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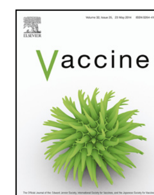

A meningococcal NOMV-FHbp vaccine for Africa elicits broader serum bactericidal antibody responses against serogroup B and non-B strains than a licensed serogroup B vaccine

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ABSTRACT

Background: Meningococcal epidemics in Sub-Sahara caused by serogroup A strains are controlled by a group A polysaccharide conjugate vaccine. Strains with serogroups C, W and X continue to cause epidemics. Protein antigens in licensed serogroup B vaccines are shared among serogroup B and non-B strains.

Purpose: Compare serum bactericidal antibody responses elicited by an investigational native outer membrane vesicle vaccine with over-expressed Factor H binding protein (NOMV-FHbp) and a licensed serogroup B vaccine (MenB-4C) against African serogroup A, B, C, W and X strains.

Methods: Human Factor H (FH) transgenic mice were immunized with NOMV-FHbp prepared from a mutant African meningococcal strain containing genetically attenuated endotoxin and a mutant sub-family B FHbp antigen with low FH binding, or with MenB-4C, which contains a recombinant sub-family B FHbp antigen that binds human FH, and three other antigens, NHba, NadA and PorA P1.4, capable of eliciting bactericidal antibody.

Results: The NOMV-FHbp elicited serum bactericidal activity against 12 of 13 serogroup A, B, W or X strains from Africa, and four isogenic serogroup B mutants with sub-family B FHbp sequence variants. There was no activity against a serogroup B mutant with sub-family A FHbp, or two serogroup C isolates from a recent outbreak in Northern Nigeria, which were mismatched for both PorA and sub-family of the FHbp vaccine antigen. For MenB-4C, NHba was expressed by all 16 African isolates tested, FHbp sub-family B in 13, and NadA in five. However, MenB-4C elicited titers ≥1:10 against only one isolate, and against only two of four serogroup B mutant strains with sub-family B FHbp sequence variants.

Conclusions: NOMV-FHbp has greater potential to confer serogroup-independent protection in Africa than the licensed MenB-4C vaccine. However, the NOMV-FHbp vaccine will require inclusion of sub-family A FHbp for coverage against recent serogroup C strains causing outbreaks in Northern Nigeria.

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1. Introduction

Epidemics of meningococcal disease have occurred in Sub-Saharan Africa for over one hundred years [1]. In 2010, a low cost serogroup A polysaccharide-protein conjugate vaccine (MenAfriVac) was introduced [2–4]. The vaccine conferred protection against invasive disease [5,6] as well as asymptomatic nasopharyngeal carriage of serogroup A strains [7–9], but failed to curtail disease or carriage by strains with serogroups C, X, or W, which also cause epidemics in the region [10–15]. Meningococcal A,C,Y and W conjugate vaccines, which are available in industrialized countries, can prevent epidemics caused by these strains. The conjugate vaccines, however, do not prevent serogroup X disease; and are not affordable in Sub-Sahara, which is one of the poorest regions in the world.

Two recently licensed serogroup B vaccines target protein antigens [16]. One vaccine (Trumenba® Pfizer), which is licensed in the United States [16], contains two Factor H binding protein (FHbp) sequence variants [17], and is referred to as "MenB-FHbp" [16]. The second vaccine (Bexsero®, GlaxoSmith Kline), which is licensed in Europe and 24 other countries including the U.S., contains FHbp and three other components capable of eliciting serum bactericidal antibodies [18]. In Europe, this vaccine is referred to as "4CMenB" and, in the U.S. as "MenB-4C" [16]. Both vaccines target antigens

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shared among serogroup B and non-group B strains. MenB-4C has been reported to elicit serum bactericidal antibody against serogroup X strains from Africa [19]. However, neither serogroup B vaccine is affordable in Sub-Sahara at current prices.

Two laboratories are developing meningococcal native outer membrane vesicle (NOMV) vaccines intended for Africa [20,21]. These vaccines are prepared from mutant African meningococcal strains with genetically attenuated endotoxin and over-expressed Factor H binding protein (FHbp). In wild-type mice, NOMV-FHbp vaccines, given alone [20,21], or in combination with a serogroup A conjugate vaccine [20], elicited high serum bactericidal titers against genetically diverse serogroup A, W, X and B strains.

Binding of FH to FHbp is specific for human and some non-human primate FH [22,23]. The immunogenicity of FHbp-based vaccines is best assessed experimentally in the presence of Factor H that binds to FHbp since data from human FH transgenic mice (reviewed in [24]), and non-human infant primates [25], indicate that binding of FH to FHbp vaccines impairs protective anti-FHbp antibody responses. The purpose of the present study was to compare the breadth of serum bactericidal antibody response elicited by a licensed serogroup B vaccine (MenB-4C), to that of a prototype NOMV-FHbp vaccine being developed for prevention of meningococcal disease in Africa, using a human FH transgenic mouse model.

2. Methods

2.1. Mice

The protocol was approved by the CHORI Animal Care and Use Committee. The human FH transgenic BALB/c mouse (TG) line has been described [26]. For the present study, only TG mice with serum human FH concentrations ≥240 μg/mL (which approximate human serum FH levels [27]) were included. Wildtype BALB/c mice (WT) were purchased from Charles Rivers (Wilmington, MA) and were housed for 3 weeks before beginning the immunization protocol.

2.2. Vaccines

A one-fifth human dose (0.1 ml) of MenB-4C, which was used in our mouse studies, contains 10 μg each of the three recombinant proteins, combined with 5 μg of OMV, which were adsorbed with aluminum hydroxide (0.1 mg Al^{3+}). The investigational NOMV-FHbp vaccine [20] was prepared from a serogroup W mutant of strain Sudan 1/06 with genetically attenuated endotoxin (deletion of *lpxl1* gene [28,29]), inactivation of capsular synthesis [20], and over-expression of a mutant R41S Factor H binding protein (FHbp) peptide identification number (ID) 9. This substitution decreased human FH binding >50 fold, compared to the wildtype FHbp antigen [26]. Strain Sudan 1/06 expresses NadA (ID 6 in group 2/3), Neisserial Heparin binding antigen (NHba) ID 96, and PorA with variable regions (VR) sequence types P1.5,2 (Table 1). This PorA VR type is prevalent among epidemic African serogroup W ST-11 strains [30]. The NOMV-FHbp dose contained 5 μg of protein to match the OMV content of the 1/5th human MenB-4C dose. By SDS PAGE, PorA represented ∼25% of the total protein content of the NOMV-FHbp vaccine (supplemental Figure S2 of our previous publication [20]), and by quantitative Western blot, FHbp was ∼5% [20]. Thus, the 5 μg NOMV-FHbp dose contained approximately 1.25 μg of PorA and 0.25 μg of FHbp. The amount of NadA or NHba has not yet been fully characterized since we are currently developing appropriate methods. By flow cytometry, the mutant vaccine strain used to prepare the vaccine expressed NHba and NadA (data not shown).

2.3. Mouse immunogenicity

Mice, ages 7- to 12-weeks, were immunized with three i.p. injections, each separated by three weeks. Twenty human FH TG animals received MenB-4C, and eight received NOMV-FHbp. We used a larger number of TG mice in the MenB-4C group to provide greater statistical power to detect serum autoantibody to human FH, which was observed previously with MenB-4C in 2 of 11 human FH transgenic mice [31]. As controls to assess immunogenicity in mice in the absence of human FH, we immunized groups of eight WT mice with MenB-4C or NOMV-FHbp. One WT NOMV-FHbp-vaccinated animal died from causes that appeared unrelated to vaccination, leaving 7 animals in that group. Negative control WT and TG mice ($N = 8$ per group) were immunized with aluminum hydroxide without a vaccine antigen (dose of 0.1 mg Al^{3+} to match the Al^{3+} content in 1/5 human dose of MenB-4C). Blood samples were obtained three weeks after the third dose. All sera were heated at 56 °C for 30 min to inactivate internal complement before use.

2.4. Neisseria meningitidis *test strains*

The MenB-4C vaccine contains four antigens known to elicit serum bactericidal antibody: FHbp, NHba, NadA, and PorA P1.4 (as part of detergent-treated outer membrane vesicles [OMV]) [18]. To assess MenB-4C antigen-specific bactericidal antibodies, we used three previously described serogroup B strains [31,32], which were each mismatched for three of the four antigens in MenB-4C. Strain H44/76 is specific for MenB-4C-induced bactericidal antibodies to FHbp, strain 5/99 to NadA [32], and strain SK016 to PorA P1. 4 [31].

We tested serum bactericidal responses against 16 African isolates (Table 1). The isolates were selected from 106 African case isolates to include representatives from different epidemics between 1963 and 2013 [30]. We included five serogroup A isolates, each with different multilocus sequence types (MLST) (i.e., ST-1, -4, -5, -7 and -2859). Because we had fewer serogroup X isolates, we included two ST-751 isolates from outbreaks in Burkina Faso in 1997 and 2003, and two ST-5403 isolates from an outbreak in Uganda and Kenya in 2006, and one ST-3687 isolate from South Africa in the 1970s. Thus, even when there were “replicates” with respect to MLST and major antigens studied, we attempted to have diversity based on differences in year of isolation or geographic area. Similarly for the three serogroup W isolates, two with ST-11 had different FHbp sub-families (A or B) and the third was from clonal complex 175. The only other replicates were two serogroup C isolates from a 2013 epidemic in Northern Nigeria, which represent a new clone spreading in Africa [12]. The percent amino acid identities of the antigens expressed by the test strains and the respective antigens in the vaccines are summarized in Supplemental Table S1.

We also tested serum anti-FHbp bactericidal antibody responses against four previously described mutants of strain H44/76 in which the gene encoding the native FHbp ID 1 had been replaced by either ID 4, 9 or 15 (sub-family B), or ID 22 (sub-family A) [25]. Each of the mutants showed similar relative expression of FHbp as that of the parent strain used to prepare the mutants as measured by flow cytometry [25].

2.5. Serum bactericidal antibody activity

The assay was performed as previously described [31]. The complement source was IgG-depleted human serum prepared as previously described [26]. The bactericidal titer was the dilution of serum that resulted in a 50% decrease in colony-forming units (CFU/ml) after 60 min of incubation at 37 °C, compared to CFU/ml in negative controls wells.

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