85.5, 95.7)	224	87.1 (81.9, 91.2)	137	86.1 (79.2, 91.4)		88.1 (81.3, 93.0)

hSBA serum bactericidal assay using human complement, LLOQ lower limit of quantification

^a Defined as the percentage of subjects achieving an hSBA titer \geq LLOQ for all four primary FHbp test strains combined

^b Number of subjects with valid and determinate hSBA titers for the given strain at both the specified time point and baseline

Table 4 Percentage of subjects in the evaluable immunogenicity population achieving hSBA titers \geq LLOQ 1 month after dose 3 according to subgroup

	Subjects with hSBA titers \geq LLOQ ^a							
	A22		A56		B24		B44	
	N ^b	% (95% CI)	N ^b	% (95% CI)	N ^b	% (95% CI)	N ^b	% (95% CI)
Total	7577	94.5 (94.0, 95.0)	5084	99.3 (99.1, 99.5)	7478	91.2 (90.5, 91.8)	5046	86.6 (85.7, 87.6)
Sex								
Male	3915	95.1 (94.4, 95.8)	2620	99.4 (99.0, 99.7)	3880	93.2 (92.4, 94.0)	2609	89.9 (88.7, 91.0)
Female	3662	93.8 (93.0, 94.6)	2464	99.3 (98.8, 99.6)	3598	88.9 (87.9, 89.9)	2437	83.2 (81.6, 84.6)
Age group, years								
10–18	6033	94.7 (94.1, 95.2)	3547	99.3 (98.9, 99.5)	5944	90.1 (89.3, 90.8)	3513	86.1 (84.9, 87.2)
10–14	4031	94.6 (93.9, 95.3)	2038	99.5 (99.1, 99.8)	3971	90.6 (89.7, 91.5)	2024	86.5 (84.9, 88.0)
15–18	2002	94.8 (93.7, 95.7)	1509	98.9 (98.3, 99.4)	1973	89.0 (87.5, 90.3)	1489	85.4 (83.5, 87.2)
19–25	1544	93.8 (92.5, 95.0)	1537	99.5 (99.0, 99.8)	1534	95.4 (94.2, 96.4)	1533	88.0 (86.3, 89.6)
Race								
White	6547	94.8 (94.3, 95.4)	4366	99.3 (99.0, 99.5)	6458	91.0 (90.2, 91.6)	4339	86.7 (85.7, 87.7)
Black	736	91.6 (89.3, 93.5)	534	99.6 (98.7, 100.0)	733	92.1 (89.9, 93.9)	527	85.6 (82.3, 88.5)
Asian	60	96.7 (88.5, 99.6)	43	100.0 (91.8, 100.0)	59	98.3 (90.9, 100.0)	43	81.4 (66.6, 91.6)
Other	234	94.0 (90.2, 96.7)	141	99.3 (96.1, 100.0)	228	92.5 (88.3, 95.6)	137	90.5 (84.3, 94.9)

hSBA serum bactericidal assay using human complement, *LLOQ* lower limit of quantification

^a 1:16 for PMB80 (A22); 1:8 for PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44)

^b Number of subjects with valid and determinate hSBA titers for the given strain

between subgroups. For sex, observed differences in the percentage of males and females achieving titers \geq LLOQ were $< 5\%$ between subgroups for all test strains except B44, for which the percent difference in response was 6.7% higher among males than females. Minor or no differences in the percentage of subjects with hSBA titers \geq LLOQ were observed across age groups for test strains A22, A56, and B44. However, for test strain B24, a higher percentage of subjects aged 19–25 years achieved titers \geq LLOQ compared with those aged 10–14, 10–18, and 15–18 years (4.8%, 5.3%, and 6.4% more respondent subjects, respectively). For race subgroups, minor between-group differences were observed for percentages with titers \geq LLOQ against each test strain.

Geometric mean titers 1 month after dose 3 are shown in Table 5. Comparisons across sex, age, and race generally indicated only minor differences between subgroups. For sex, observed GMTs for all four test strains were slightly higher in males compared with females, with the greatest difference observed for test strain A56 (171.8 vs. 157.3, respectively). With regard to age, the 19- to 25-year-old age group showed higher observed GMTs against all four test strains than seen in the other age subgroups, with the greatest differences observed for test strains A56 and B24. Across races, minor differences in GMTs were observed for all four test strains.

The percentage of subjects achieving titers $\geq 1:4$ across each of the four test strains after dose 3 is shown in Table 6. Overall, only minor

Table 5 hSBA GMTs in the evaluable immunogenicity population 1 month after dose 3 according to subgroup

	hSBA GMT							
	A22		A56		B24		B44	
	N ^a	GMT (95% CI)	N ^a	GMT (95% CI)	N ^a	GMT (95% CI)	N ^a	GMT (95% CI)
Total	7577	66.5 (65.0, 68.1)	5084	164.6 (160.0, 169.3)	7478	30.0 (29.3, 30.8)	5046	40.4 (38.9, 42.1)
Sex								
Male	3915	70.0 (67.8, 72.3)	2620	171.8 (165.3, 178.7)	3880	32.0 (31.0, 33.1)	2609	45.0 (42.7, 47.4)
Female	3662	63.0 (60.9, 65.1)	2464	157.3 (151.0, 163.8)	3598	28.0 (27.0, 29.0)	2437	36.1 (34.0, 38.3)
Age group, years								
10–18	6033	64.3 (62.8, 65.9)	3547	159.0 (153.8, 164.3)	5944	26.2 (25.5, 26.9)	3513	37.1 (35.5, 38.8)
10–14	4031	62.4 (60.6, 64.2)	2038	161.9 (155.4, 168.7)	3971	25.4 (24.6, 26.1)	2024	37.3 (35.2, 39.5)
15–18	2002	68.4 (65.3, 71.5)	1509	155.1 (147.0, 163.6)	1973	28.0 (26.7, 29.3)	1489	36.9 (34.4, 39.5)
19–25	1544	75.9 (71.6, 80.5)	1537	178.4 (169.0, 188.3)	1534	50.9 (47.9, 54.0)	1533	49.3 (45.6, 53.3)
Race								
White	6547	67.7 (66.0, 69.4)	4366	166.5 (161.4, 171.7)	6458	30.0 (29.2, 30.8)	4339	41.0 (39.3, 42.8)
Black	736	55.5 (51.6, 59.7)	534	144.8 (134.2, 156.2)	733	29.0 (27.1, 31.1)	527	35.0 (31.3, 39.2)
Asian	60	67.0 (53.1, 84.6)	43	165.7 (129.5, 212.0)	59	34.3 (26.9, 43.8)	43	33.0 (20.8, 52.4)
Other	234	72.7 (64.3, 82.1)	141	187.8 (159.5, 221.2)	228	31.9 (27.8, 36.6)	137	48.5 (37.7, 62.4)

GMT geometric mean titer, hSBA serum bactericidal assay using human complement

^a Number of subjects with valid and determinate hSBA titers for the given strain

differences in the percentage of subjects achieving titers $\geq 1:4$ were observed by sex, age, and race across each of the four test strains.

DISCUSSION

Robust immunogenicity of MenB-FHbp has been individually shown in each of the 11 clinical studies collectively enrolling > 20,000 adolescents and adults [9]. A pooled analysis from seven of these clinical studies, which included > 8000 subjects from the clinical development program, was conducted to detect any emergent effects of demographic factors on MenB-FHbp immunogenicity. In this subgroup analysis, immunogenicity was similar across sex, ages assessed, and race (predominantly white and black). Some variation in hSBA

responses was observed between individual test strains across all groups analyzed; this is expected based on differences in FHbp sequences and cell surface expression levels across MenB strains [33, 34]. Moreover, although minor differences by sex were observed among percentages of subjects with ≥ 4 -fold rise in titers from baseline, percentages of subjects with titers \geq LLOQ, and GMTs, the percentages of subjects with titers $\geq 1:4$ against each test strain were highly consistent. Because an hSBA titer of 1:4 is the accepted correlate of protection from meningococcal disease [31, 32], the slight differences in immunogenicity end points reported here are unlikely to be clinically meaningful and do not impact current MenB-FHbp vaccination recommendations [5]. Although the current analysis was focused on immunogenicity only, it should be noted that a

Table 6 Percentage of subjects in the evaluable immunogenicity population achieving hSBA titers $\geq 1:4$ 1 month after dose 3 according to subgroup

	Subjects with hSBA titers $\geq 1:4$							
	A22		A56		B24		B44	
	N ^a	% (95% CI)	N ^a	% (95% CI)	N ^a	% (95% CI)	N ^a	% (95% CI)
Total	7577	94.9 (94.4, 95.4)	5084	99.4 (99.1, 99.6)	7478	92.2 (91.6, 92.8)	5046	88.2 (87.3, 89.1)
Sex								
Male	3915	95.6 (94.9, 96.2)	2620	99.5 (99.1, 99.7)	3880	94.4 (93.7, 95.1)	2609	91.1 (89.9, 92.2)
Female	3662	94.1 (93.3, 94.9)	2464	99.3 (98.9, 99.6)	3598	89.9 (88.9, 90.8)	2437	85.1 (83.7, 86.5)
Age group, years								
10–18	6033	95.0 (94.4, 95.5)	3547	99.4 (99.0, 99.6)	5944	91.3 (90.5, 92.0)	3513	87.3 (86.2, 88.4)
10–14	4031	94.9 (94.1, 95.5)	2038	99.5 (99.1, 99.8)	3971	91.6 (90.7, 92.5)	2024	87.9 (86.4, 89.3)
15–18	2002	95.2 (94.2, 96.1)	1509	99.1 (98.5, 99.5)	1973	90.5 (89.1, 91.8)	1489	86.6 (84.7, 88.3)
19–25	1544	94.6 (93.3, 95.6)	1537	99.5 (99.0, 99.8)	1534	96.1 (95.0, 97.0)	1533	90.3 (88.7, 91.7)
Race								
White	6547	95.2 (94.7, 95.7)	4366	99.4 (99.1, 99.6)	6458	92.1 (91.4, 92.8)	4339	88.4 (87.4, 89.4)
Black	736	92.1 (89.9, 94.0)	534	99.6 (98.7, 100.0)	733	92.6 (90.5, 94.4)	527	86.0 (82.7, 88.8)
Asian	60	96.7 (88.5, 99.6)	43	100.0 (91.8, 100.0)	59	98.3 (90.9, 100.0)	43	83.7 (69.3, 93.2)
Other	234	94.4 (90.7, 97.0)	141	99.3 (96.1, 100.0)	228	93.0 (88.9, 95.9)	137	92.0 (86.1, 95.9)

hSBA serum bactericidal assay using human complement

^a Number of subjects with valid and determinate hSBA titers for the given strain

previous analysis identified no safety concerns among data pooled from adolescents and adults in the MenB-FHbp clinical development program (unpublished data).

Sex, age, and race were selected as factors to include in this analysis because these characteristics have previously been associated with variable immunogenicity of numerous vaccines [10–12, 15–23]. These demographic influences also interact with one another, illustrated in part by fluctuations in sex-dependent immune responses at different times throughout the lifespan [15, 19, 24]. A commonly observed influential variable is age, which is typically associated with decreased immunogenicity in infants and adults aged ≥ 65 years [10, 11]. As an example, clinical trials with live-attenuated and inactivated influenza vaccines are of

interest to highlight differences in vaccine efficacy by age group. In a study of children aged 6–59 months, there were 54.9% fewer cases of culture-confirmed influenza among study children who received the live-attenuated vaccine compared with the group who received the inactivated vaccine [35]. In contrast, in a study of adults aged 18–49 years, the inactivated vaccine provided a 50% reduction in confirmed influenza compared with those given the live-attenuated vaccine [36]. Among children, adolescents, and young adults, aging may either increase or decrease immune responses depending on the vaccine [37–40]. Variable vaccine efficacy among the above-listed age groups has also been shown specifically for some strain-specific MenB outer membrane vesicle (OMV) vaccines. For example, a case-

control study of an OMV antigen-based vaccine developed in Cuba found that protective efficacy was greater among Brazilian adults aged 24–47 years compared with those aged < 24 years [39]. In a review of OMV antigen-based MenB vaccines with vaccine efficacy or hSBA data published before 2015, several studies showed variability across age groups in both vaccine effectiveness and hSBA responses [40]. Additionally, there is evidence to suggest immune responses to vaccines can vary even within the specific age range included in this study. Two studies investigating the immunogenicity of a bivalent human papillomavirus vaccine among female subjects aged 10–25 years found that antibody responses following vaccination were higher in subjects aged 10–14 years compared with those aged 15–25 years [13, 14]. However, in the study presented here, the small differences observed in immune responses between different age groups were not considered clinically meaningful.

Sex differences in vaccine response have also been reported for some vaccines [15–19]. Although the reasons for these differences are not fully understood [15], underlying mechanisms may include sex-based differences in innate and adaptive immunity [17, 18], modulations of immune cell function by sex hormones [15–17, 24], genetic influences [15, 17, 24], and sex-specific features of the diet or microbiome [15]. Most vaccines elicit stronger immune responses in women than in men [15, 17], and this trend persists throughout the lifespan from infancy into late adulthood [19, 24]. An example of this observation is the seasonal trivalent inactivated influenza vaccine, which produces significantly higher GMTs in women compared with men, regardless of dose amount or age [41].

Additionally, some vaccines are associated with variable immune responses based on race or geographic location of the vaccinated subject [20–23, 42, 43]. For example, compared with infants from other countries, those from the Philippines showed lower seroprotection rates and geometric mean concentrations against hepatitis B after vaccination with the combined diphtheria, tetanus, and whole cell pertussis–hepatitis B virus and *Haemophilus influenzae*

type b conjugate vaccine with oral live attenuated poliovirus vaccine (DTPw-HBV/Hib-TT + OPV) coadministered with either a 7- or 10-valent pneumococcal conjugate vaccine [43]. These and other variable responses could result from genetic or environmental factors, although the precise contributions of each are unclear [20–23]. Because the predominant disease-causing vaccine serotypes may differ across global regions [44, 45], responses to vaccinations may also differ geographically.

The effects of sex, age, and race have not been comprehensively reported for licensed, broad-spectrum MenB vaccines. Controlled studies that investigate the possible influence of demographics on vaccine immunogenicity are important for informing vaccine recommendations [15, 16, 19, 24]. The main strength of this subgroup analysis was its large sample size of > 8000 subjects from the pooled evaluable immunogenicity population across seven randomized clinical studies conducted with similar methodology. Limitations include the relatively restricted age range of subjects (10–25 years), although forthcoming data could potentially address subgroup differences in immunogenicity among younger cohorts. Moreover, generalizability of age and race results is limited by the age groups and races included in this study, as most of the evaluable population was aged 10–18 years (80.7%) and white (87.0%). Additionally, most of the racial diversity from this analysis came from only a small number of studies; most of the subjects included were white or black, with Asians and other races representing 0.8% and 3% of the total evaluable immunogenicity population, respectively. As such, studies including a greater number of Asians and other races are needed to reach meaningful conclusions regarding immune responses to MenB-FHbp in these groups. Furthermore, this study focuses on the three-dose MenB-FHbp vaccination schedule; the effects of sex, age, and race on immune responses following a two-dose (0-, 6-month) schedule, which is also approved [5], were not evaluated. Despite these considerations, it is notable that these analyses suggested no clinically meaningful differences in immunogenicity between groups based on sex, ages assessed, or races

evaluated, which indicates that no changes in the clinical management of these subpopulations are warranted regarding vaccination with MenB-FHbp. Additional insight could be provided by long-term follow-up from studies further evaluating the impact of demographics on immunogenicity.

CONCLUSIONS

The immunogenicity profile of the MenB-FHbp vaccine suggested that there were no clinically meaningful differences by sex, age groups assessed or race (predominantly white and black) across three-dose data pooled from the clinical development program. The robust immune responses and lack of clinically significant differences across demographic groups support the continued use of MenB-FHbp for prevention of MenB disease in these populations, as is currently recommended by health authorities.

ACKNOWLEDGEMENTS

Funding. This work was sponsored by Pfizer Inc. The Rapid Service Fees of Infectious Diseases and Therapy have been funded by Pfizer Inc.

Authorship. All named authors had full access to all of the data in this study, meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Medical Writing, Editorial, and Other Assistance. Editorial/medical writing support was provided by Anna L. Stern, PhD, of ICON plc (North Wales, PA, USA) and was funded by Pfizer Inc.

Prior Presentation. This manuscript is based on work that was previously presented at the

IDWeek 2019 conference that took place in Washington, DC, USA, on October 2–6, 2019.

Disclosures. Johannes Beeslaar, Paula Peyrani, Judith Absalon, Jason Maguire, Joseph Eiden, Paul Balmer, Roger Maansson, and John L. Perez are current or former employees of Pfizer Inc. and may hold stock or stock options. Joseph Eiden was an employee of Pfizer Inc and is currently is retired.

Compliance with Ethics Guidelines. The data in this article were derived from previously conducted studies; as such, this article does not describe any new studies with human participants or animals performed, and no new ethical approvals were needed.

Data Availability. Upon request, and subject to certain criteria, conditions, and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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