Immunogenicity Studies of MenB Vaccines in Adults

ACIP

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Background

- Men A, C, Y and W capsular based vaccines, minimal antigenic variability within a capsular group
- Disease-causing MenB strains, protein antigens have large variability in amino acid sequence and expression, which can affect susceptibility to serum bactericidal activity
- For vaccine MenB licensure, efficacy was inferred based on data against a limited number of “reference strains”
- Gaps in knowledge
  - Extent of protection against more diverse disease-causing strains
  - Effect of vaccination schedule (2 doses vs 3), and duration of protection
Three Separate MenB Immunogenicity Studies in Adults

• Not designed to provide comparison data between vaccines
• Independent of industry
• No relevant potential conflicts of interest – other than inventor on patents related to meningococcal vaccines (assigned to UCSF Benioff Children’s Hospital)
Conclusions

• One month post dose 2, both vaccines elicited protective bactericidal antibody (titers ≥1:4) against most strains

• Some strains are relatively resistant to bactericidal activity despite prediction of susceptibility by sequence analysis and antigen expression

• After dose 2, titers can decline within 4 to 6 months, especially for strains with low antigen expression
## Study 1, MenB-4C*
### Immunogenicity in Adults

| Study Sites | Oxford Vaccine Clinic, UK (N=15)  
| UCB SF Benioff Children’s Hospital Oakland (N=5) |

| Median age, years | 29 |
| Healthcare or lab worker, No. (%) | 12 (60) |
| Vaccine Schedule, Mos. | 2 doses, 0,1 or 0, 2 |

*Bexsero, GSK

Giuntini et al, Clinical Vaccine Immunol, 2016
In press
MenB-4C: Four Antigens

FHbp (sub-family B)  NHba  NadA  PorA (P1.4)

OMV  PorB  PorA  LPS  NspA

From, O’Oran et al, Drugs 2014
≥4-Fold Increases in Serum Bactericidal Antibody Titer to MenB-4C*

Studies 1 and 2, data from FDA package Insert; Current study, N=20

*1 Mo Post dose 2/Pre
Sub-family B FHbp sequence variants (ID)

Adapted from, Granoff et al, J Infect Dis 2015
Serum Bactericidal Antibody Responses of Healthy Adults Immunized with 2 Doses of MenB-4C

FHbp Sub-Family B Strains

<table>
<thead>
<tr>
<th>Strain</th>
<th>ID 1</th>
<th>ID 15</th>
<th>ID 510</th>
<th>ID 276</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC Santa Barbara</td>
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<tr>
<td>College, RI</td>
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<tr>
<td>Quebec 2009</td>
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<tr>
<td>Quebec 2013</td>
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<tr>
<td>Ohio Univ</td>
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<tr>
<td>Santa Clara Univ</td>
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<tr>
<td>Princeton Univ</td>
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</tr>
</tbody>
</table>

≥4-fold titer Increases (1 mo Post-dose 2/Pre)

Outbreak Strains

* or ++ NHba
† or ++ NadA

MenB-4C has Sub-family B FHbp

Giuntini et al,
Clin Vac Immunol 2016, in press
Serum Bactericidal Antibody Responses of Adults Immunized with 2 Doses of MenB-4C*

MenB-4C has Subfamily B FHbp

* Giuntini et al, Clin Vac Immunol 2016, in press
# Study 2, MenB-FHbp* Immunogenicity in Adults

<table>
<thead>
<tr>
<th>Study Sites</th>
<th>UCSF Benioff Children’s Hospital Oakland (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>University of Massachusetts Medical Center (N=5)</td>
</tr>
<tr>
<td>Median age, years</td>
<td>40</td>
</tr>
<tr>
<td>Healthcare or lab worker, No. (%)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Vaccine Schedule, Mos.</td>
<td>3 doses, 0, 2 and 6</td>
</tr>
</tbody>
</table>

*Trumenba, Pfizer

*Lujan et al, International Pathogenic Neisseria Conference (IPNC), 2016
MenB-FHbp (Trumenba, Pfizer)

FHbp Sub-family A and B

Sub-family B

BO1

Sub-family A

AO5
Serum Bactericidal Antibody Responses of Adults Immunized with MenB-FHbp: 0,2 Mo Schedule*

1 Mo Post Two Doses

FHbp Sub-Family A Strains

100
80
60
40
20
0

Percent (95% CI)

M4407
CH740
Rutgers Univ
03S-0673
SK016
03S-0451

≥4-fold Increases in titers
(1 mo post-dose 2/Pre)

* Lujan et al, IPNC 2016

Pfizer Data

Data from Package Insert
Serum Bactericidal Antibody Responses of Adults Immunized with Two Doses of MenB-FHbp: 0,2 Mos

≥4-Fold titer Increases (1 Mo Post dose 2/Pre titers

Lujan et al, IPNC 2016
Subjects with <4-fold Increases in SBA Titer 1 Mo After Vaccination Can have “Protective” Serum Bactericidal Titers ($\geq 1:4$)

Bactericidal Titers for a Representative Strain (Quebec 2013, Hyperendemic)

FHbp sub-family B (ID 15)
Also expresses NHba
Serum Bactericidal Antibody Responses: Quebec 2013

Two Doses, Separated by 1 to 2 Mos.

MenB-4C

1/Bactericidal titer

MenB-FHbp

Third Dose

MenB-FHbp

PD2, post dose 2
PD3, post dose 3

Subjects with pre-titers ≥1:4 excluded
Study 3, MenB-4C Immunogenicity in Santa Clara University Students

- January 31-February 3, 2016, 3 cases (2 culture confirmed), ST 32 clonal complex
- MenB-4C vaccination clinics
  - Feb 4-8, 4,921 persons received first vaccine dose
  - March 18 and April 6-8, 4,731 persons immunized (most receiving second dose)
- Sera collected May 23-25, from 246 students - 0 dose, N=52; 1 dose, N=91; and 2 doses, N=101
- Measured serum bactericidal against the college outbreak strains
Princeton University Outbreak Strain

• 9 cases, 1 death
• Outbreak strain, expressed two MenB-4C antigens, FHbp subfamily B and NHba
• Previous study
  – 66% of students immunized with 2 doses of MenB-4C, had protective serum bactericidal titers ≥1:4 (Basta et al, NEJM 2016)
Prevalence of Serum Bactericidal Titers of Santa Clara Univ. Students Immunized with MenB-4C

Interim results

Strain expresses two MenB-4C antigens, FHbp subfamily B (ID 276) and NHba

Interim results
MenB-4C Bactericidal Activity

- Complex vaccine, 4 antigens capable of eliciting serum bactericidal activity
- Antigen-specific reference strains are more susceptible to vaccine-induced bactericidal antibodies than many circulating disease-causing strains
- Some strains are relatively resistant to bactericidal activity despite prediction of susceptibility by sequence analysis and antigen expression
- Great majority of subjects have titers of ≥1:4 at 1 mo post dose 2 against most strains
- Titers decline by 4 to 6 mos, especially against low FHbp-expressing strains
MenB-FHbp, 2 Injections, Separated by 2 Mos

- At 1 Mo post dose 2, similar ≥4-fold increases in serum bactericidal activity as MenB-4C (against most strains)
- Great majority of subjects have titers of ≥1:4 at 1 mo post dose 2 against most strains
- Titers decline by 4 mos, especially against low FHbp-expressing strains
- Recommended third dose of MenB-FHbp at 6 months boosts titers
- Additional data on antibody persistence needed (should include strains relatively resistant to vaccine-induced bactericidal activity)
Limitations of Current Studies

• Not designed to provide comparison data between vaccines
• Relatively few sera 4 to 6 months post-dose 2
• Serum bactericidal assays used research assays (not FDA validated)
• Data on sera from Santa Clara University study are antibody prevalence and interim analyses
MenB-4C
Immunogenicity Study

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MenB-FHbp
Immunogenicity Study

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Outbreak Strains, CDC