ORIGINAL ARTICLE

# A Bivalent Meningococcal B Vaccine in Adolescents and Young Adults

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## ABSTRACT

### BACKGROUND

MenB-FHbp is a licensed meningococcal B vaccine targeting factor H–binding protein. Two phase 3 studies assessed the safety of the vaccine and its immunogenicity against diverse strains of group B meningococcus.

### METHODS

We randomly assigned 3596 adolescents (10 to 18 years of age) to receive MenB-FHbp or hepatitis A virus vaccine and saline and assigned 3304 young adults (18 to 25 years of age) to receive MenB-FHbp or saline at baseline, 2 months, and 6 months. Immunogenicity was assessed in serum bactericidal assays that included human complement (hSBAs). We used 14 meningococcal B test strains that expressed vaccine-heterologous factor H–binding proteins representative of meningococcal B epidemiologic diversity; an hSBA titer of at least 1:4 is the accepted correlate of protection. The five primary end points were the proportion of participants who had an increase in their hSBA titer for each of 4 primary strains by a factor of 4 or more and the proportion of those who had an hSBA titer at least as high as the lower limit of quantitation (1:8 or 1:16) for all 4 strains combined after dose 3. We also assessed the hSBA responses to the primary strains after dose 2; hSBA responses to the 10 additional strains after doses 2 and 3 were assessed in a subgroup of participants only. Safety was assessed in participants who received at least one dose.

### RESULTS

In the modified intention-to-treat population, the percentage of adolescents who had an increase in the hSBA titer by a factor of 4 or more against each primary strain ranged from 56.0 to 85.3% after dose 2 and from 78.8 to 90.2% after dose 3; the percentages of young adults ranged from 54.6 to 85.6% and 78.9 to 89.7%, after doses 2 and 3, respectively. Composite responses after doses 2 and 3 in adolescents were 53.7% and 82.7%, respectively, and those in young adults were 63.3% and 84.5%, respectively. Responses to the 4 primary strains were predictive of responses to the 10 additional strains. Most of those who received MenB-FHbp reported mild or moderate pain at the vaccination site.

### CONCLUSIONS

MenB-FHbp elicited bactericidal responses against diverse meningococcal B strains after doses 2 and 3 and was associated with more reactions at the injection site than the hepatitis A virus vaccine and saline. (Funded by Pfizer; ClinicalTrials.gov numbers, NCT01830855 and NCT01352845.)

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*Neisseria meningitidis* causes invasive meningococcal disease, which occurs predominantly in infants, adolescents, and young adults.[1] Patients frequently present with symptoms similar to those of meningitis or septicemia. Death occurs in up to 15% of infected persons,[1] and up to 20% of survivors have long-term impairments.[2,3]

Serogroup B (meningococcal B) accounts for a large proportion of invasive meningococcal disease in the United States, Europe, and other regions.[4-8] Capsular polysaccharide-based vaccines can prevent infection with serogroups A, C, W, and Y, but these vaccines are unsuitable for serogroup B disease because the meningococcal B capsular polysaccharide is not immunogenic.[9] Vaccines that target the outer-membrane vesicle have effectively controlled epidemics caused by single meningococcal B strains,[10,11] but such vaccines are generally ineffective when used against strains other than the targeted strain. Consequently, efforts to develop a meningococcal B vaccine have focused on surface-exposed proteins with the intention of eliciting protective bactericidal antibodies across diverse global invasive strains.

LP2086, a conserved, surface-exposed bacterial lipoprotein that functions as a human complement factor H–binding protein, has been identified as a vaccine target.[12] Epidemiologic studies have suggested that a vaccine containing a factor H–binding protein variant from each of the two immunologically distinct protein subfamilies (A and B) protects against diverse, disease-causing meningococcal B strains.[13,14] These findings spurred the development of bivalent rLP2086, or MenB-FHbp (Trumenba, Pfizer), which consists of one factor H–binding protein variant from each subfamily. On the basis of data from phase 1 and 2 studies,[15-21] MenB-FHbp was the first meningococcal B vaccine licensed in the United States; licensure of 4CMenB (Bexsero, Novartis), the other meningococcal B vaccine available in the United States, followed. The Advisory Committee on Immunization Practices recommends meningococcal B vaccination for at-risk persons 10 years of age and older and recommends that vaccination be considered for persons 16 to 23 years of age for protection against meningococcal B disease.[22,23]

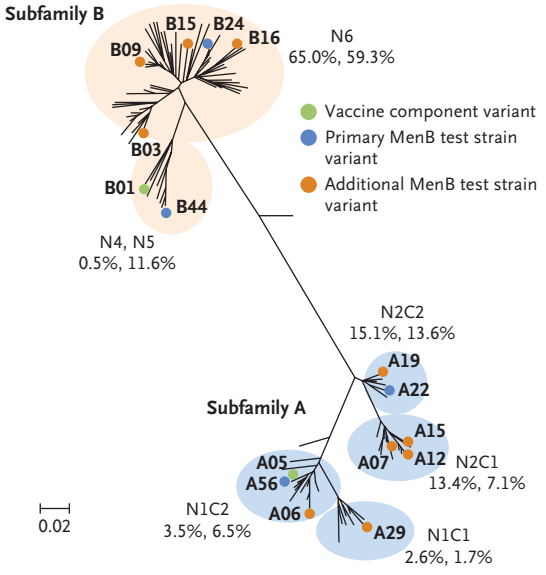
Large-scale efficacy studies of meningococcal vaccines are challenging owing to the low incidence of disease, which precludes the use of clinical disease outcomes. Because protection against invasive meningococcal disease requires the use of serum bactericidal antibodies against meningococcal capsular polysaccharides or protein antigens,[1] vaccine effectiveness is often inferred by measuring bactericidal antibodies in serum bactericidal assays with human complement (hSBAs). An hSBA titer of at least 1:4 is the accepted correlate of protection.[24-27]

MenB-FHbp is designed to afford broad protection against diverse disease-causing strains. Although each invasive meningococcal B strain expresses only one factor H–binding protein variant, numerous such variants have been identified. Therefore, an assessment of vaccine coverage with hSBAs requires an approach to testing strain selection that is different from that used for polysaccharide vaccines, which use only one strain to assess individual serogroup coverage. Four primary test strains that met specific requirements (representative factor H–binding protein expression and epidemiologic diversity among circulating strains and expression of such sequence variants different from vaccine antigens) were selected without bias.[28] To supplement the responses to hSBA obtained with primary strains and to evaluate whether these responses predicted responses against other meningococcal B strains, additional, antigenically diverse meningococcal B test strains that express prevalent factor H–binding protein variants were selected in a manner similar to that used for the primary strains and were used in hSBAs. We conducted two phase 3 randomized, controlled, observer-blinded, multicenter trials to assess the immunogenicity and safety of MenB-FHbp in healthy adolescents and young adults.

## METHODS

### TRIAL DESIGN

Randomization was stratified according to geographic regions, and trials were completed in 10 countries. Enrollment in the trial involving adolescents occurred in Canada (114 participants), the Czech Republic (116), Finland (590), Germany (184), Italy (185), Poland (440), the United Kingdom (161), and the United States (1806). This trial was conducted from April 18, 2013, through June 17, 2015. Enrollment in the trial involving young adults occurred in Canada (367 participants), Denmark (451), Finland (454), Poland (83), Spain (301), and




| Strain | fHbp Variant | fHbp Subgroup | Clonal Complex | Country of Origin | Year of Isolation |
|---|---|---|---|---|---|
| Primary strains | | | | | |
| Subfamily A | | | | | |
| PMB2001 | A56 | N1C2 | CC213 | France | 2002 |
| PMB80 | A22 | N2C2 | CC41/44 | U.S. | 2002 |
| Subfamily B | | | | | |
| PMB2707 | B44 | N4, N5 | CC269 | U.K. | 2006 |
| PMB2948 | B24 | N6 | CC32 | France | 2001 |
| Additional strains | | | | | |
| Subfamily A | | | | | |
| PMB3010 | A06 | N1C2 | CC461 | U.K. | 2001 |
| PMB3040 | A07 | N2C1 | CC162 | Germany | 2004 |
| PMB824 | A12 | N2C1 | CC35 | U.S. | 2001 |
| PMB1672 | A15 | N2C1 | CC103 | France | 2002 |
| PMB1989 | A19 | N2C2 | CC8 | U.K. | 2002 |
| PMB3175 | A29 | N1C1 | CC32 | U.S. | 2000 |
| Subfamily B | | | | | |
| PMB1256 | B03 | N6 | CC41/44 | U.K. | 2001 |
| PMB866 | B09 | N6 | CC269 | U.K. | 2005 |
| PMB431 | B15 | N6 | CC41/44 | U.S. | 2000 |
| PMB648 | B16 | N6 | CC41/44 | U.K. | 2003 |

**Figure 1. Phylogenetic Tree for Factor H–Binding Protein.**

A total of 4 primary and 10 additional meningococcal B (MenB) test strains that expressed vaccine-heterologous factor H–binding protein (fHbp) and that were representative of the epidemiologic diversity of MenB were used in serum bactericidal assays that included human complement (hSBAs) in the clinical development of the MenB-FHbp vaccine. Participant responses to the 4 primary test strains (expressing fHbp variants A22, A56, B24, and B44) were predictive of responses to the 10 additional strains. Percentages shown in the phylogenetic tree are the suggested subgroup prevalence as determined with the use of the percentage of the 1263 isolates in the MenB hSBA strain pool; in each case, the first percentage indicates prevalence in the United States and the second indicates prevalence in the United States and Europe combined.[28]

the United States (1648). This trial was conducted from May 3, 2013, through July 9, 2015.

Adolescents underwent randomization in a ratio of 5:2:2:3 to receive one of three manufacturing lots (hereafter referred to as lots) of MenB-FHbp or hepatitis A virus vaccine (Havrix, GlaxoSmithKline) and saline, and young adults underwent randomization in a ratio of 3:1 to receive MenB-FHbp or saline (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Staff members who administered the vaccines were aware of trial-group assignments and did not assess safety; other trial personnel, the sponsor (Pfizer), and participants were unaware of trial-group assignment.

The sponsor was involved in the trial design and in data collection and analysis. All the authors had access to the data, vouch for the accuracy and completeness of the data, and made the decision to submit the manuscript for publication. The first draft of the manuscript was developed by medical writers funded by the sponsor under the direction of the authors.

### TRIAL OBJECTIVES

The primary immunogenicity objectives included the assessment of immune responses as measured in hSBA titers to 4 primary test strains expressing factor H–binding protein variants A22, A56, B24, and B44 (Fig. 1)[13] 1 month after the administration of dose 3 to satisfy the five primary end points related to immunogenicity. Key secondary objectives included the assessment of hSBA responses to 4 primary strains 1 month after the administration of dose 2 and responses to 10 additional strains (expressing factor H–binding protein variants A06, A07, A12, A15, A19, A29, B03, B09, B15, and B16 [Fig. 1]) 1 month after the administration of dose 3. Primary safety objectives were evaluated on the basis of comparisons of safety outcomes between participants who received MenB-FHbp and controls.

### TRIAL PARTICIPANTS

To be included in the trials, participants had to be healthy. Participants in the trial involving adolescents had to be between 10 to 18 years of age, and

those in the trial involving young adults had to be 18 to 25 years of age. All the participants had to comply with trial procedures. Written informed consent was obtained from the participants, their parents, or otherwise authorized representatives before enrollment. Details regarding the criteria used for trial inclusion and exclusion and the recruitment method are available in the Supplementary Appendix and the protocol, available at NEJM.org.

### INTERVENTIONS

Investigational products were administered intramuscularly into the upper deltoid muscle at baseline and at 2 and 6 months. MenB-FHbp and hepatitis A virus vaccine were formulated as described in the Supplementary Appendix and elsewhere.[29,30] Age-specific doses of hepatitis A virus vaccine were supplied in accordance with country-specific guidelines. Saline was administered at a dose of 0.5 ml. Participants provided approximately 20 ml of blood for hSBAs before receiving dose 1 and approximately 1 month after receiving doses 2 and 3.

### IMMUNOGENICITY

The hSBAs were based on assays described by the World Health Organization[31] and Borrow et al.[25] and were performed as reported previously.[19] Primary and additional meningococcal B test strains are described in Figure 1 and in the Supplementary Appendix. The modified intention-to-treat population included all the participants who had undergone randomization and who had at least one valid and determinate assay result related to the analysis. The per-protocol population included eligible participants who had undergone randomization, received the correct investigational product, had baseline and postvaccination blood draws within the correct intervals, had valid and determinate assay results, and had no major violation of the protocol, a procedure that was consistent with the conduct of preventive vaccine trials in which the objective is estimation of the biologic efficacy of the vaccine and not assessment of a therapeutic effect.[32]

Four primary end points were the proportion of participants who had an increase in the hSBA titer by a factor of at least 4 for each of the four primary meningococcal B test strains from baseline to 1 month after receipt of dose 3 (see the Supplementary Appendix). The fifth primary end point was the proportion of participants who had an hSBA titer that reached or exceeded the lower limit of quantitation for all four primary meningococcal B test strains combined 1 month after the receipt of dose 3 (composite response). The 95% confidence interval for the lower limit for each primary end point was assessed (see the Supplementary Appendix); success was declared when the lower limits of the 95% confidence interval were higher than the defined thresholds. In the trial involving adolescents, the thresholds for A22, A56, B24, and B44 for an increase in the hSBA titer by a factor of at least 4 were 75%, 85%, 65%, and 60%, respectively; the threshold for the composite response was 75%. In the trial involving young adults, the corresponding thresholds for an increase in the hSBA titer by a factor of at least 4 were 55%, 85%, 50%, and 60%, and the threshold for the composite response was 60%. Null and alternative hypotheses are defined in the Supplementary Appendix.

The lower limit of quantitation for strains expressing factor H–binding protein variants A07, A15, A29, A56, B03, B09, B15, B16, B24, and B44 was 1:8, and the lower limit of quantitation for strains expressing A06, A12, A19, and A22 was 1:16. (Details regarding the determination of lower limit of quantitation are provided in the Supplementary Appendix.)

There were several additional end points for immunogenicity. For the primary strains, these end points included the proportion of participants who had an increase in the hSBA titer by a factor of 4 or more and a composite response from baseline to 1 month after receiving dose 2. For all strains, these end points included the proportion of participants who had an hSBA titer that was greater than or equal to the lower limit of quantitation for meningococcal B test strains at baseline and 1 month after receiving doses 2 and 3, the proportion who had a defined hSBA titer at baseline and 1 month after receiving doses 2 and 3, and hSBA geometric mean titers at baseline and 1 month after doses 2 and 3.

### SAFETY

Safety was evaluated for all the participants who received at least one dose of an investigational product. Data regarding injection-site reactions and systemic events, including fever, were collected

in an electronic diary for the first 7 days after each injection. Unsolicited adverse events were reported by investigators and assessed with regard to onset, duration, severity, relationship to the investigational product, and seriousness. Local reactions and systemic events may also have been reported as unsolicited adverse events. Immediate adverse events (those occurring within 30 minutes after injection) were reported. Among all adverse events, serious adverse events, medically attended adverse events, and newly diagnosed chronic medical conditions were assessed for a period of 6 months after the administration of dose 3. See the Supplementary Appendix for additional details.

### STATISTICAL ANALYSIS

In the adolescent group, we determined that the inclusion of 880 participants in the MenB-FHbp group who were able to be evaluated and who received lot 1 would provide a power of more than 99% for the primary immunogenicity hypotheses (see the Supplementary Appendix for details). Thus, a total of 3600 participants (with 1500 in the MenB-FHbp group receiving lot 1) were to be enrolled, with a randomization ratio of 5:2:2:3 (lot 1:lot 2:lot 3:heptitis A vaccine and saline). In the young adult group, we determined that including 1700 participants in the MenB-FHbp group who were able to be evaluated would provide power of more than 99% for the primary immunogenicity hypotheses, for a total enrollment of 3300 participants. The randomization ratio for MenB-FHbp to saline was 3:1, and there was an assumption that 30% of enrollees could not be evaluated. The overall type I error level was 5% for end points related to primary objectives. No control for a type I error level was conducted for end points related to secondary objectives.

The observed proportions of participants were summarized with exact two-sided 95% confidence intervals with the use of the Clopper–Pearson method. All hSBA titers and geometric mean titers were computed with two-sided 95% confidence intervals constructed by means of the back transformation of confidence limits computed for the mean of logarithmically transformed assay data on the basis of Student's t-distribution. Post hoc analyses of positive predictive values determined the association between primary and additional test strains that expressed factor H–binding proteins in the same subfamily. Safety was summarized descriptively. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

## RESULTS

### PARTICIPANTS

Among the 3596 adolescents who underwent randomization, 3272 (91.0%) completed the vaccination phase. Among the 3304 young adults who underwent randomization, 2474 (74.9%) completed the vaccination phase (Fig. 2). In each trial, the demographic characteristics of the MenB-FHbp group and the control group were similar (Table 1).

### IMMUNOGENICITY

In the two trials, the induction of broadly protective antibodies by MenB-FHbp was inferred because all five primary end points for immunogenicity were met. In the modified intention-to-treat population, after dose 3, the percentages of participants in whom the hSBA titers against the four primary test strains increased by a factor of at least 4 ranged from 78.8 to 90.2% among adolescents and from 78.9 to 89.7% among young adults, depending on the strain tested (see Fig. 3A and 3B, and Table S2 in the Supplementary Appendix for results in the modified intention-to-treat population, and see Fig. S2A and Table S3 in the Supplementary Appendix for results in the per-protocol population); percentages in the control groups were 11.0% or less. Composite hSBA responses were 82.7% in adolescents and 84.5% in young adults after dose 3 of MenB-FHbp and 7.4% or less in controls. Among the recipients of MenB-FHbp, after dose 2, 56.0 to 85.3% of adolescents and 54.6 to 85.6% of young adults had hSBA titers that increased by a factor of 4 or more, and 53.7% of adolescents and 63.3% of young adults had a composite response.

Before vaccination, most participants had hSBA titers below the lower limit of quantitation (1:8 or 1:16, depending on strain) (Fig. 3C and 3D, and Tables S2 and S3 and Fig. S2B in the Supplementary Appendix). Among the recipients of MenB-FHbp, the percentages with an hSBA titer that was equal to or greater than the lower limit of quantitation for the primary strains were 64.0 to 99.0% among the adolescents and 67.3 to 97.4% among the young adults after dose 2; the corresponding values after dose 3 were 86.4 to 99.5%

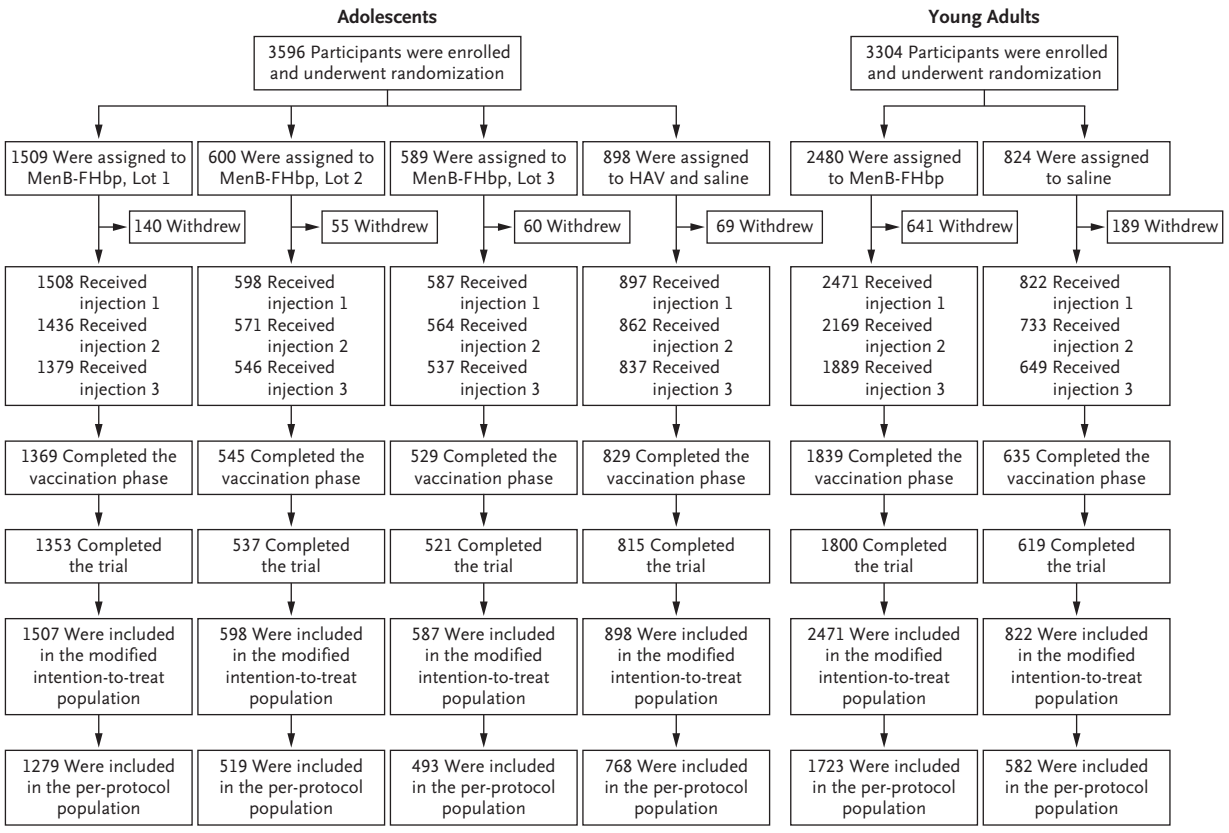



**Figure 2. Disposition of Participants in Both Trials.**

The vaccination phase represents the time from the administration of dose 1 to 1 month after the administration of dose 3. The reasons for withdrawal from both trials are summarized in Table S1 in the Supplementary Appendix. The modified intention-to-treat population included all participants who underwent randomization and who had at least one valid and determinate assay result related to the analysis. The per-protocol population included all participants who underwent randomization, received the correct investigational product, and had baseline and postvaccination blood draws collected within correct intervals, valid and determinate assay results, and no other major protocol violations. HAV denotes hepatitis A virus vaccine.

and 87.1 to 99.3%. The percentages of participants who had defined levels of hSBA titers for primary strains after doses 2 and 3 were substantially higher among MenB-FHbp recipients than among controls (Fig. S3 in the Supplementary Appendix). The hSBA geometric mean titers increased after each dose of MenB-FHbp (Fig. 3E and 3F, and Tables S2 and S3 and Fig. S2C in the Supplementary Appendix). Controls showed negligible hSBA responses. Similar results were obtained for all primary immunogenicity analyses in the per-protocol and modified intention-to-treat populations (Table S4 in the Supplementary Appendix). Sensitivity analyses that were conducted to explore the effects of missing data were completed. Modeling approaches that used partial data yielded conclusions that were similar to the primary findings with respect to the hSBA geometric mean titer and to the increase in titer by a factor of 4 or more (Table S5 in the Supplementary Appendix).

For the additional meningococcal B strains tested with the use of serum samples from a random subgroup of participants, percentages of participants with an hSBA titer that was at least as high as the lower limit of quantitation, percentages with a defined hSBA titer, and percentages with an hSBA geometric mean titer increased substantially from baseline to 1 month after receipt of doses 2 and 3 (Fig. 3C through 3F, and Tables S2 and S3, Fig. S2B and S2C, and Fig. S3 in the Supplementary Appendix).

**Table 1. Demographic Characteristics of the Trial Participants.***

| Characteristic | Adolescents | | | | Young Adults | |
|---|---|---|---|---|---|---|
| | MenB-FHbp, Lot 1 (N=1508) | MenB-FHbp, Lot 2 (N=598) | MenB-FHbp, Lot 3 (N=587) | HAV and Saline (N=897) | MenB-FHbp (N=2471) | Saline (N=822) |
| Age at first vaccination — yr | | | | | | |
| Mean | 13.9±2.6 | 14.0±2.6 | 13.9±2.6 | 13.9±2.6 | 21.5±2.1 | 21.5±2.2 |
| Median† | 14 | 14 | 14 | 14 | 21 | 22 |
| Range | 10–19 | 10–18 | 10–18 | 10–18 | 18–25 | 18–25 |
| | | | | | | |
| Male — no. (%) | 771 (51.1) | 312 (52.2) | 313 (53.3) | 454 (50.6) | 1019 (41.2) | 340 (41.4) |
| Race — no. (%)‡ | | | | | | |
| White | 1307 (86.7) | 526 (88.0) | 522 (88.9) | 779 (86.8) | 1880 (76.1) | 627 (76.3) |
| Black | 129 (8.6) | 46 (7.7) | 39 (6.6) | 78 (8.7) | 515 (20.8) | 169 (20.6) |
| Asian | 7 (0.5) | 2 (0.3) | 4 (0.7) | 3 (0.3) | 38 (1.5) | 13 (1.6) |
| Other | 65 (4.3) | 24 (4.0) | 22 (3.7) | 37 (4.1) | 38 (1.5) | 13 (1.6) |
| Ethnic group — no. (%)‡ | | | | | | |
| Non-Hispanic or non-Latino | 1428 (94.7) | 563 (94.1) | 549 (93.5) | 841 (93.8) | 2042 (82.6) | 686 (83.5) |
| Hispanic or Latino | 80 (5.3) | 35 (5.9) | 38 (6.5) | 56 (6.2) | 427 (17.3) | 136 (16.5) |
| Unknown | 0 | 0 | 0 | 0 | 2 (0.1) | 0 |

* Plus–minus values are means ±SD. HAV denotes hepatitis A virus vaccine. Percentages may not total 100 because of rounding.
† One participant in the trial involving adolescents was 18 years old at randomization, but the first vaccination was delayed because of antibiotic use.
‡ Race and ethnic group were reported by the participants. Two participants in the trial involving young adults were unwilling to disclose race or ethnic group. For analysis purposes, the participants have been pooled with participants who reported race as "other" and ethnic group is considered to be "unknown."

Analyses of positive predictive value assessed whether observed hSBA responses to primary strains predicted immune responses to additional strains that expressed factor H–binding proteins from the same subfamily. The higher the positive predictive values, the more likely it was that the responses to the primary strains predicted responses to diverse meningococcal B strains. Among adolescents, the positive predictive values for subfamily A strains after doses 2 and 3 were 64.4 to 100% and 75.6 to 99.6%, respectively, and for subfamily B strains the corresponding values were 78.9 to 100% and 86.4 to 99.6% (Table S6 in the Supplementary Appendix). Among young adults, the corresponding values were 61.6 to 100% and 72.2 to 100% for subfamily A strains and 70.0 to 100.0% and 80.5 to 98.8% for subfamily B strains.

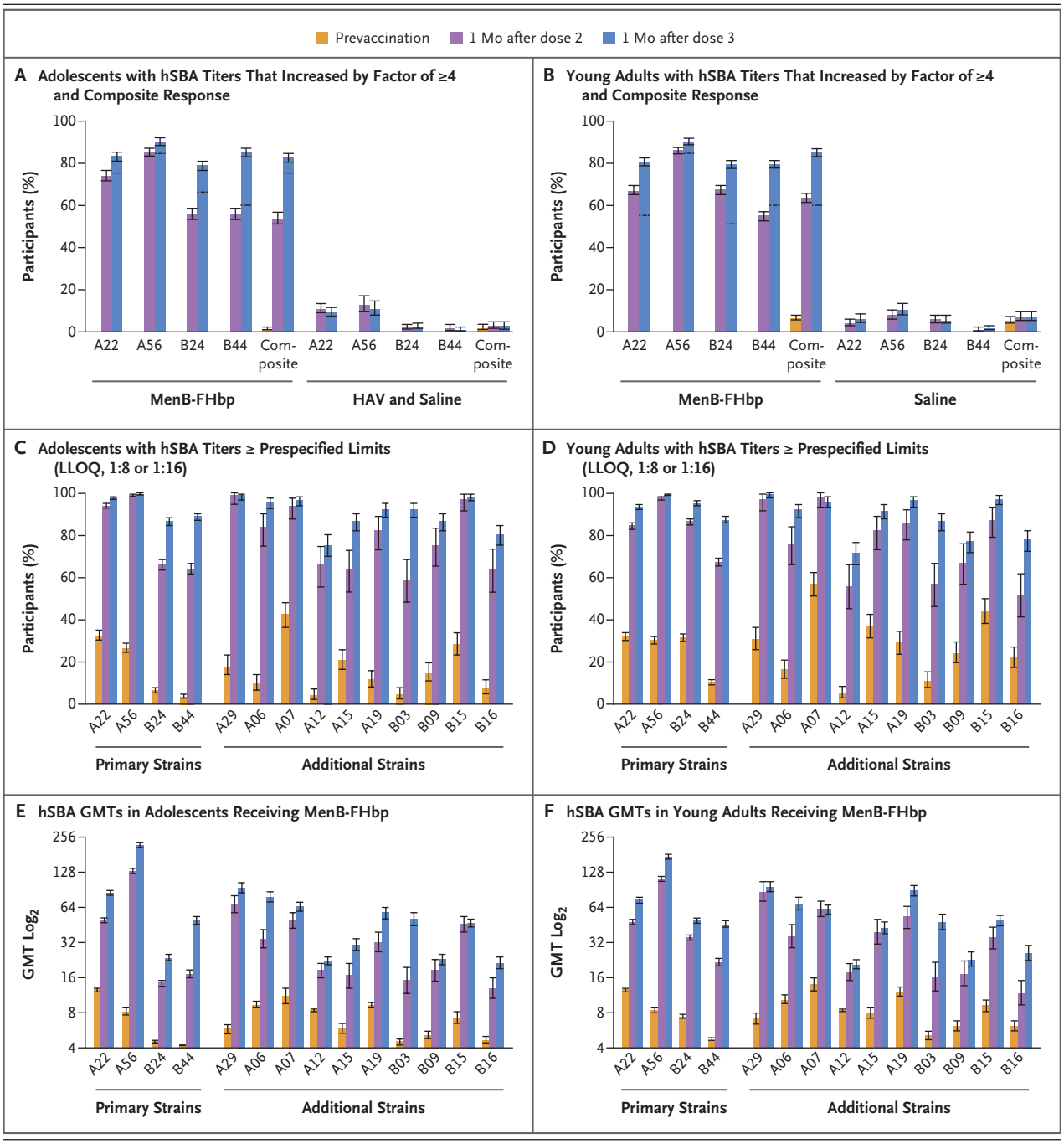
### INJECTION-SITE REACTIONS

Pain was the most common reaction in the two trial groups (Fig. 4A, and Table S7 in the Supplementary Appendix). Among the recipients of MenB-FHbp, the frequency of the reaction was generally highest after dose 1. Six adolescents (all MenB-FHbp recipients) and three young adults (two MenB-FHbp recipients and one saline recipient) withdrew because of local reactions. Few participants (≤1.1%) reported increased severity of reaction with subsequent doses. Among the MenB-FHbp recipients, the median onset of the reaction was 1 to 2 days, and the median duration was 1 to 3 days.

### SYSTEMIC EVENTS

Headache and fatigue were the most common systemic events among both adolescents and young adults (Fig. 4B, and Table S7 in the Supplementary Appendix). The frequency of systemic events was highest after dose 1 in all groups.

One adolescent recipient of MenB-FHbp withdrew because of a systemic event (chills). Four young adults withdrew because of systemic events (three MenB-FHbp recipients because of fever,




mild arthralgia, and moderate myalgia and one saline recipient because of mild chills). Among the MenB-FHbp recipients, the median onset of symptoms was 1 to 5 days, and the median duration was 1 to 2 days.

One adolescent in the control group had a fever higher than 40.0°C after dose 3 (dose 2 of the hepatitis A virus vaccine). One young adult who received MenB-FHbp had a fever of 40.7°C after dose 3, which resolved after day 1. Among adolescents receiving MenB-FHbp, antipyretics were used by 862 of 2686 (32.1%); among controls, antipyretics were used by 180 of 893 (20.2%). Among the young adults, antipyretics were used

**Figure 3 (facing page). Immunogenicity End Points in Adolescents and Young Adults.**

Panel A shows the percentage of participants in the adolescent group who had a baseline serum bactericidal assay with human complement (hSBA) titer for each meningococcal B primary test strain that increased by a factor of 4 or more or a composite response (i.e., hSBA titers that reached or exceeded the lower limit of quantitation [LLOQ] for all four primary meningococcal B test strains combined) at prevaccination and at 1 month after dose 2 and 1 month after dose 3. Panel B shows the same percentages for participants in the young adult group. Panel C shows the percentages of adolescents with hSBA titers greater than or equal to the prespecified limits (LLOQ, 1:8 or 1:16) for the primary meningococcal B strains and for additional test strains. Panel D shows the same percentages for the young adult group. Panels E and F show hSBA geometric mean titers for the adolescent group and the young adult group, respectively. Data are from the modified intention-to-treat population. The increase in the hSBA titer by a factor of 4 or more is defined as follows: for participants with a baseline hSBA titer below the limit of detection (LOD) (hSBA titer <1:4), a response is defined as an hSBA titer greater than or equal to 1:16 or the LLOQ (whichever titer is higher); for participants with a baseline hSBA titer that is greater than or equal to the LOD and lower than the LLOQ, a response is defined as an hSBA titer that is at least four times as high as the LLOQ; and for participants with a baseline hSBA titer that is greater than or equal to the LLOQ, a response is defined as an hSBA titer that is at least four times as high as the baseline titer. Data for the adolescents trial are from MenB-FHbp lot 1 only, for which there was a power of more than 99% for the primary immunogenicity hypotheses. Observed proportions of participants were summarized with the use of exact two-sided 95% confidence intervals, in accordance with the Clopper–Pearson method. I bars represent 95% confidence intervals. GMT denotes geometric mean titer, and HAV hepatitis A virus vaccine. For additional information, including participant numbers, see the Supplementary Appendix.

in 606 of 2438 (24.9%) of those receiving MenB-FHbp and in 121 of 808 (15.0%) of controls.

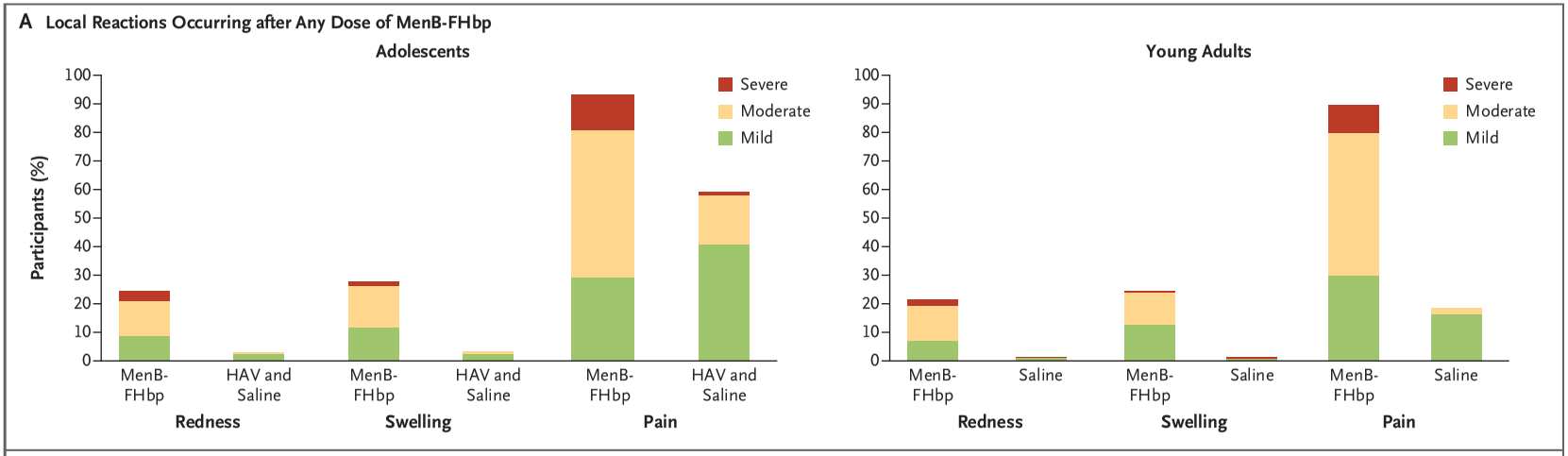
### ADVERSE EVENTS

The overall frequency of adverse events was similar in the MenB-FHbp group and the control group (Table 2, and Tables S7 and S8 in the Supplementary Appendix). Most adverse events and most vaccine-related adverse events that occurred within 30 days after any dose were mild to moderate in severity. Among the young adults, after any vaccination, a greater number of these events were reported by recipients of MenB-FHbp than by controls (4.5% vs. 2.3%). Among the young adults, the between-group difference in reporting vaccine-related adverse events of any type was driven by local reactions and systemic events reported in the clinical database in addition to those captured in participant-reported electronic diaries. Among adolescents, serious adverse events were reported by 1.9% of MenB-FHbp recipients and 2.5% of control recipients; no vaccine-related serious adverse events were reported. Among the young adults, serious adverse events were reported by 1.3% of MenB-FHbp recipients and 1.3% of control recipients; among MenB-FHbp recipients, three participants (0.1%) reported vaccine-related serious adverse events.

## DISCUSSION

Broadly protective hSBA responses were observed in both of these phase 3 trials after three doses of MenB-FHbp (administered at baseline and at 2 and 6 months), and primary immunogenicity end points were met. Immune responses were also reported after the first and second doses. These results are consistent with those from phase 2 licensure trials.[15-21] Immunogenicity was reported on the basis of hSBA titers against an antigenically and epidemiologically diverse panel of primary test strains. These strains were representative of disease-causing meningococcal B isolates expressing factor H–binding proteins that are different from vaccine antigens. Immunogenicity end points required titers above the accepted correlate of protection for invasive meningococcal disease (i.e., ≥1:4). The requirement for an increase in the hSBA titer by a factor of 4 or more also allowed for the assessment of the added benefit of vaccination in populations in whom naturally acquired baseline immunity may be higher than the norm. Furthermore, the composite responses simultaneously measured the hSBA response to all four primary strains combined, which provided an assessment of the ability of vaccine-elicited antibodies to recognize factor H–binding proteins across diverse meningococcal B strains. More than 99% of the participants had a response (hSBA titer ≥ the lower limit of quantitation) to at least one meningococcal B test strain.

In polysaccharide-conjugate and outer-membrane–vesicle vaccines, the antigenic structure of



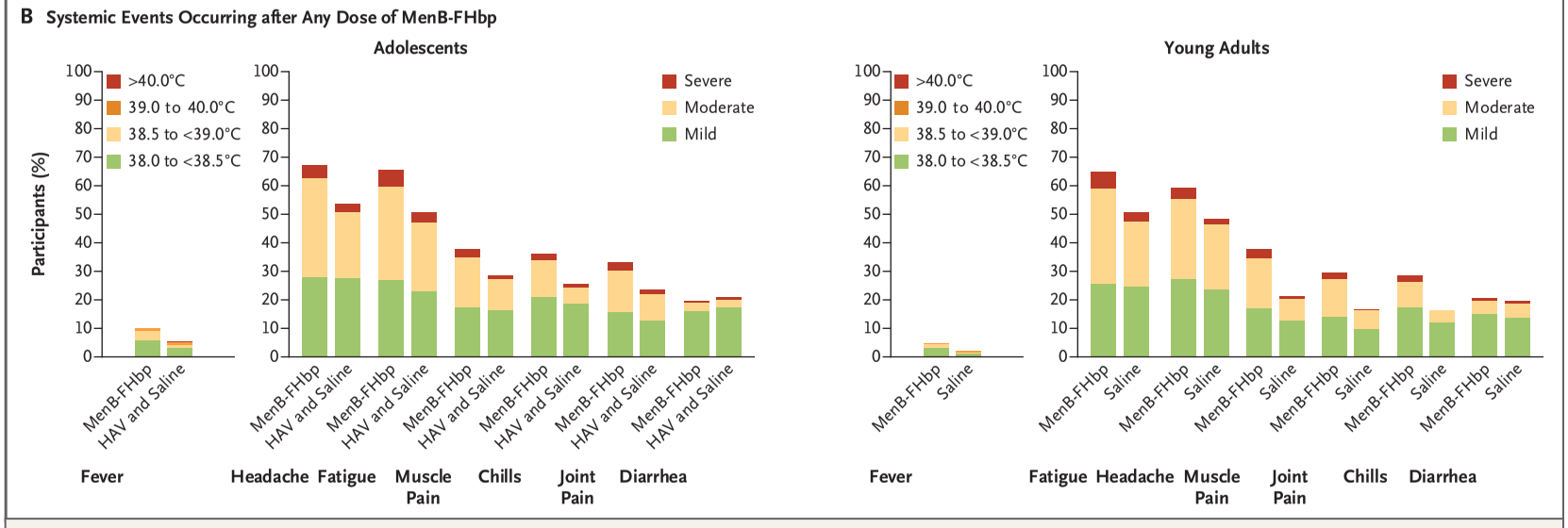




**Figure 4. Injection-Site Reactions and Systemic Events Occurring after Any Dose of MenB-FHbp.**

Panel A shows injection-site reactions, which included redness and swelling (mild, 2.5 to 5.0 cm in diameter; moderate, 5.5 to 10.0 cm in diameter; severe, >10.0 cm in diameter) and pain (mild, does not interfere with activity; moderate, interferes with activity; severe, prevents daily activity). Data were collected with the use of electronic diaries for 7 days after each immunization. Individual data for each dose and after any dose are summarized in Table S7 in the Supplementary Appendix. Percentages for MenB-FHbp recipients are based on 2686 participants in the trial involving adolescents and 2438 in the trial involving young adults. Panel B shows the percentages of severe, moderate, and mild systemic events. HAV denotes hepatitis A virus vaccine. All data presented represent the reactions and events related to all three lots of the vaccine. Muscle pain refers to pain that is occurring in areas other than the injection site.

**Table 2. Participants Reporting at Least One Adverse Event.***

| Characteristic of Event | Adolescents | | Young Adults | |
|---|---|---|---|---|
| | MenB-FHbp† (N=2693) | HAV and Saline (N=897) | MenB-FHbp (N=2471) | Saline (N=822) |
| | *number (percent)* | | | |
| Occurred during vaccination phase‡ | 1097 (40.7) | 392 (43.7) | 771 (31.2) | 256 (31.1) |
| Mild | 673 (25.0) | 242 (27.0) | 494 (20.0) | 175 (21.3) |
| Moderate | 610 (22.7) | 197 (22.0) | 364 (14.7) | 116 (14.1) |
| Severe | 89 (3.3) | 35 (3.9) | 71 (2.9) | 16 (2.0) |
| Related | 52 (1.9) | 16 (1.8) | 114 (4.6) | 20 (2.4) |
| Occurred within 30 days after any vaccination | 682 (25.3) | 240 (26.8) | 523 (21.2) | 155 (18.9) |
| Mild | 375 (13.9) | 143 (15.9) | 313 (12.7) | 104 (12.7) |
| Moderate | 348 (12.9) | 111 (12.4) | 234 (9.5) | 68 (8.3) |
| Severe | 53 (2.0) | 20 (2.2) | 50 (2.0) | 10 (1.2) |
| Related | 52 (1.9) | 15 (1.7) | 110 (4.5) | 19 (2.3) |
| Occurred within 30 min after any vaccination | 10 (0.4) | 3 (0.3) | 11 (0.4) | 7 (0.9) |
| Serious‡§ | 51 (1.9) | 22 (2.5) | 33 (1.3) | 11 (1.3) |
| Related | 0 | 0 | 3 (0.1) | 0 |
| Newly diagnosed chronic condition§ | 15 (0.6) | 10 (1.1) | 10 (0.4) | 2 (0.2) |
| Mild | 6 (0.2) | 7 (0.8) | 3 (0.1) | 0 |
| Moderate | 8 (0.3) | 3 (0.3) | 7 (0.3) | 2 (0.2) |
| Severe | 1 (0.04) | 0 | 0 | 0 |
| Related | 0 | 0 | 0 | 0 |
| Medically attended adverse event§ | 872 (32.4) | 319 (35.6) | 541 (21.9) | 174 (21.2) |
| Mild | 509 (18.9) | 193 (21.5) | 306 (12.4) | 104 (12.7) |
| Moderate | 543 (20.2) | 183 (20.4) | 271 (11.0) | 88 (10.7) |
| Severe | 57 (2.1) | 21 (2.3) | 44 (1.8) | 6 (0.7) |
| Related | 22 (0.8) | 3 (0.3) | 17 (0.7) | 5 (0.6) |

* HAV denotes hepatitis A virus vaccine. Adverse events were unsolicited events as reported by the investigator. Local reactions and systemic events could have also been reported as unsolicited adverse events. Serious adverse events were any untoward medical occurrences at any dose that resulted in death, were life-threatening, required hospitalization or prolongation of hospitalization, resulted in congenital anomaly or birth defect, or were related to lack of efficacy in an approved indication. Severe events were those that interfered significantly with the participant's usual function.
† Data are for participants who received vaccine from lots 1, 2, and 3.
‡ Information on serious adverse events is provided in Table S8 in the Supplementary Appendix.
§ These events occurred throughout the trial.

vaccine antigens and those on targeted strains is the same, which means that selection of multiple hSBA strains is not required to establish vaccine coverage. In contrast, several hundred distinct variants of factor H–binding protein have been identified on meningococcal B strains, which means that the approach to the selection of hSBA test strains to assess MenB-FHbp must be unbiased and must also support the demonstration of broader vaccine coverage.[28] Four primary meningococcal B test strains reflecting factor H–binding protein surface expression, sequence diversity, and overall prevalence of disease-causing variants in Europe and the United States were identified. Responses from an additional 10 test strains provided support for the breadth of response observed with the primary strains. Together, these 14 test strains capture the sequence

diversity observed across the two factor H–binding protein subfamilies (Fig. 1). Furthermore, by demonstrating with positive predictive value analyses the ability of 4 primary test strains to predict coverage with the use of 10 additional test strains, our findings provide assurance that observed immune responses to the primary strains are representative and indicative of vaccine responses to diverse disease-causing meningococcal B strains.

The method that is used to assess breadth of coverage of meningococcal B vaccines is an important consideration in determining their potential for the prevention of endemic disease and the spread of outbreaks. This view was highlighted in a recent study of the 4CMenB vaccine in which hSBA responses to a recent university outbreak strain were compared with vaccine reference strains expressing vaccine-homologous antigens.[33] In contrast to our trial, other trials of 4CMenB predominantly used the Meningococcal Antigen Typing System (MATS) to estimate coverage.[34,35] MATS, which uses pooled serum data, consists of three enzyme-linked immunosorbent assays to detect three of the four 4CMenB antigens: factor H–binding protein, neisserial heparin-binding antigen, and neisserial adhesin A. The fourth antigen, porin protein A (PorA), is evaluated with the use of genotyping.[34,35] Basta and colleagues reported that a lower proportion of participants had a response to 4CMenB when hSBAs were performed with the outbreak strain than when the assays were performed with the vaccine reference strain, which expressed vaccine-homologous antigens (66% for the outbreak strain vs. 87 to 100% for the vaccine reference strain).[33] The response against this outbreak strain was also not as strong as that predicted by MATS in earlier trials.[33] Similar findings have been reported in another trial.[36]

The limitations of our trials are that vaccine efficacy could not be assessed with the use of a clinical disease end point because of the relatively low incidence of meningococcal B disease and the fact that only short-term antibody responses were assessed, which precluded the assessment of antibody persistence. However, the short-term hSBA response, the accepted surrogate of vaccine efficacy, has been used to license other meningococcal vaccines, including meningococcal B outer-membrane vesicle vaccines, and post-licensure surveillance data have supported this approach.[11,24-26,37] A further limitation of our trial involving young adults is the completion rate (2419 of 3304 participants, or 73.2%). This disappointing completion rate may be attributable to the independence of this age group, which has characteristically low adherence to vaccination.[38] Despite a lower-than-desired completion rate, the criteria for success were met.

In conclusion, in two phase 3 trials involving adolescents and young adults, we found that MenB-FHbp was safe and immunogenic after dose 2 and dose 3. The vaccine was also associated with more injection-site reactions than hepatitis A virus vaccine and saline.

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