Breadth and Duration of Meningococcal Serum Bactericidal Activity in Health Care Workers and Microbiologists Immunized with the MenB-FHbp Vaccine

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ABSTRACT MenB-FHbp is a meningococcal serogroup B vaccine with two factor H binding protein (FHbp) antigens from subfamilies A and B. For licensure, efficacy was inferred from serum bactericidal antibody (SBA) responses to four reference strains. Only limited information is available on the breadth or duration of protective SBA responses to genetically diverse disease-causing strains. Seventeen health care or laboratory workers were immunized with two (n = 2) or three (n = 15) doses of MenB-FHbp at 0, 2, and 6 months. SBA levels were measured against 14 serogroup B case isolates, including 6 from U.S. college outbreaks and 2 from Quebec during hyperendemic disease. Compared with preimmunization titers, the proportion of subjects with ≥4-fold increases in SBA titer 1 month after 2 doses of vaccine ranged from 35% to 94% for six isolates with FHbp subfamily A and from 24% to 76% for eight isolates with subfamily B FHbp. The respective proportions with ≥4-fold titer increases at 1 month after dose 3 were 73% to 100% and 67% to 100%. At that time point, the proportion of subjects with titers of ≥1:4 (presumed sufficient for short-term protection) ranged from 93% to 100% for all 14 isolates. By 9 to 11 months after dose 3, 50% or fewer of the subjects with follow-up sera had protective titers of ≥1:4 for 4 of 9 isolates tested. Three doses of MenB-FHbp elicited short-term protective SBA responses to diverse disease-causing serogroup B strains. For some strains, serum titers declined to <1:4 by 9 to 11 months, which raises concerns about the duration of broad, long-term protection. (This study has been registered at Clinical-Trials.gov under registration no. NCT02569632.)

KEYWORDS Trumenba, FHbp, factor H binding protein, meningococcal vaccine, Neisseria meningitidis, vaccines

The meningococcal serogroup B vaccine MenB-factor H binding protein (MenB-FHbp) (Trumenba; Pfizer Vaccines) was licensed under an accelerated approval pathway in 2015 by the U.S. Food and Drug Agency for use in adolescents and young adults (1). The vaccine contains two lipidated recombinant factor H binding protein (FHbp) sequence variants, one from each of subfamilies A and B (2). Efficacy was inferred from serum bactericidal activity (SBA) demonstrated in phase II immunogenicity trials using four serogroup B reference strains, two with FHbp subfamily A and two with subfamily B. The vaccine is currently undergoing regulatory evaluation for licensure in Europe.

Susceptibility of meningococci to anti-FHbp SBA is affected by a number of factors, including antigenic relatedness between the vaccine antigen and the strain antigen (3). In general, even within a subfamily, SBA responses are lower when homology between
TABLE 1 FHbp antigen expression of meningococcal test isolates

| Strain designation or collection site (alternative designation[s]) | Location of isolate collection (yr of collection, no. of cases) | Reference(s) | MLST designation (clonal complex) | FHbp subfamily (peptide ID) | FHbp expression |
|---------------------------------------------------------------|---------------------------------------------------------------|----------------|---------------------------------|--------------------------|----------------|
| M4407 (CH258, B11)                                           | Minnesota, USA (1996, endemic)                                | 4, 12          | 6160 (41/44) B (19)             | A (19)                   | +              |
| CH740 (B2, M11051)                                           | Georgia, USA (2003, endemic)                                 | 4              | 13 (260) A (19)                 | +                        | +              |
| Rutgers University (CH865, M39535)                            | New Jersey, USA (2016, 2 cases)                              | 4, 13          | 11 (11) A (19)                 | +/-                      | +              |
| 03S-0673 (CH862, NM01405)                                     | California, USA (2003, endemic)                              | 4              | 1304 (32) A (23)               | +                        | +              |
| SK016 (CH526, NM01593)                                        | North Carolina, USA (2001, endemic)                          | 4              | 103 (103) A (25)               | +                        | +              |
| CH862 (03S-0451, NM01394)                                     | California, USA (2003, endemic)                              | 4              | 32 (32) A (76)                 | +                        | +              |
| H44/76 (H44/76-SL)                                            | Norway, Europe (1976, hyperendemic)                          | 4, 14          | 32 (32) B (1)                  | +                        | +              |
| University of California, Santa Barbara (CH840, M27846)        | California, USA (2013, 5 cases)                              | 4, 15          | 32 (32) B (1)                  | +                        | +              |
| College in Rhode Island (CH852, M29429)                        | Rhode Island, USA (2015, 2 cases)                            | 4, 16          | 9069 (364) B (1)               | +                        | +              |
| Quebec 2009 (CH860, 100681)                                   | Quebec, Canada (2009, hyperendemic)                          | 4, 17          | 269 (269) B (15)               | +                        | +              |
| Quebec 2013 (CH861, 122747)                                   | Quebec, Canada (2013, hyperendemic)                          | 4, 17          | 269 (269) B (15)               | +                        | +              |
| Ohio University (CH855, M21294)                               | Ohio, USA (2010, 13 cases)                                   | 4, 18          | 269 (269) B (15)               | +                        | +              |
| Princeton University (CH819, M26312)                          | New Jersey, USA (2013, 9 cases)                              | 4, 19, 15      | 409 (41/44) B (276)            | +                        | +              |
| Santa Clara University (CH863, M39090)                         | California, USA (2016, 3 cases)                              | 4, 20, 43      | 11910 (32) B (510)             | +                        | +              |

*Further details of each of the strains are provided in Table 1 of a previous study (4). MLST, multilocus sequence typing.

*The FHbp (peptide) ID is shown in parentheses as annotated in the relevant public database (http://pubmlst.org/neisseria/fHbp/).

*Antigen expression was measured by flow cytometry using live bacteria and monoclonal antibodies or polyclonal mouse sera as previously described (4). + represents high FHbp expression, + represents medium expression, and +/- represents low expression in comparison with strains H44/76 (subfamily B) and M4407 (subfamily A), which naturally express FHbp at high levels. Depending on the subfamily, the reference strain was tested in parallel with each test strain.

RESULTS

The recommended 3-dose schedule for MenB-FHbp is 0, 1 to 2, and 6 months. One month after administration of two doses separated by 2 months, ≧70% of the subjects had ≧4-fold increases in SBA titer for three of the six FHbp subfamily A case isolates (Fig. 1A) and for two of the eight FHbp subfamily B case isolates (Fig. 1B). One month after a third dose, ≧70% of subjects had ≧4-fold increases in SBA responses to all six FHbp subfamily A isolates and to seven of eight FHbp subfamily B case isolates. The exception after dose 3 was the Quebec 2013 isolate with subfamily B FHbp (identifier [ID] 15), with a response rate of 67%. The subfamily A and B FHbp sequence variants in MenB-FHbp are ID 45 (also referred to as A05) and ID 55 (B01), respectively. There was no obvious relationship between ≧4-fold SBA responses to a given strain and its FHbp sequence relatedness with either vaccine antigen (Fig. 1C).

Figure 2 depicts the SBA titers of individual subjects at different time points in relation to immunization as measured against three representative case isolates with FHbp subfamily A (panel A), two case isolates with FHbp subfamily B, and one mutant with lower expression of FHbp subfamily B (panel B). Graphs with the corresponding data for the remaining 9 case isolates are shown in Fig. S1 in the supplemental material. For each isolate, the data are stratified by preimmunization SBA titers of ≧1:8 (the persons likely to benefit most from immunization) and those with preimmunization...
titers of >1:8 (the persons with high levels of natural immunity who were likely protected prior to vaccination). As previously reported for adults immunized with MenB-4C (Bexsero; GSK) (4), subjects in the present study who had preimmunization SBA titers of >1:8 tended to respond to MenB-FHbp vaccination with higher postimmunization SBA titers than subjects with preimmunization titers of ≤1:8. There also appeared to be a relationship between the amount of strain FHbp expression and the postvaccination SBA titer. For example, for the three strains with FHbp subfamily A, the Rutgers University strain had the lowest level of FHbp expression (Table 1) and the titers associated with that strain were lowest after vaccination (Fig. 2A). Similarly, SBA titers were lower with the H44/76 mutant with ~50% less FHbp expression than the parental wild-type (WT) strain (6) than with the parental H44/76 strain, which, as noted above, has naturally high FHbp expression (5) (Fig. 2B).

Figure 3 summarizes the reciprocal geometric mean titers (GMT) before immunization and at different time points after 2 or 3 doses of MenB-FHbp. In this analysis, we excluded data from subjects with preimmunization titers of >1:8. What is notable is the rapid decline in titers seen between 1 month after dose 2 and 4 to 6 months later and the high booster response seen 1 month after dose 3. At 1 month after dose 3, the reciprocal GMT ranged from 33 to >151 for the six case isolates with FHbp subfamily A and from 22 to 76 for the eight FHbp case isolates and one mutant with FHbp subfamily B. The high prevalence of protective titers of ≥1:4 (94% to 100% of the
Subjects with the 14 case isolates and one mutant) was consistent with these high GMTs.

We obtained follow-up sera at 9 to 11 months from 13 of the 15 subjects who received the recommended three doses of vaccine. From the 14 case isolates, we selected 9 to measure SBA persistence, including 3 with FHbp subfamily A and 6 with FHbp subfamily B. We also tested the persistence of SBA against the H44/76 mutant with lower FHbp expression (i.e., a total of 10 test strains). The main criterion for inclusion of a strain was having a minimum of 10 subjects for evaluation with preimmunization titers of \(1:8\).

Against strains CH740, SK016, and Rutgers University, which all express subfamily A FHbp, 80%, 55%, and 27%, respectively, maintained protective titers of \(1:4\) at 9 to 11 months (Fig. 4A). For the strains with FHbp subfamily B (panel B), 50% or fewer of the subjects maintained protective titers at 9 to 11 months against three case isolates (33% for the Quebec 2013 isolate, 42% for the isolate from a college in Rhode Island, and 50% for the Ohio University strain) and against the one mutant tested with lower FHbp expression (43%). Interestingly, among the subjects with preimmunization titers of \(1:8\), the prevalence of protective SBA titers at 9 to 11 months after dose 3 was 85% (11/13) against the Quebec 2009 strain compared with...
33% against the Quebec 2013 strain (4/12 subjects with preimmunization titers of \( \geq 1:8 \), \( P = 0.015 \) by the Fisher exact test). The two strains had identical respective multilocus sequence types (ST), PorA variable region sequence types, and FHbp sequence variants, and the two isolates had similar FHbp expression levels (Table 1 and Fig. 5).

We investigated the basis for the greater anti-FHbp resistance of the Quebec 2013 strain than of the 2009 strain using predose and 1-month-post-dose serum pools from immunized adults. The two strains showed low levels of binding with antibodies in preimmunization serum by flow cytometry which increased in postimmunization serum and were similar for the two strains (Fig. 5A). In 12 independent SBA assays, the postdose 2 immunization pool had a higher reciprocal GMT against the Quebec 2009 strain than against the Quebec 2013 strain (27 versus 11, \( P < 0.0001 \)), which confirmed the relative resistance of the 2013 strain. We also tested a panel of mouse monoclonal Abs (MAbs) to different meningococcal antigens (Fig. 5B). The two strains showed similar levels of binding with the anti-capsular or anti-PorA MAbs by flow cytometry and had similar levels of bactericidal activity. Thus, the anti-FHbp resistant Quebec 2013 strain was not inherently more resistant than the 2009 strain to antibodies directed at other antigens.

By flow cytometry, there was no evidence of lower FHbp expression in the 2013 strain than in the 2009 strain, which could have been an explanation for the greater resistance

![Graph A](image1.png)

![Graph B](image2.png)

**FIG 3** Geometric mean serum bactericidal titers. (A) Strains with FHbp subfamily A sequence variants. (B) Strains with FHbp subfamily B sequence variants. Subjects with preimmunization titers of \( \geq 1:8 \) were excluded. The numbers above the bars indicate the FHbp sequence ID, as described in Table 1. Further details regarding the number of sera tested against each strain at different time points can be found in Table S1 in the supplemental material.
of the 2013 strain to anti-FHbp bactericidal activity. The most notable finding was that of 50-fold-higher binding of the 2013 strain with the anti-neisserial surface protein A (NspA) MAb than of the 2009 strain. Conceivably, the high NspA expression in the Quebec 2013 strain contributed to its relative resistance to anti-FHbp bactericidal activity since, in a previous study, binding of FH to NspA was responsible for resistance of some serogroup B strains to anti-FHbp bactericidal activity (9).

**DISCUSSION**

In the present study, we measured SBA responses of 17 laboratory and health care personnel immunized with the recently licensed MenB-FHbp vaccine. An important strength of our study was the use of a large panel of serogroup B clinical isolates, which were representative of different hypervirulent lineages causing the majority of serogroup B disease in the United States (22). The strain panel also included case isolates from six meningococcal outbreaks on U.S. college campuses and two case isolates from Quebec during a period of hyperendemic disease. Our most important finding was that, compared with the response rates seen with two doses, separated by 2 months, response rates increased following a third dose at 6 months, which resulted in greater uniformity in protective titers between strains than after 2 doses. Thus, the recommended three-dose MenB-FHbp schedule elicited broad short-term protection in nearly all individuals against all isolates tested. The findings are in agreement with that of a large multicenter MenB-FHbp immunogenicity study in healthy European adolescents.

**FIG 4** Persistence of serum bactericidal antibody titers of ≥1:4 at 9 to 11 months after dose 3. (A) Three case isolates with FHbp subfamily A sequence variants. (B) Six case isolates with FHbp subfamily B and one H44/76 mutant with ~50% lower expression of FHbp subfamily B than the parental strain. Strain FHbp sequence variant (peptide ID) and expression data are summarized in Table 1. Subjects with preimmunization titers of >1:8 were excluded. Numbers in parentheses below the x-axis represent the numbers of tested subjects with samples collected before administration of dose 3, 1 month after dose 3, and 9 to 11 months after dose 3 (three sera from each subject). The horizontal line represents 50% of subjects with protective titers of ≥1:4.
which reported that 88% to 99% of subjects achieved protective SBA titers at 1 month after a third dose against four serogroup B reference strains used for licensure of MenB-FHbp (23). Also, two smaller immunogenicity studies reported broadly protective SBA titers at 1 month after dose 3 using a panel of case isolates with FHbp sequence variants that were more divergent than the four reference isolates (10, 11).

Few data are available on the persistence of protective SBA titers in adolescents immunized with three doses of MenB-FHbp. In one study in which 93% to 100% of subjects had achieved protective titers 1 month after a third dose against the four reference strains, the prevalence rates of protective titers at 6 months were found to have decreased to 57% to 89% for three of the reference strains and to 40% for the fourth reference strain (21). In that study, a protective SBA titer was defined as one that was greater than or equal to the lower limit of quantification (≥1:16 for one reference strain and ≥:1:8 for three strains).

In the present study, we measured the persistence of protective SBA titers of ≥:1:4 at 9 to 11 months after a third MenB-FHbp dose. For 4 of the 9 case isolates tested, and for one mutant with lower FHbp expression, ≤50% of the subjects tested at 9 to 11 months maintained protective titers of ≥:1:4. Thus, the broad immunity present 1 month after three doses of MenB-FHbp may be short-lived. However, it is possible that protective immunity could theoretically be maintained despite SBA titers of <:1:4 (24, 25).

For example, meningococci can be killed by opsonophagocytosis in the absence of...
SBA (25–27), and immunized persons with certain inherited complement deficiencies who cannot mount SBA responses, but who can mount opsonic antibody responses, can be protected from developing meningococcal disease (25, 28). A recent postmarketing study found high short-term effectiveness in infants immunized in the United Kingdom with the MenB-4C vaccine (29). Similar postmarketing studies are needed in the United States for teenagers being immunized with MenB-FHbp to determine whether protection against meningococcal disease wanes or persists over time coincident with decreasing prevalence of protective SBA titers of ≥1:4.

Finally, the three-dose MenB-FHbp schedule of administration at 0 months, 1 to 2 months, and 6 months was approved by the FDA for teenagers and young adults when the first two doses are separated by 1 to 2 months. In contrast, the FDA-approved schedule for MenB-4C is two doses separated by 1 to 2 months and does not include a third booster dose (30). We recently reported SBA responses of healthy adults immunized with two doses of MenB-4C, separated by 1 to 2 months (4). That study and the present MenB-FHbp study were not designed to provide comparative immunogenicity data. However, considering all of the strains, the respective ≥4-fold SBA responses to two doses of either vaccine were similar across the strain panel. Conceivably, the lack of benefit of a third dose of MenB-4C seen in prelicensure studies in Chile (31, 32) resulted from a high proportion of the Chilean subjects having titers of ≥1:4 before immunization, which would be expected to result in higher responses to vaccination than in a population that was immunologically naive. Also, the Chilean study tested responses to vaccination using only three antigen-specific indicator strains. The anti-NadA indicator strain, 5/99, is more susceptible to MenB-4C vaccine-induced SBA than case isolates with NadA (4). Also, the anti-FHbp and anti-PorA P1.4 indicator strains used in the Chilean study, and in other studies that have been used as a basis for MenB-4C vaccine licensure (33), are matched exactly for the amino acid sequence of the respective antigens in the vaccine, which rendered these strains more susceptible to vaccine-induced SBA than genetically diverse strains in which the respective antigen sequences varied or had low expression (4).

MATERIALS AND METHODS

Study design. A total of 18 microbiologists or health care workers were enrolled in a postlicensure immunogenicity study of the MenB-FHbp vaccine given at the recommended three-dose schedule of 0, 2, and 6 months. Thirteen subjects were enrolled at University of California, San Francisco (UCSF)-Benioff Children’s Hospital Oakland, Oakland, CA, and 5 subjects at the University of Massachusetts School of Medicine, Worcester, MA. Subjects were eligible if they had no significant underlying diseases that might be expected to impair immune responses and if they provided written informed consent. The protocols and consent forms were approved by the Institutional Review Boards of UCSF-Benioff Children’s Hospital Oakland (protocol 2014-079) and the University of Massachusetts School of Medicine (protocol H00007204). The study is registered at clinicaltrials.gov (ClinicalTrials registration no. NCT02569632).

For the final analyses, data from one subject enrolled in Oakland were excluded because of a diagnosis of biliary cancer after dose 2. Of the remaining 17 subjects, 15 completed the recommended three doses, and 2 subjects withdrew before receiving a third dose, one because of severe local reactions to doses 1 and 2 and the other because of pregnancy. The data for these two subjects were included in analyses of the responses to doses 1 and 2. Thus, for the predose time point and 1 month after dose 2, there were sera from 17 subjects, and for 1 month after dose 3, there were 15 sera. We also obtained sera at 4 to 6 months after dose 2 from 10 subjects, including 2 who did not receive the third dose.

The median age of the 17 subjects included in the final analyses was 40 years (range, 24 to 66 years). Nine (45%) subjects were males; 11 (65%) were of European white ancestry, 1 (6%) was African-American, 2 (12%) were of Asian/Indian ancestry, and 3 (18%) were of other Asian ancestry. Serum samples were obtained immediately prior to dose 1 and 1 month after dose 2 from all 17 subjects and at 1 month after dose 3 from all 15 subjects given three doses. Ten subjects provided an elective serum sample at 4 to 6 months after dose 2, and 12 of the 15 subjects given three doses of vaccine provided a serum sample at 9 to 11 months after dose 3.

Neisseria meningitidis strains. We measured SBA titers against 14 previously described case isolates and one mutant with 50% lower FHbp expression than the parental H44/76 isolate (4, 6), which has naturally high expression (5). Six of the case isolates had FHbp subfamily A, and eight had FHbp subfamily B. Six case isolates were from recent outbreaks on U.S. college campuses (Princeton University [15, 19], University of California, Santa Barbara [15], Ohio University [18], Santa Clara University [20, 43], a college in Rhode Island [16, 34], and Rutgers University [13]). Two additional case isolates were from patients hospitalized between 2009 and 2013 in Quebec, Canada, during a period of hyperendemic serogroup B disease (17). Detailed descriptions of the regions and years of isolation, genetic lineages, and levels of vaccine antigen expression of the isolates have been previously published (4). For convenience,
the strain designations, clonal complexes identified on the basis of multilocus sequence analysis (35), and FHbp sequence variants and their relative expression levels as measured by flow cytometry (36) are summarized in Table 1.

**Serum bactericidal assay.** The assay was performed as previously described (4). In brief, the bacteria were grown to mid-exponential phase in Frantz medium supplemented with 4 mM D-lactate (Sigma) and 2 mM CMP-N-acetylneuraminic acid (Carbosynth). Test sera were heated for 30 min at 56°C to inactivate endogenous complement. Exogenous complement consisted of pooled sera from three healthy adults that had been subjected to IgG depletion using a protein G column as previously described (37). The bactericidal titer was defined as the serum dilution that resulted in a 50% decrease in the CFU count per milliliter compared to the CFU count per milliliter in negative-control wells after a 60-min incubation at 37°C.

**Statistical analysis.** The primary outcome variables were the proportion of subjects with SBA titers of ≥1:4, which were considered sufficient for protection (38, 39), and the proportion of subjects with ≥4-fold increases in SBA titers 1 month after dose 2 or after dose 3, compared to the preimmunization titer, which were considered representative of more-robust responses (4). The proportions were computed along with 95% exact confidence intervals. For calculation of GMT, titers below the limit of detection were assigned half the value of the lowest dilution tested (i.e., 1:2 for titers of <1:4). For calculation of ≥4-fold increases in SBA titers, we required a minimum postimmunization titer of 1:16 for subjects with titers of <1:4 to achieve a ≥4-fold response, which is the definition used by FDA for licensure of serogroup B vaccines in the United States (see Table 1 in the Bexsero U.S. package insert [https://www.gsksource.com/pharma/content/dam/Usa/Prescribing_Information/Bexsero/pdf/BEXSERO.PDF]). All statistical tests were two-tailed; probability (P) values of ≤0.05 were considered statistically significant.

**SUPPLEMENTAL MATERIAL**

Supplemental material for this article may be found at https://doi.org/10.1128/CVI.00121-17.

**SUPPLEMENTAL FILE 1,** PDF file, 0.8 MB.

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D.M.G. and S.R. are inventors listed on patent applications or on issued patents in the area of meningococcal vaccines. Rights to these inventions have been assigned to UCSF Benioff Children’s Hospital Oakland and the University of Massachusetts School of Medicine, respectively. S.R. is a consultant for companies (Achillion and Annexon) that develop therapeutic complement inhibitors. E.L., S.G., and E.P. have declared that they have no conflicts of interest.

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