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) UCSF 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)

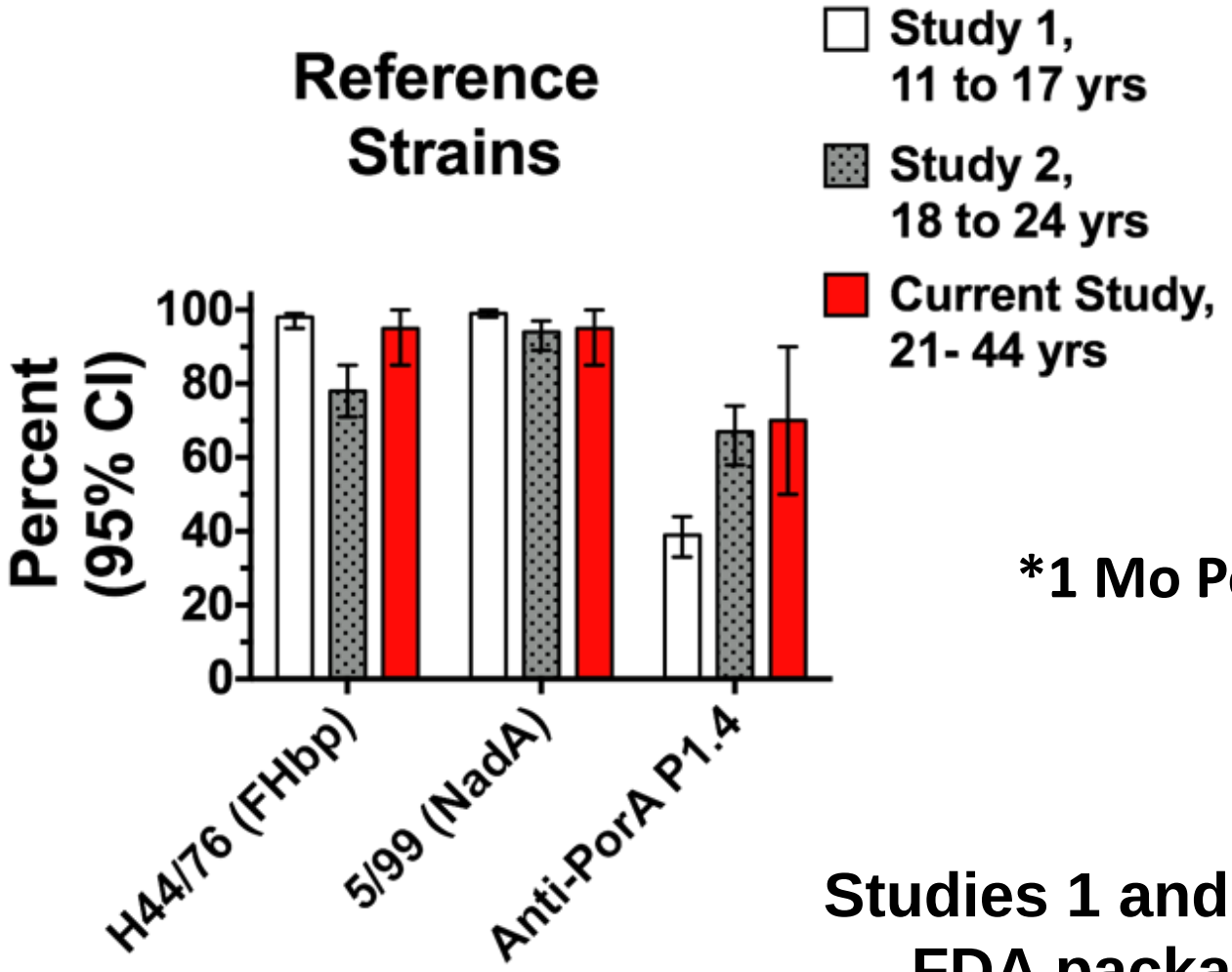
NHba

NadA

PorA (P1.4)

From, O'Oran et a, Drugs 2014

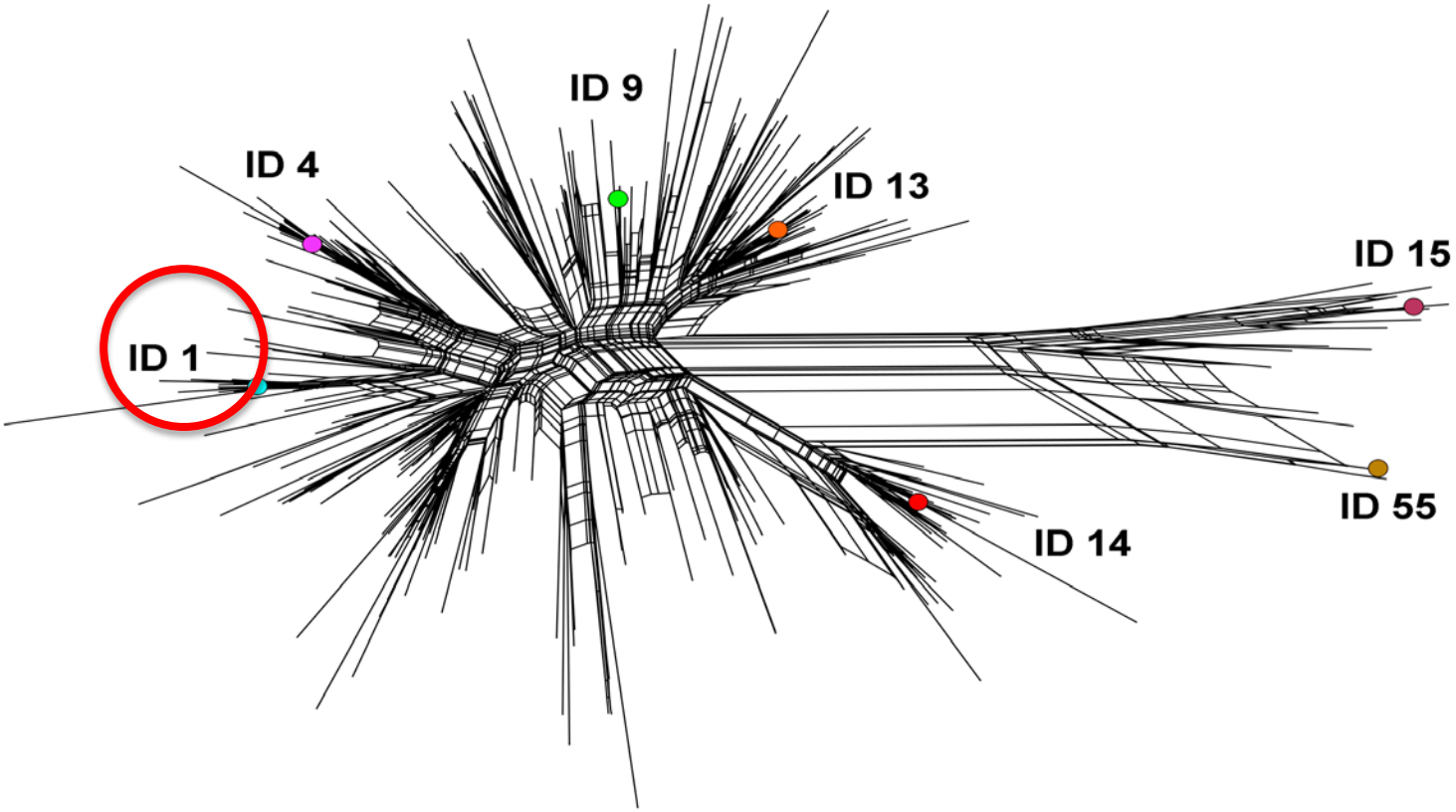
≥4-Fold Increases in Serum Bactericidal Antibody Titer to MenB-4C*



*1 Mo Post dose 2/Pre

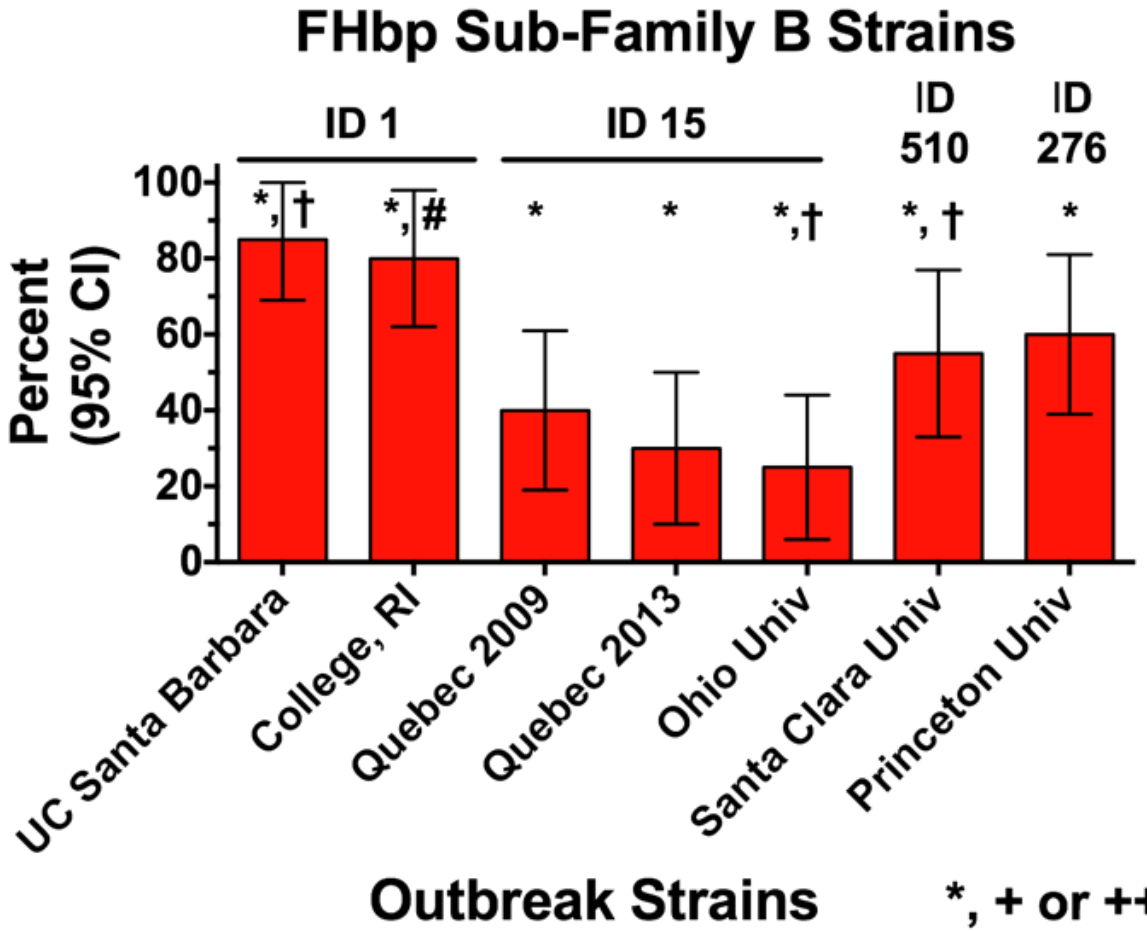
Studies 1 and 2, data from FDA package Insert; Current study, N=20

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



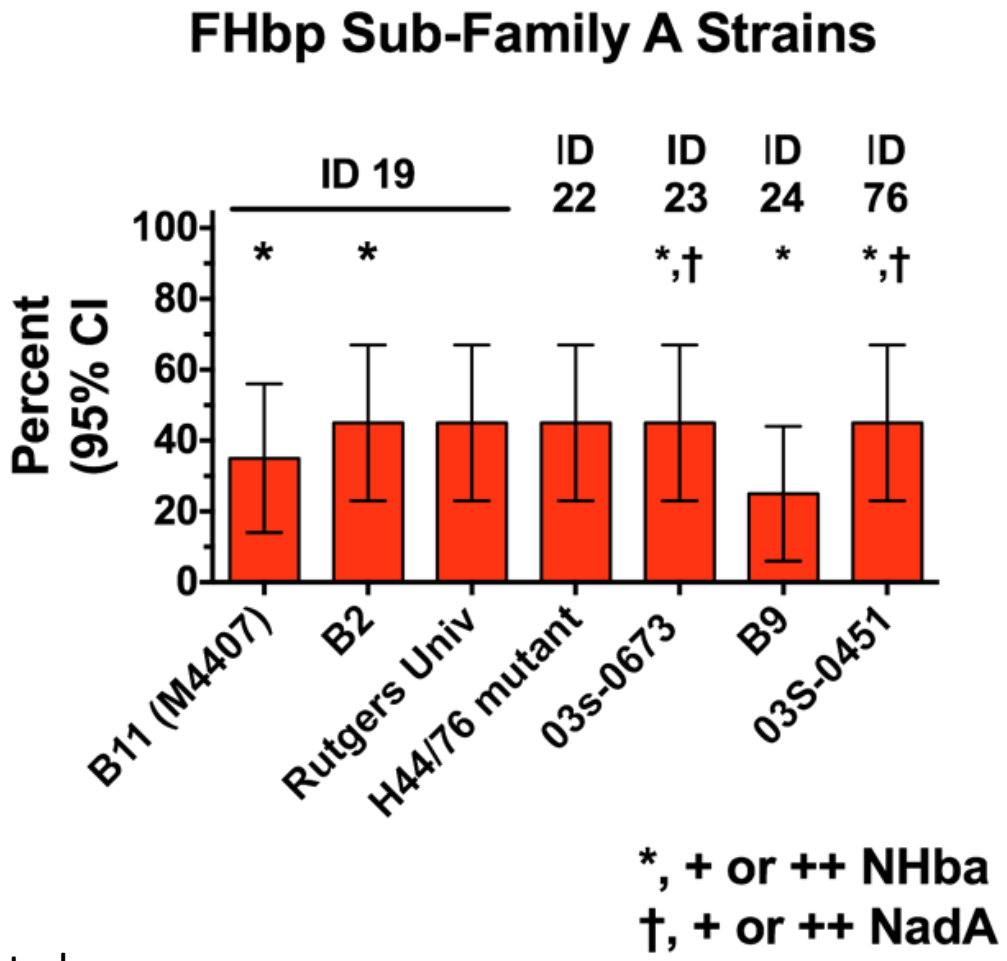
≥4-fold titer Increases (1 mo Post-dose 2/Pre)

***, + 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*



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

***, + or ++ NHba**
†, + or ++ NadA

MenB-4C has Sub-family B FHbp

Giuntini et al,
Clin Vac Immunol 2016, in press

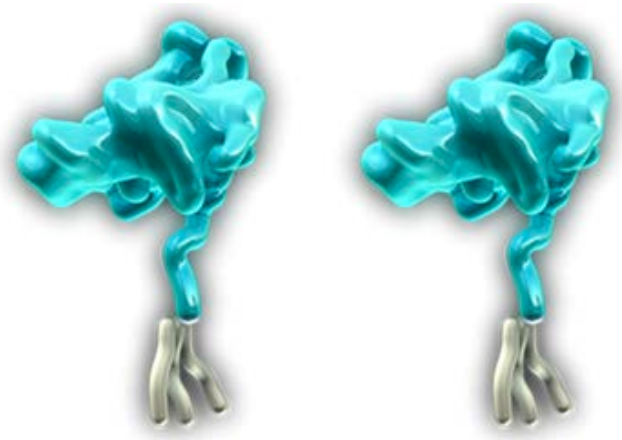
Study 2, MenB-FHbp* Immunogenicity in Adults

Study Sites	UCSF Benioff Children's Hospital Oakland (N=12) University of Massachusetts Medical Center (N=5)
Median age, years	40
Healthcare or lab worker, No. (%)	17 (100)
Vaccine Schedule, Mos.	3 doses, 0, 2 and 6

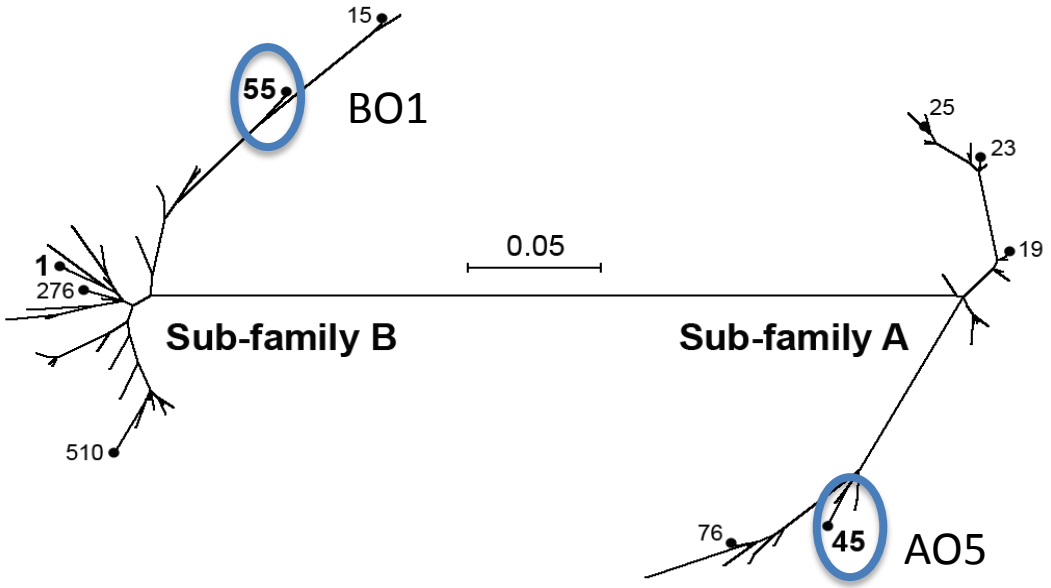
*Trumenba, Pfizer

*Lujan et al, Interational Pathogenic Neisseria Conference (IPNC), 2016

MenB-FHbp (Trumenba, Pfizer)

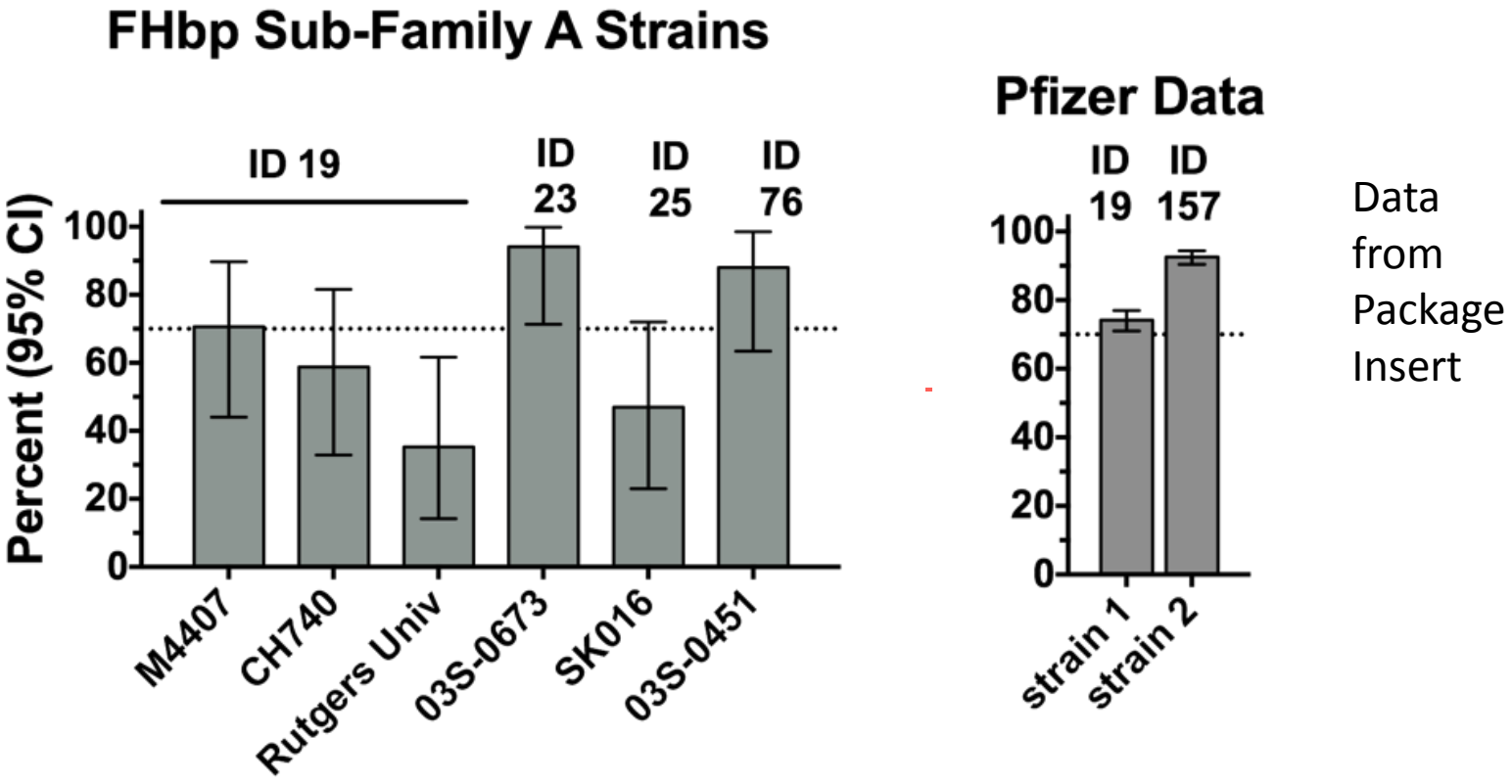


FHbp Sub-family A and B



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

1 Mo Post Two Doses



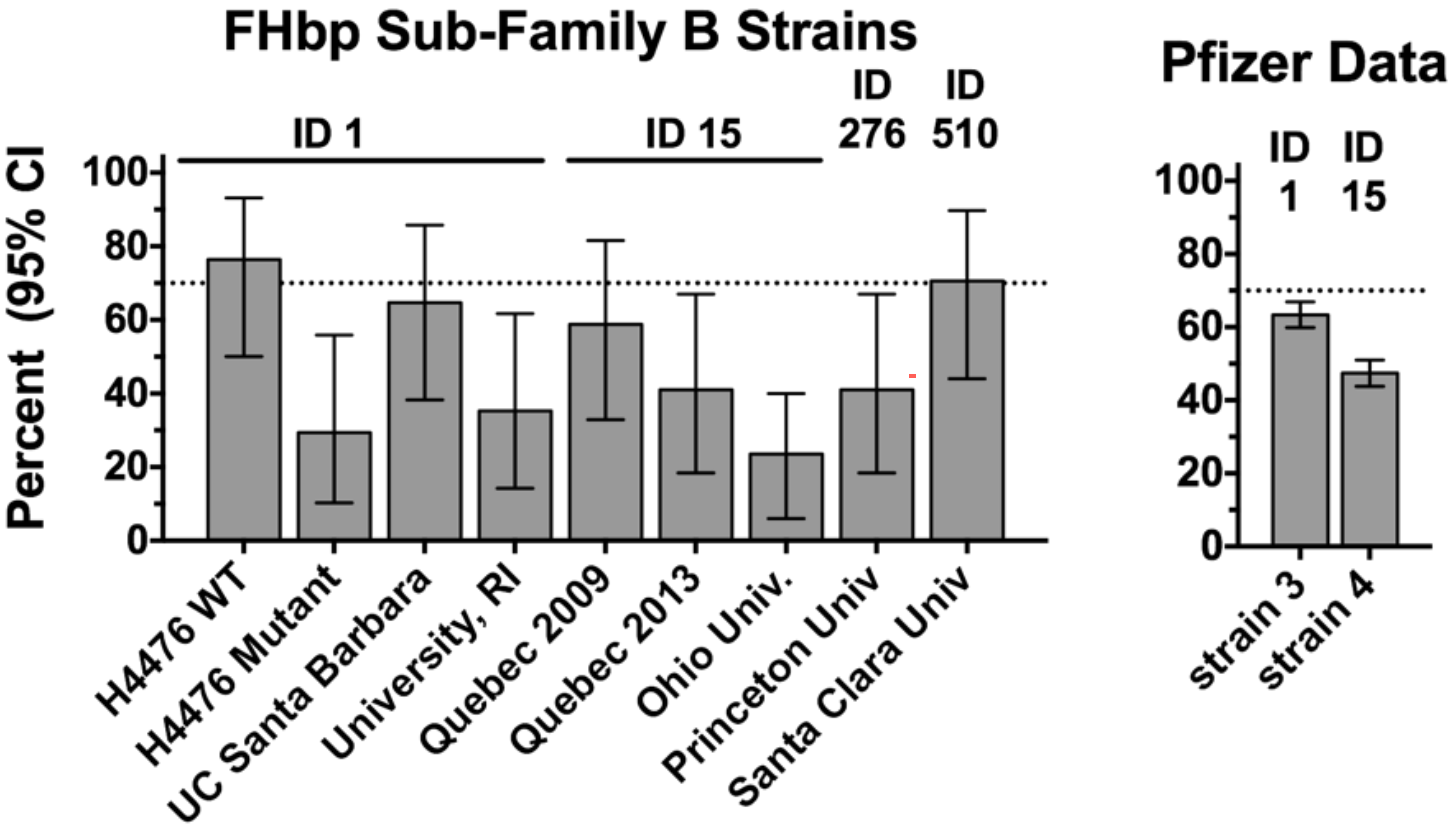
Data from Package Insert

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

***Lujan et al, IPNC 2016**

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 (≥1:4)

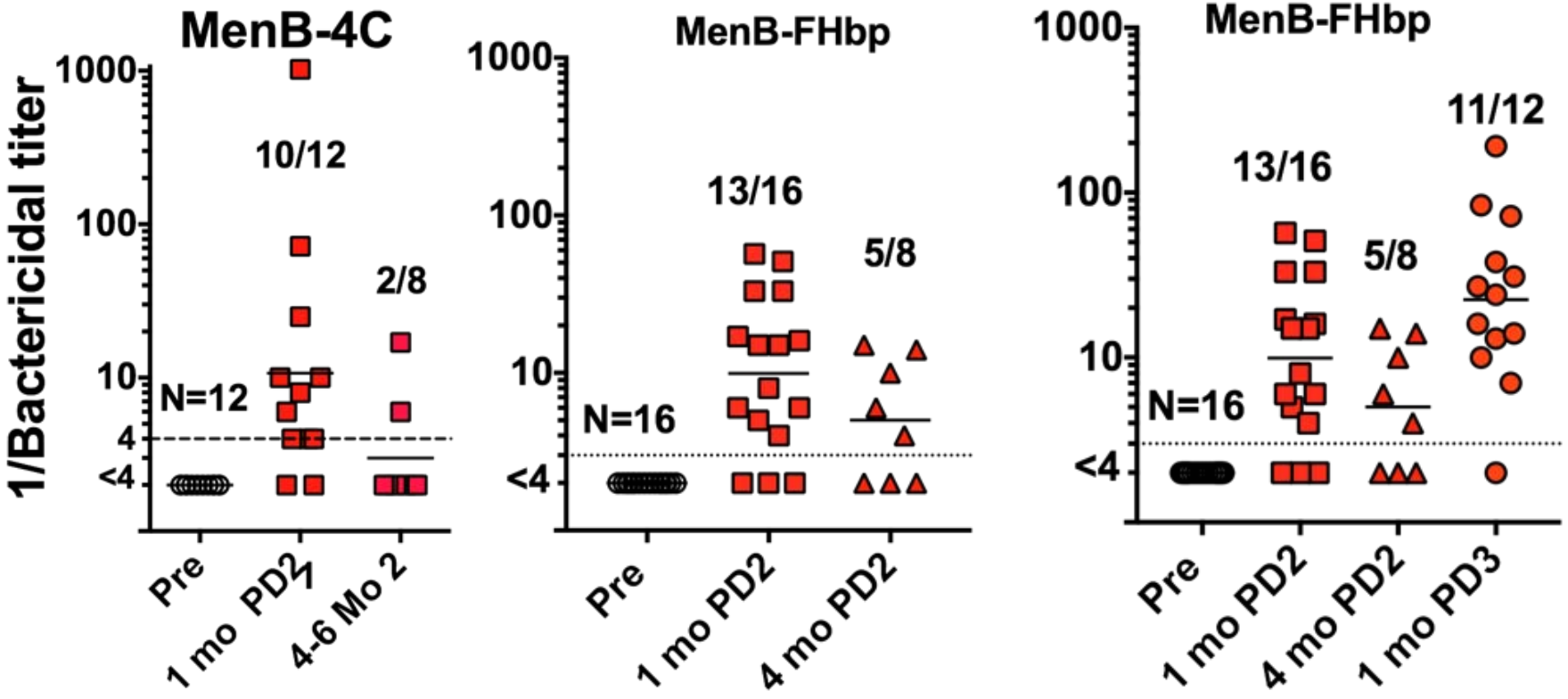
Bactericidal Titers for a Representative Strain (Quebec 2013, Hyperendemic)

FHbp sub-family B (ID 15)
Also expresses NHba

Serum Bactericidal Antibody Responses: Quebec 2013

Two Doses, Separated by 1 to 2 Mos.

Third Dose



PD2, post dose 2
PD3, post dose 3

Subjects with pre-titers ≥1:4 excluded

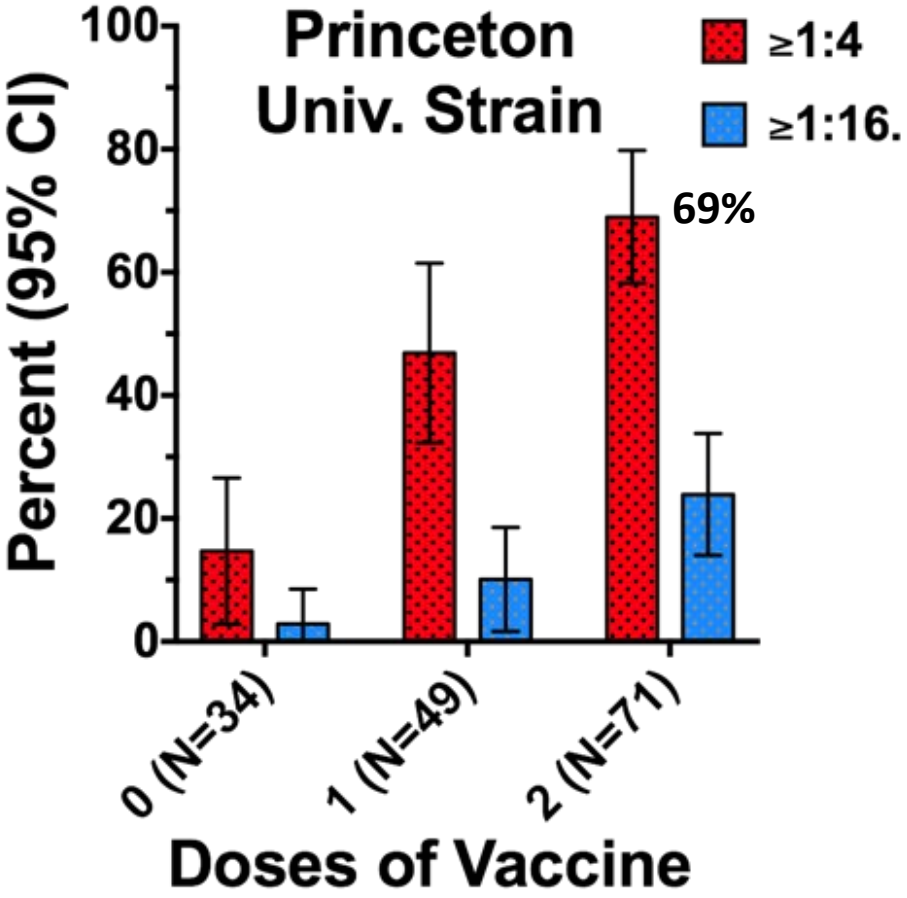
Study 3, MenB-4C Immunogenicity in Santa Clara University Students

- 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



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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