

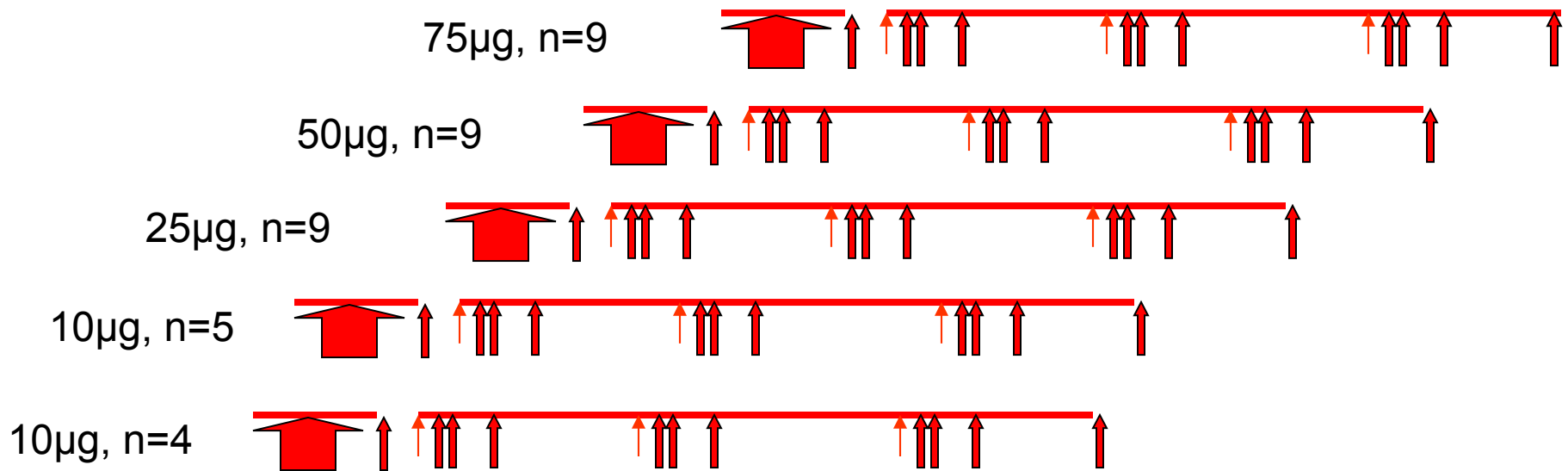
A Phase I Trial of the
HOPS-G NOMV vaccine for group B
Neisseria meningitidis.

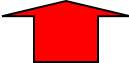


Paul B. Keiser, M.D.
Walter Reed Army Institute of Research

Study Overview

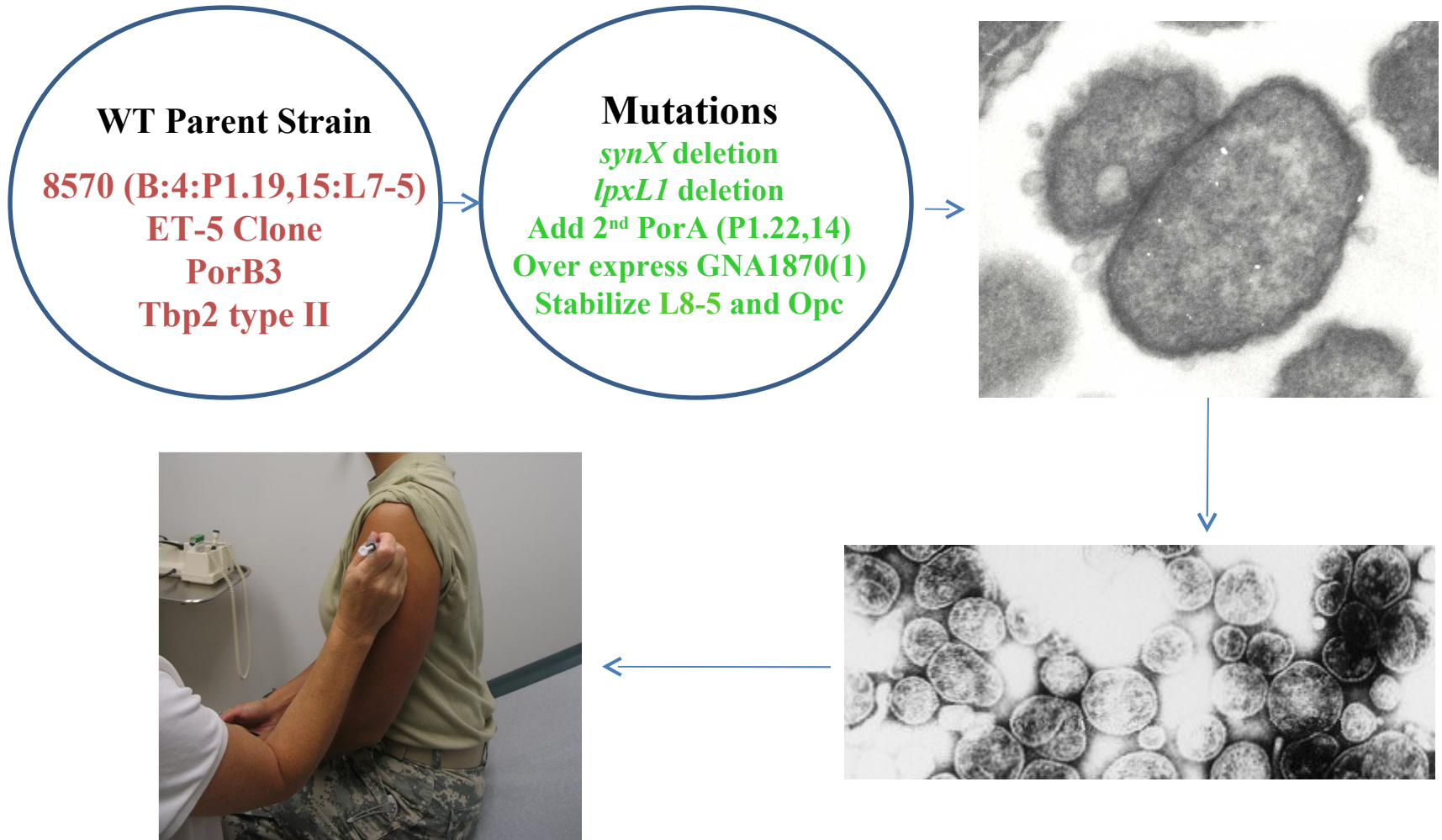
- Volunteers were assigned to one of 4 dose groups (10mcg, 25mcg, 50mcg, 75mcg, each with alum) based on the order in which they were found eligible.
- Total of 36 volunteers (9 per group)
- Three IM vaccinations six weeks apart.

The Schedule



-  - SCREENING
-  - ASSESSMENT
-  - VACCINATION

From bench to bedside



Genetic modifications to parent strain

- Deletion of *lpxL1* (*htrB*)
 - Stabilize *Opc*
 - Add 2nd *PorA* (P1.22,14)
 - *synX* deletion
 - Over express factor H binding protein (var. 1)
 - *GNA1870*(1)
- H
 - O
 - P
 - S
 - G

Safety Data: injection site pain

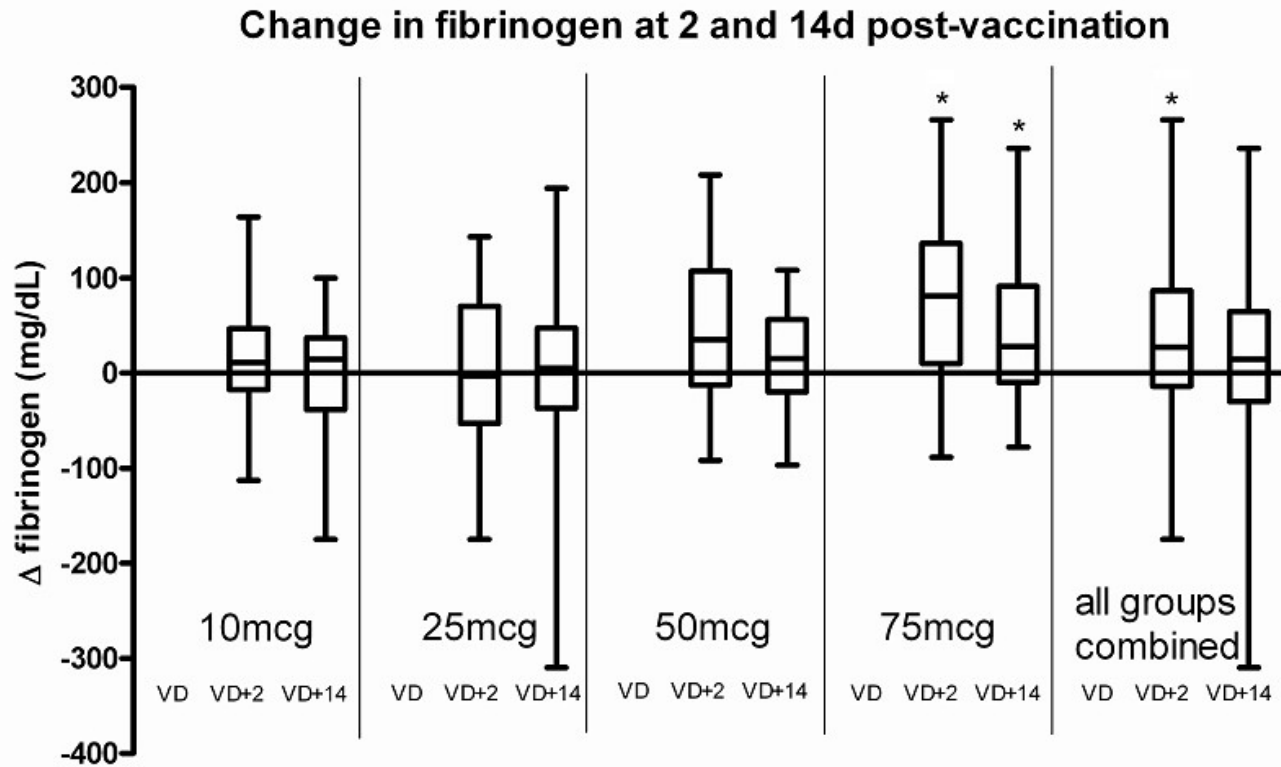
| | Inj 1 | Inj 2 | Inj3 | cum |
|--------|-------------------|-------|------|-------------------|
| 10 mcg | 1.11 | 0.57 | 0.57 | 0.78 |
| 25 mcg | 1.11 | 1.00 | 0.78 | 0.96 |
| 50 mcg | 1.00 | 0.89 | 0.89 | 0.93 |
| 75 mcg | 1.67 | 1.11 | 1.11 | 1.30 [‡] |
| all | 1.22 [†] | 0.91 | 0.85 | 1.00 |

Injection site pain scoring:
 no noticeable pain = 0
 noticeable = 1
 affects daily activities = 2
 prevents daily activities = 3

[†] More pain after first vaccination (Kruskall-Wallis p=0.03)
 vs the second (Mann-Whitney p<0.0629)
 vs the third (Mann-Whitney p<0.0367).

[‡] More pain with 75mcg dose (Kruskall-Wallis p=0.03);
 vs 10mcg, Mann-Whitney p=0.0117
 vs 25mcg Mann-Whitney p=0.1173
 vs 50mcg Mann-Whitney p=0.042.

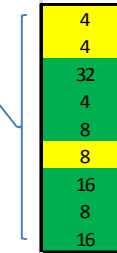
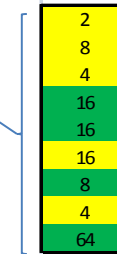
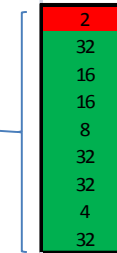
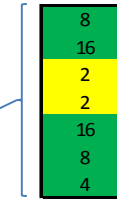
Safety Data: Plasma Fibrinogen



Was there a response to the parent strain?

Log₂ titers of bactericidal antibody against the vaccine parent strain.

| | Day 0 GM titer | Day 98 GM titer | P-value (paired t-test) |
|--------|----------------|-----------------|-------------------------|
| 10 mcg | 0.71 | 2.57 | 0.0004 |
| 25 mcg | 1.11 | 3.78 | 0.0003 |
| 50 mcg | 1.44 | 3.22 | 0.0012 |
| 75 mcg | 1.11 | 3.11 | 0.0003 |
| all | 1.12 | 3.21 | 0.0001 |



YES

At all doses tested, a significant increase in bactericidal antibody titer against the parent strain was seen 2 weeks after the third dose.

green = ≥ 4x increase in SBA vs. day 0
 yellow = 2x increase
 red=no change

Do multiple doses increase titers?

(Was the increase in titer versus day 0 higher after 3 doses than after 1?)

| | Day 14 (Dose 1) ↑titer | Day 98 (Dose 3) ↑titer | P-value |
|--------|------------------------------|------------------------------|---------|
| 10 mcg | 1.57 | 1.86 | NS |
| 25 mcg | 2.33 | 2.67 | NS |
| 50 mcg | 1.33 | 1.78 | NS |
| 75 mcg | 1.44 | 2.00 | 0.0955 |
| all | 1.68 | 2.09 | 0.0062 |

| | |
|----|----|
| 4 | 8 |
| 8 | 16 |
| 1 | 2 |
| 2 | 2 |
| 16 | 16 |
| 16 | 8 |
| 4 | 4 |

| | |
|----|----|
| 2 | 2 |
| 32 | 32 |
| 8 | 16 |
| 8 | 16 |
| 2 | 8 |
| 64 | 32 |
| 32 | 32 |
| 4 | 4 |
| 32 | 32 |

| | |
|----|----|
| 2 | 2 |
| 8 | 8 |
| 8 | 4 |
| 4 | 16 |
| 8 | 16 |
| 16 | 16 |
| 4 | 8 |
| 4 | 4 |
| 32 | 64 |

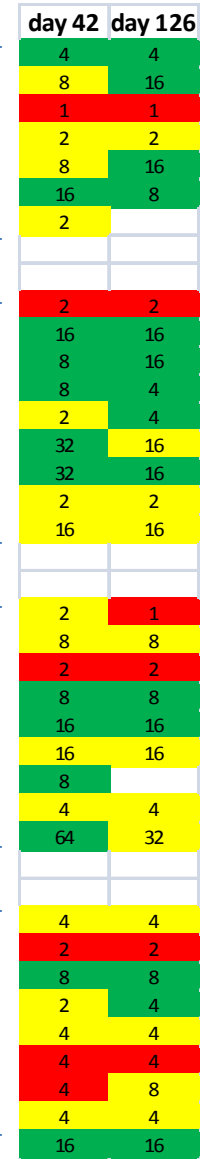
| | |
|----|----|
| 4 | 4 |
| 2 | 4 |
| 8 | 32 |
| 2 | 4 |
| 8 | 8 |
| 4 | 8 |
| 8 | 16 |
| 8 | 8 |
| 32 | 16 |

YES

The highest bactericidal response was seen two weeks after the third dose.

Do multiple doses prolong response?

| | ↑ titer 42 d p dose 1 | ↑ titer 42 d p dose 3 | P-value |
|--------|--------------------------|--------------------------|---------|
| 10 mcg | 1.33 | 1.50 | NS |
| 25 mcg | 1.89 | 1.78 | NS |
| 50 mcg | 1.50 | 1.25 | NS |
| 75 mcg | 1.00 | 1.22 | NS |
| all | 1.44 | 1.44 | NS |



NO

The bactericidal response was no more sustained after the third dose than it had been after the first.

Was the response sustained?

| | Day 98 ↑titer | Day 126 ↑titer | P-value |
|--------|------------------|-------------------|---------|
| 10 mcg | 2.67 | 2.33 | NS |
| 25 mcg | 3.78 | 2.89 | 0.0022 |
| 50 mcg | 3.25 | 2.75 | NS |
| 75 mcg | 3.11 | 2.33 | NS |
| all | 3.25 | 2.59 | 0.0621 |

| | |
|----|----|
| 8 | 4 |
| 16 | 16 |
| 2 | 1 |
| 2 | 2 |
| 16 | 16 |
| 8 | 8 |
| 4 | |

| | |
|----|----|
| 2 | 2 |
| 32 | 16 |
| 16 | 16 |
| 16 | 4 |
| 8 | 4 |
| 32 | 16 |
| 32 | 16 |
| 4 | 2 |
| 32 | 16 |

| | |
|----|----|
| 2 | 1 |
| 8 | 8 |
| 4 | 2 |
| 16 | 8 |
| 16 | 16 |
| 16 | 16 |
| 8 | |
| 4 | 4 |
| 64 | 32 |

| | |
|----|----|
| 4 | 4 |
| 4 | 2 |
| 32 | 8 |
| 4 | 4 |
| 8 | 4 |
| 8 | 4 |
| 16 | 8 |
| 8 | 4 |
| 16 | 16 |

NO

Titers at the end of the study were lower than after the third vaccination just four weeks earlier.

What was the extent of cross-protection?

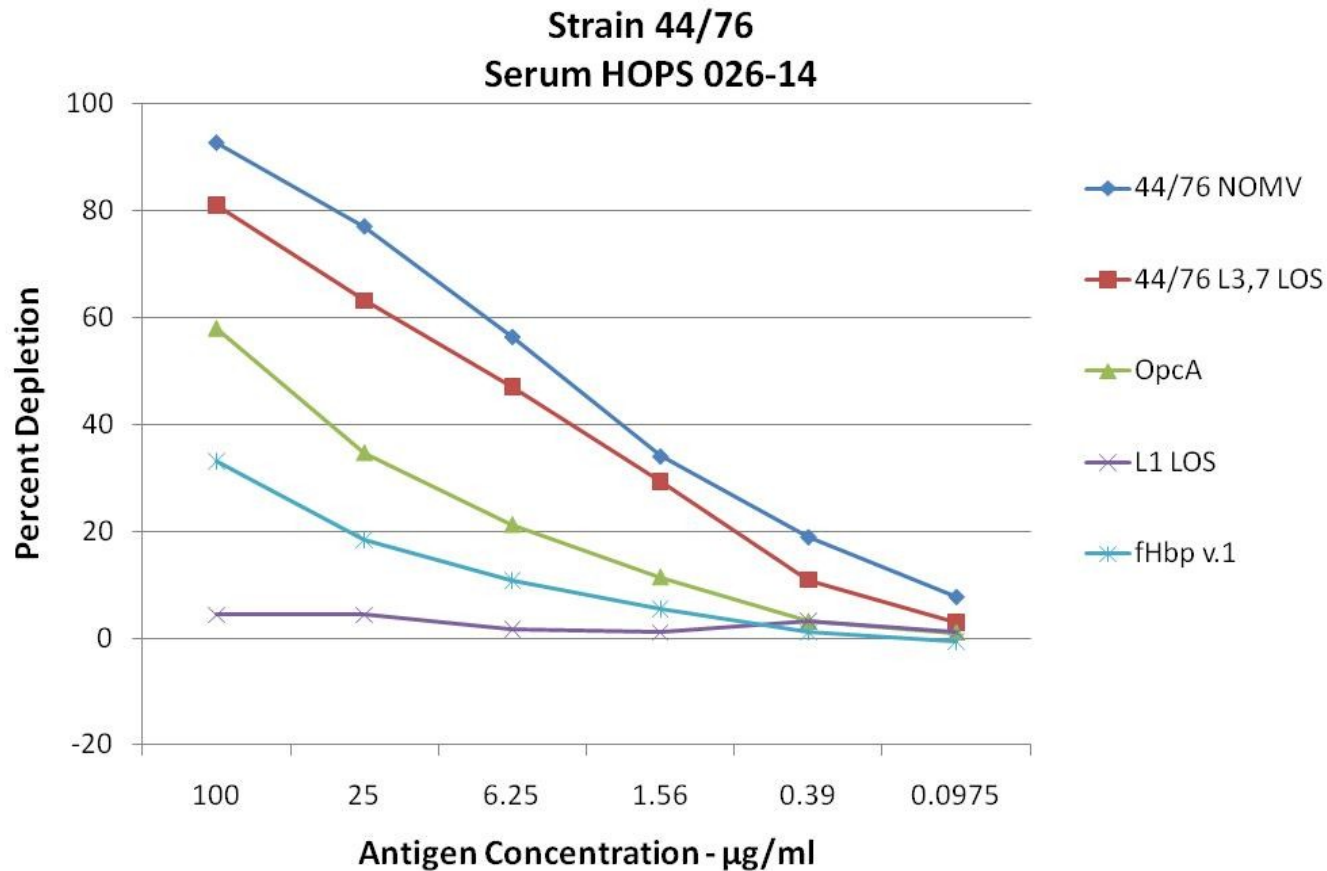
| strain | fHbp v1 | Opc | porA | LOS |
|---------|---------|-----|----------------------|------|
| HOPSG | ++ | ++ | P1.19,15 P1.22,14 | L7-5 |
| 8570 WT | + | +/- | P1.19,15 | L8-5 |
| 44/76 | + | +/- | P1.7,16 | L3,7 |
| 298I | + | - | P1.14 | L1 |
| 99M | - | - | P1.5,2 | L3,7 |
| 9162 | + | +/- | P1.7-2,3 | L3,7 |

NOT SO GREAT SO SO RESPONSE BEST RESPONSE

↓ ↓ ↓ ↓

| L7-5 | L8-5 | | 44/76 | 298I | 99M | 9162 |
|------|------|--|-------|------|-----|------|
| 8 | 32 | | 128 | 8 | 32 | 64 |
| 16 | 8 | | 32 | 8 | 32 | 16 |
| 2 | 128 | | 16 | 1 | 32 | 64 |
| 2 | 4 | | 2 | 1 | 8 | 8 |
| 16 | 32 | | 32 | 4 | 64 | 32 |
| 8 | 2 | | 4 | 1 | 8 | 32 |
| 4 | 4 | | 16 | 1 | 16 | 8 |
| | | | | | | |
| 2 | 8 | | 16 | 2 | 32 | 256 |
| 32 | 256 | | 16 | 8 | 32 | 32 |
| 16 | 16 | | 16 | 4 | 16 | 16 |
| 16 | 16 | | 64 | 4 | 64 | 32 |
| 8 | 32 | | 8 | 2 | 64 | 64 |
| 32 | 64 | | 16 | 4 | 64 | 64 |
| 32 | 16 | | 8 | 4 | 256 | 64 |
| 4 | 2 | | 8 | 1 | 32 | 4 |
| 32 | 16 | | 16 | 8 | 64 | 32 |
| | | | | | | |
| 2 | 2 | | 8 | 1 | 32 | 2 |
| 8 | 16 | | 64 | 8 | 64 | 16 |
| 4 | 16 | | 8 | 2 | 32 | 16 |
| 16 | 64 | | 16 | 4 | 32 | 8 |
| 16 | 64 | | 32 | 4 | 16 | 16 |
| 16 | 256 | | 128 | 16 | 64 | 16 |
| 8 | 64 | | 1 | 2 | 32 | 32 |
| 4 | 2 | | 16 | 2 | 32 | 16 |
| 64 | 32 | | 64 | 8 | 32 | 128 |
| | | | | | | |
| 4 | 8 | | 8 | 4 | 32 | 8 |
| 4 | 2 | | 64 | 4 | 16 | 8 |
| 32 | 16 | | 64 | 32 | 64 | 32 |
| 4 | 32 | | 32 | 8 | 16 | 16 |
| 8 | 32 | | 16 | 4 | 32 | 8 |
| 8 | 64 | | 4 | 8 | 32 | 16 |
| 16 | 128 | | 64 | 16 | 32 | 32 |
| 8 | 32 | | 64 | 16 | 64 | 16 |
| 16 | 32 | | 32 | 16 | 16 | 64 |

Depletion assays show contributions to the bactericidal activity



Conclusions

- Injection site pain was the only solicited adverse event that occurred consistently.
- Subclinical increases in temperature, wbc and fibrinogen were also observed.
- The majority of vaccinees responded to the parent strain and to strains with the L3,7 immunotype.
- Factor H binding protein and Opc, as well as porA, also contributed to the bactericidal response.
- A future study will look at this as one of three NOMV components in a multivalent vaccine.

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