

# Approaches to Licensure of Meningococcal Serogroup B Vaccines

## **Novartis 4CMenB Vaccine**

Vaccines and Related Biological Products  
Advisory Committee Meeting

April 7, 2011 • Gaithersburg, MD

# Agenda

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## Vaccine Composition

**Rino Rappuoli**

President of Research

Novartis Vaccines & Diagnostics

## Vaccine Immune Response

**John Donnelly**

MenB Project Leader,

Research Serology

Novartis Vaccines & Diagnostics

## Vaccine Coverage

## Conclusions

# Introduction

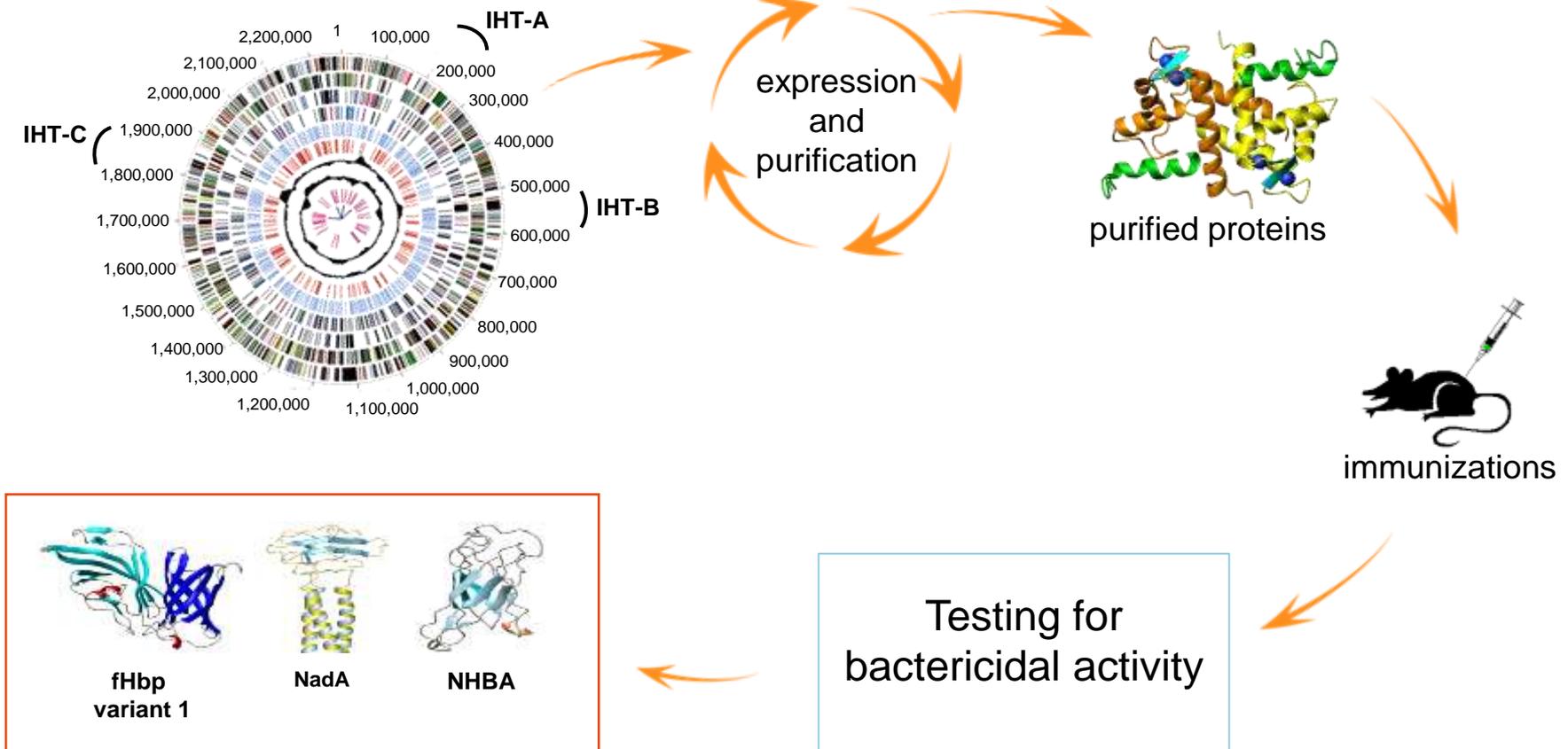
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- Capsular polysaccharide vaccines work for other serogroups (e.g. A,C,W,Y) but don't work for MenB
  - MenB capsule is a self antigen
- Non-capsular antigens must be used for MenB
  - Meningococcal surface antigens are highly diverse
  - Proteins vary in sequence and level of expression, and this can affect antibody recognition
- Novartis has developed a new method based on the bacterial genome to identify and select antigens
- Novartis uses multiple surface protein antigens in a multicomponent vaccine

# Reverse Vaccinology Allowed the Identification of Novel MenB Antigens

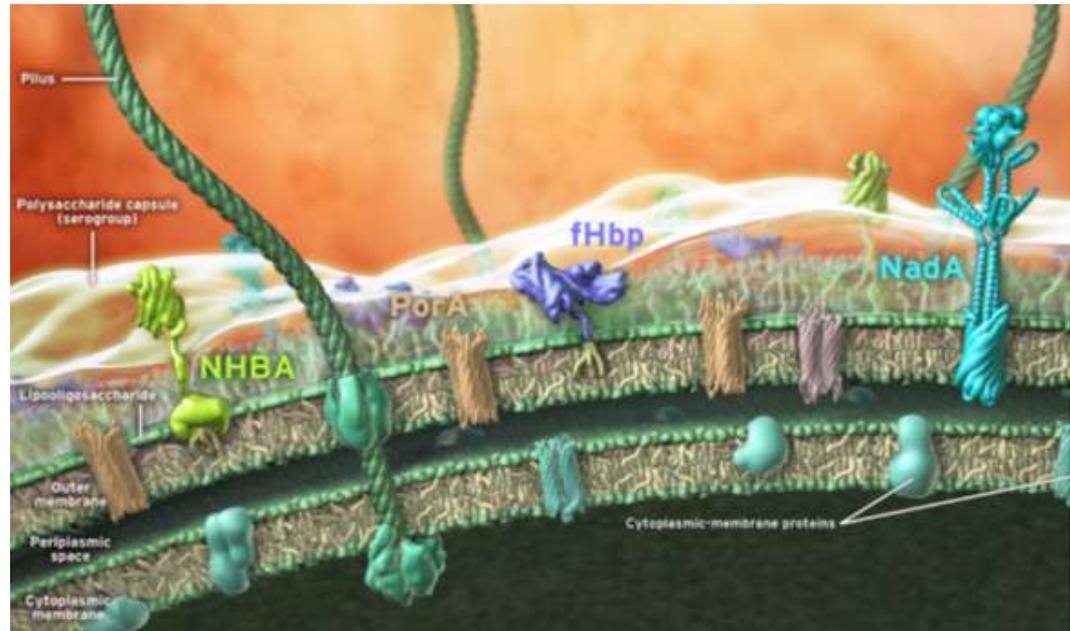
Based on the genome sequence of MC58, 600 ORFs that potentially encoded novel surface exposed or exported proteins were identified

~350 proteins successfully expressed in *E.coli*, purified, and used to immunize mice



# Antigenic Components Discovered by Reverse Vaccinology

Each surface antigen important for survival or virulence



1. Comanducci M, et al. *J Exp Med.* 2002;195:1445-1454; 2. Capecchi B, et al. *Mol Microbiol.* 2005;55:687-698; 3. Mazzon C, et al. *J Immunol.* 2007;179:3904-3916; 4. Veggi D, et al. Presented at IPNC. Banff, Canada. September 11-16, 2010; 5. Madico G, et al. *J Immunol.* 2006;177:501-510; 6. Schneider MC, et al.; *J Immunol.* 2006;176:7566-7575; 7. Serruto D, et al. *Proc Natl Acad Sci U S A.* 2010;107:3770-3775; 8. Welsch JA, et al. *J Infect Dis.* 2003;188:1730-1740; 9. Plested, et al. *Clin Vaccine Immunol.* 2008;15:799-804.

# Antigenic Components Discovered by Reverse Vaccinology

Each surface antigen important for survival or virulence

- **NadA: Neisseria adhesin A**

- Promotes adherence to and invasion of human epithelial cells<sup>1-3</sup>
- Possible importance in colonization

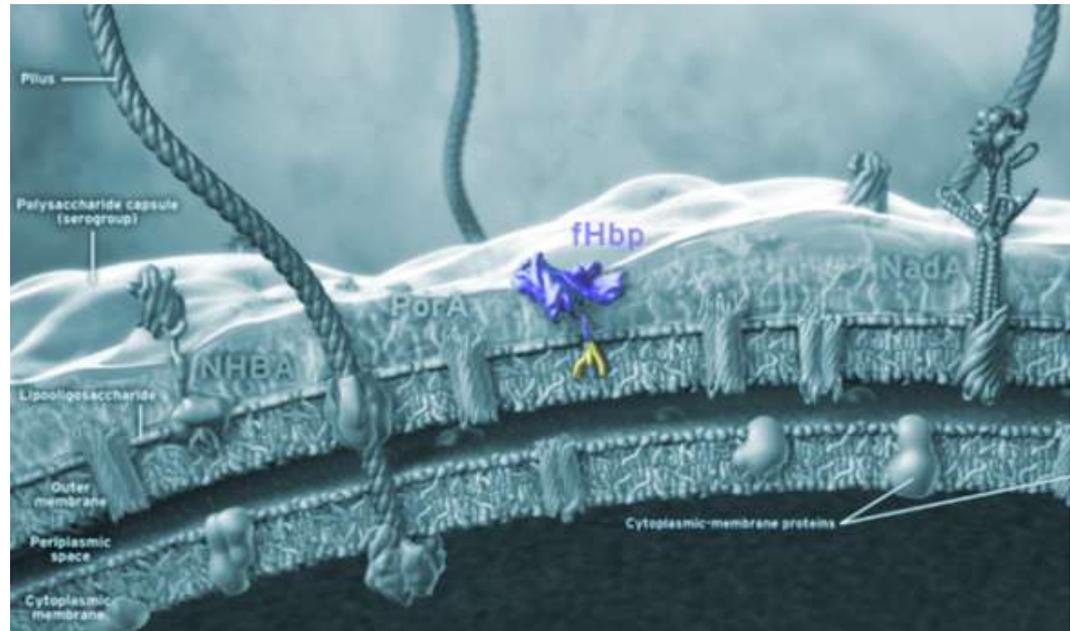


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  - Binds factor H, which enables bacterial survival<sup>5,6</sup>

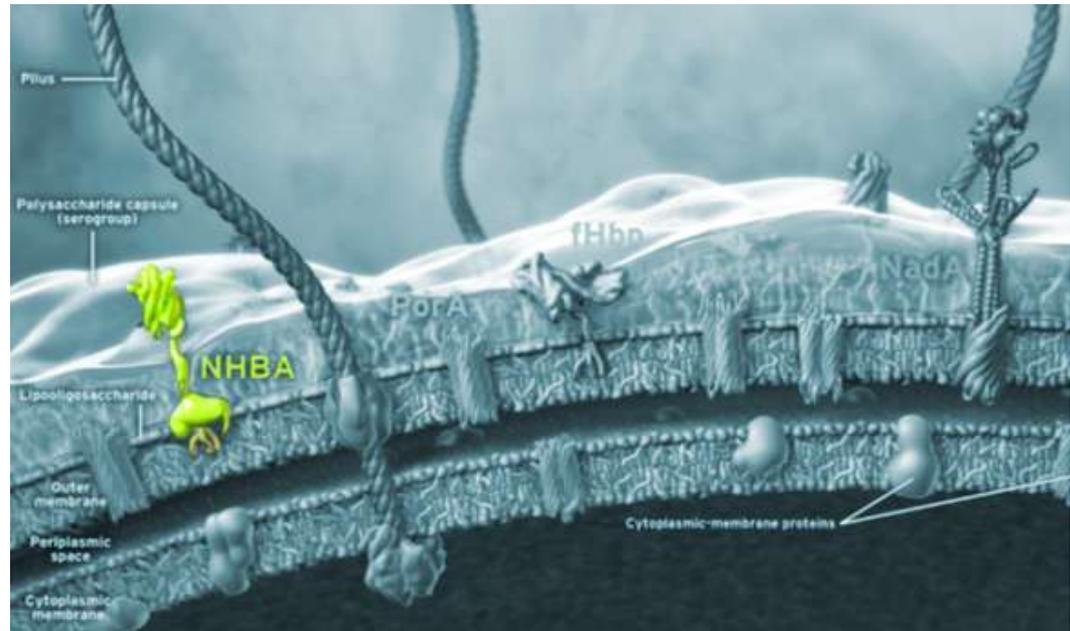


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  - Binds heparin, which may increase the serum resistance of bacteria<sup>7-9</sup>

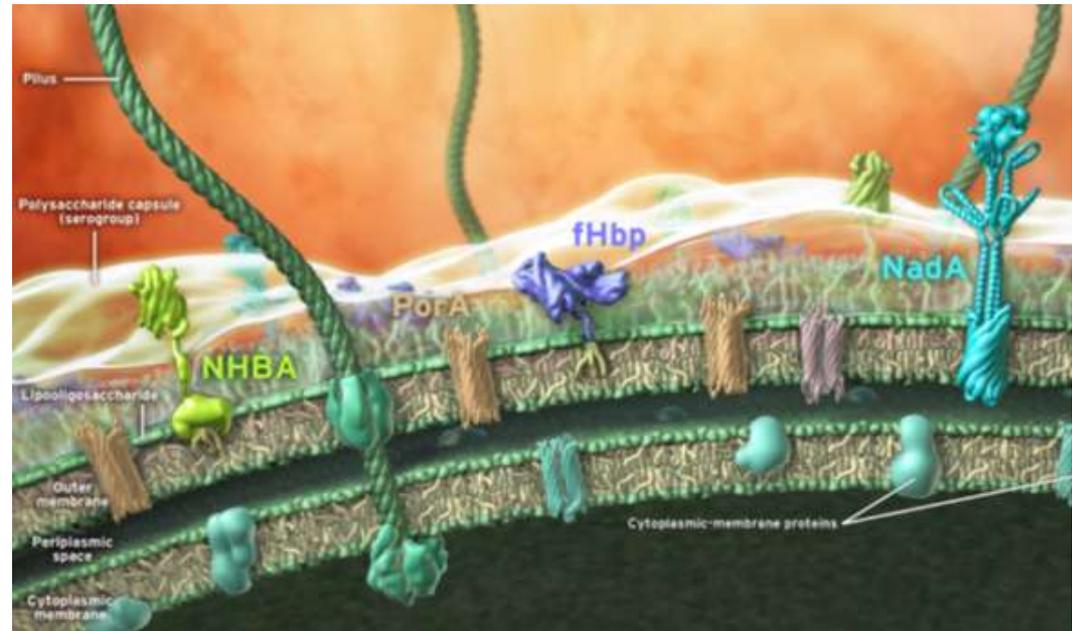


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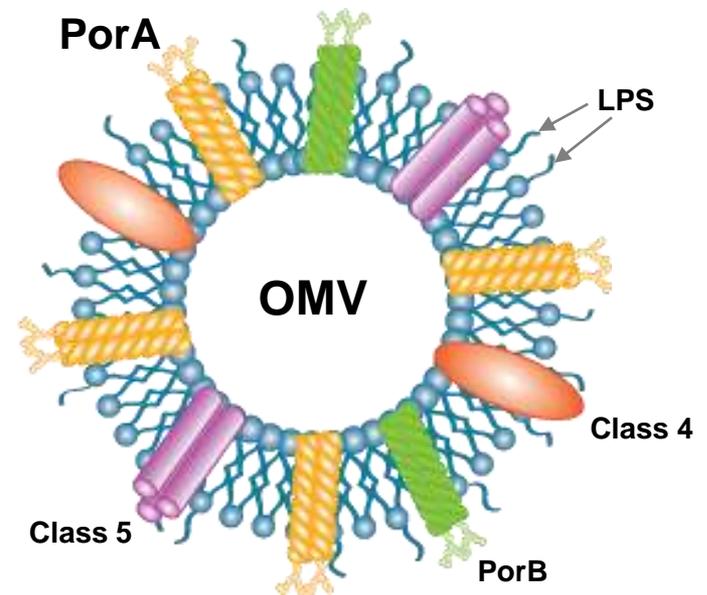
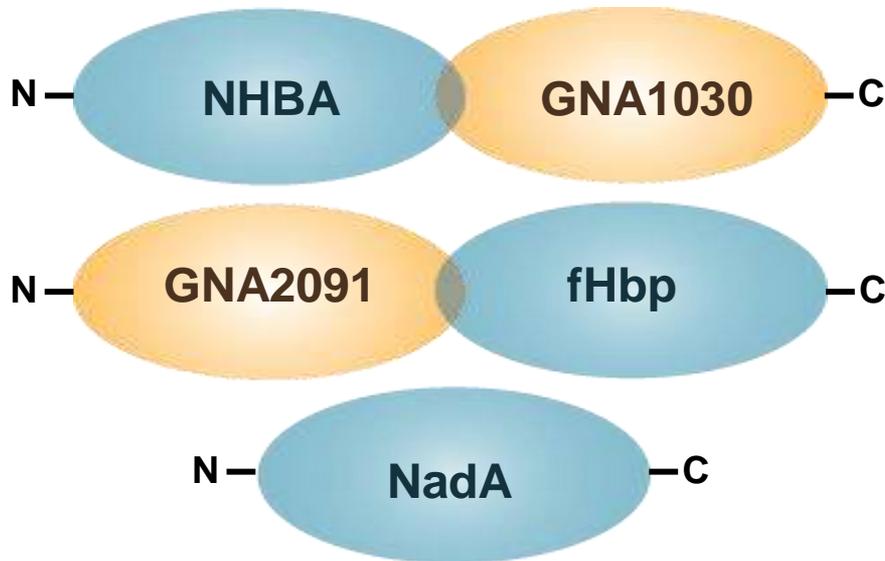
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  - Binds heparin, which may increase the serum resistance of bacteria<sup>7-9</sup>
- **Utilizing multiple antigens**
  - Provides broad coverage
  - Maintains coverage against potential emergence of escape mutants



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# 4CMenB Vaccine Composition

- Three protein antigens (two fusion proteins and one single polypeptide)
- Outer Membrane Vesicle (OMV) component (NZ PorA is P1.4)



- 4CMenB is a suspension for injection

Dose	NHBA-GNA1030	fHbp-GNA2091	NadA	OMV	Al <sup>3+</sup>
0.5ml	50 µg	50 µg	50 µg	25 µg	0.5 mg

# Rationale for Multicomponent 4CMenB Vaccine

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- Provided broad coverage in all age groups
- Minimize potential impact of escape mutants
- Induce synergistic bactericidal activities with multiple target antigens
- Include OMV:
  - Contains PorA, an important antigen
  - Induced protective immunity in all age groups in New Zealand
  - Provided coverage of hypervirulent clonal complex (41/44; Lineage 3)
  - Proven effective in clinical trials

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MenB Project Leader,

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# Serum Bactericidal Activity as Surrogate Marker of Protection

- Serum bactericidal antibodies have been accepted as a surrogate for protection for Meningococcus including B
  - Established by Goldschneider et al
  - Clinical efficacy demonstrated in Norway, Chile, Cuba, Brazil and New Zealand\*
- Bacteria are killed based on the cumulative actions of all the antibodies in the serum against all the antigens on the bacteria
  - Does not discriminate between effects of different antigens but only whether or not bacteria are killed – does not say which antigen(s) are responsible

\*Milagres LG, Ramos SR, Sacchi CT, et al. (1994) Immune response of Brazilian children to a Neisseria meningitidis serogroup B outer membrane protein vaccine: comparison with efficacy. *Infect Immun* 62:4419-24., Bjune G, Høiby EA, Grønnesby JK, et al. (1991) Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. *Lancet* 338:1093-6. et al., J. Boslego, J. Garcia-, C. Cruzl, W. Zollinger et al Efficacy, safety, and immunogenicity of a meningococcal group B (15:P1.3) outer membrane protein vaccine in Iquique, Chile *Vaccine*, Vol. 13, No. 9, pp. 821-829, 1995; Colleen Kelly<sup>1,3</sup>, Richard Arnold<sup>1</sup>, Yvonne Galloway<sup>2</sup>, and Jane O'Hallahan<sup>2</sup> A Prospective Study of the Effectiveness of the New Zealand Meningococcal B Vaccine *Am J Epidemiol* 2007;166:817–823

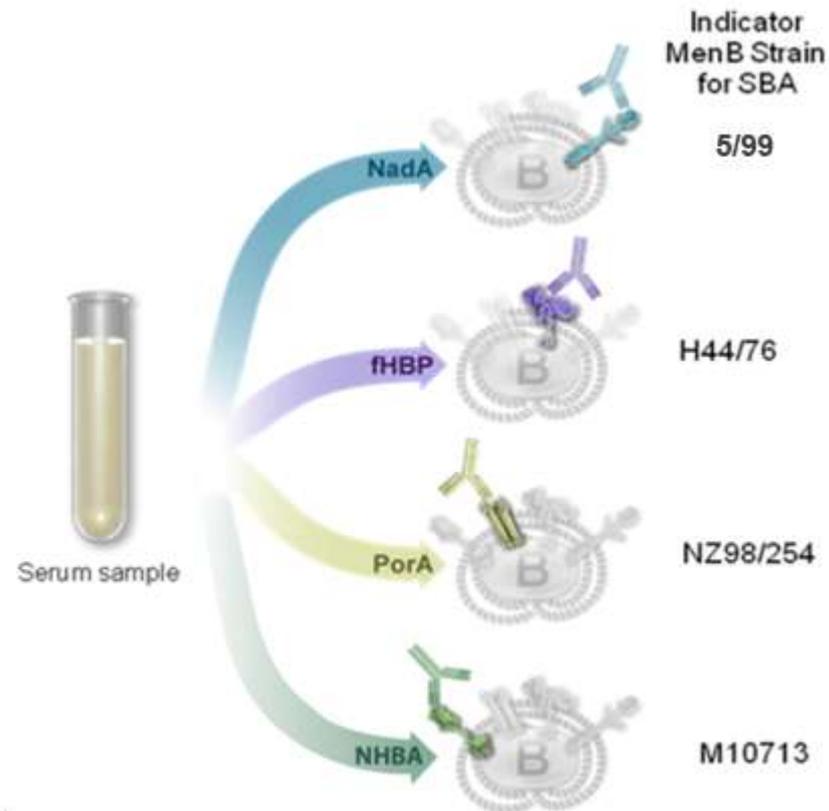
# Novartis Assessment of the Functional Immune Response to Each Specific Antigen

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- SBA detects cumulative effect of all the antibodies in the serum
- To show that each component in the vaccine elicits bactericidal response we exploited bacterial diversity to find strains with all but the target vaccine antigen mismatched or missing
- We confirmed the specificity of killing by competitive inhibition of the SBA for each antigen

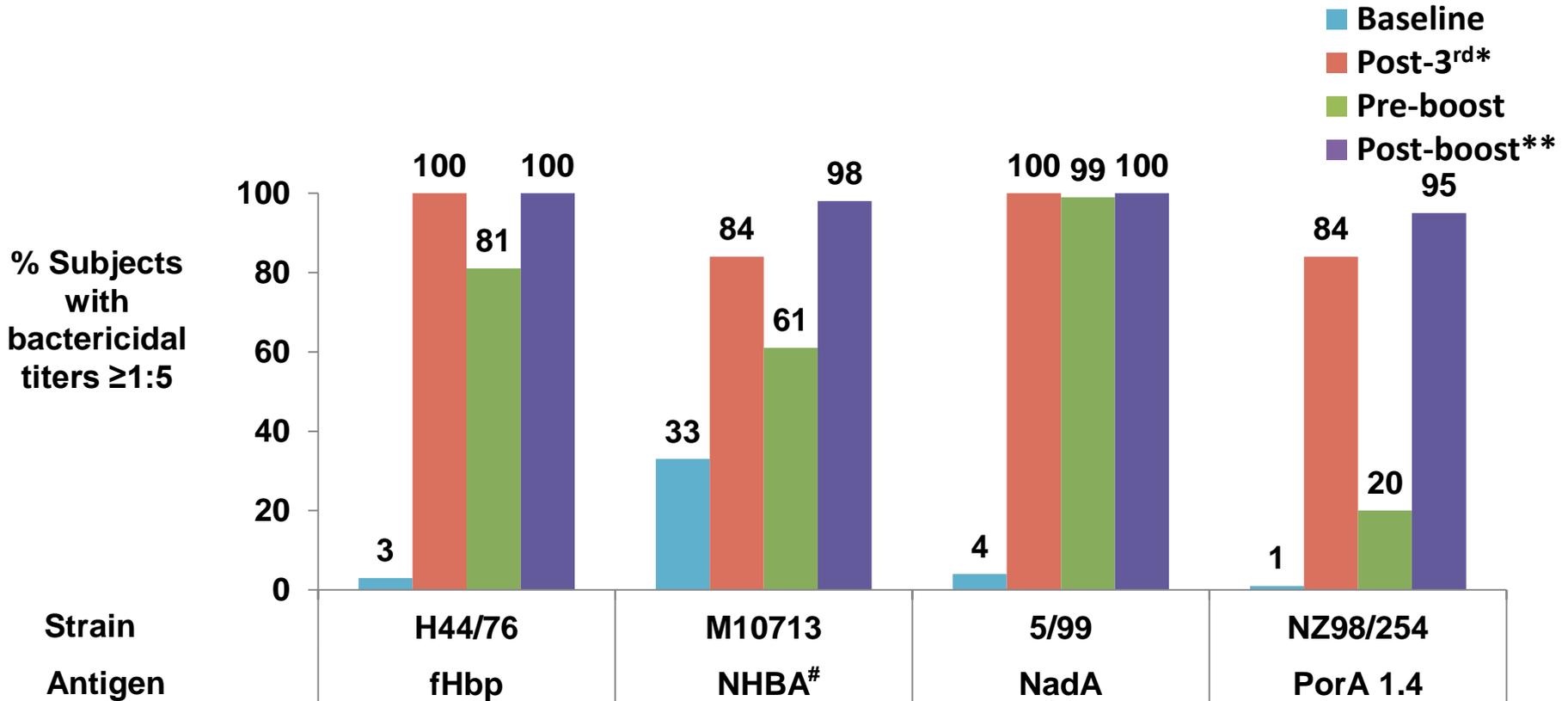
# Novartis Strain Panel for Demonstrating Antigen-specific Bactericidal Responses

- **NadA:** 5/99, NadA allele 2 (vaccine is allele 3)
- **fHbp:** H44/76, variant 1.1
- **OMV:** NZ98/254, source of OMV and therefore matched to PorA and also the other OMV components
- **NHBA:** M10713, variant 10 (vaccine is variant 2)



# Each Component of 4CMenB Induces a Robust Antigen-specific Bactericidal Response

*Infants immunized at 2, 4, 6 and 12 months of age in European Ph III*



\* Blood drawn at 7 months, N-1149-1152

\*\* Blood drawn at 13 months, N-421-424

# N=100

# Agenda

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**John Donnelly**

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# Properties of the Bacteria that Can Affect Killing in the SBA

- **Number of antigens expressed**
  - Strains may express none, some, or all of the antigens in the vaccine
- **Level of expression of the antigens**
  - Amount of antigen on the target cell surface
  - Insufficient antigen density results in decreased killing due to inefficient complement activation
- **Antigenic variation**
  - Similarity of the target antigen to the antigen in the vaccine (types & subtypes)
  - Differences can result in reduced antibody binding and reduced killing
    - Effect may be overcome in part by higher level of antigen expression
    - Extent of effect may differ among different age groups or depending on number of immunizations
- **In natural isolates, all of these factors are at work simultaneously to affect vaccine coverage**

# Effect of Antigenic Variation of fHbp on Killing in SBA in Different Age Groups

*Comparison in a recombinant strain changing only one antigen at a time*

		Killing of strains complemented with different fHbp subvariants											
		5/99	5/99 NHBA & NadA KO	1.1	1.2	1.4	1.5	1.10	1.12	1.13	1.14	1.15	3.28
<b>Adult serum pool</b>													
<b>4CMenB</b>													
	Pre	<32	16										
	Post 3 <sup>rd</sup>	512	16										
<b>Infant serum pool</b>													
<b>4CMenB</b>													
	Pre	<8	<2										
	Post 3 <sup>rd</sup>	>256	<2										
	Post 4 <sup>th</sup>	>512	<2										
		↓	↓										
		Killing mediated by <b>NadA</b>	No killing in the KO strain										

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		Killing mediated by <b>NadA</b>	No killing in the KO strain									No killing in the C3.28 strain	
				8 - 32 fold titer difference									

# Naturally Occurring Strains (with Multiple Antigens) are Killed by Infant Sera Against Multicomponent Vaccine

- In 24 naturally occurring strains harboring different fHbp sub-variants, all were killed by pooled infant sera post boost

Number of naturally occurring strains killed / number of strains tested <sup>a</sup>						
fHbp sub-variants	1.1	1.4	1.12	1.13	1.14	1.15
<b>Serum pool (Infants)</b>						
4CMenB						
Pre	0/3	0/3	0/3	0/7	0/2	0/6
Post 3 <sup>rd</sup>	3/3	3/3	2/3	5/7	1/2	3/6
Post booster	3/3	3/3	3/3	7/7	2/2	6/6

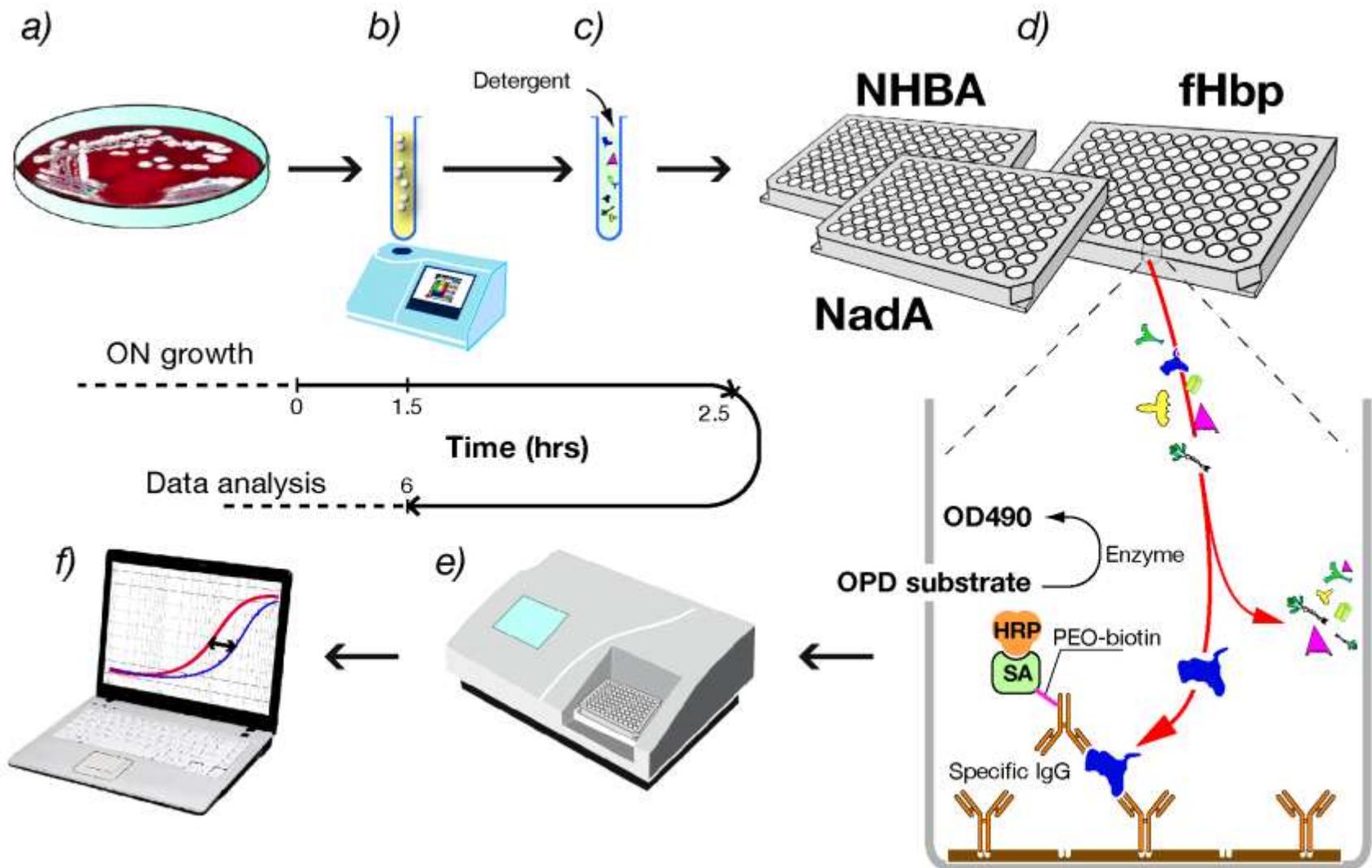
<sup>a</sup> Killing defined as SBA titer  $\geq 8$

# Meningococcal Antigen Typing System (MATS)

*Assessing coverage: Which disease strains can be killed by vaccine induced human antibodies?*

- No existing typing system was sufficient because the antigens in the vaccine are novel
- We developed a novel typing system – MATS to link each antigen to killing in SBA
  - Sandwich immunoassay using rabbit polyclonal antibodies raised against vaccine antigens for capture and detection
    - reflects both level of expression and antigenic variation for fHbp, NHBA, NadA
  - PorA sequence typing of hypervariable (VR2) loop – extensive literature data supporting predictivity of VR2 homology for coverage by OMV vaccines

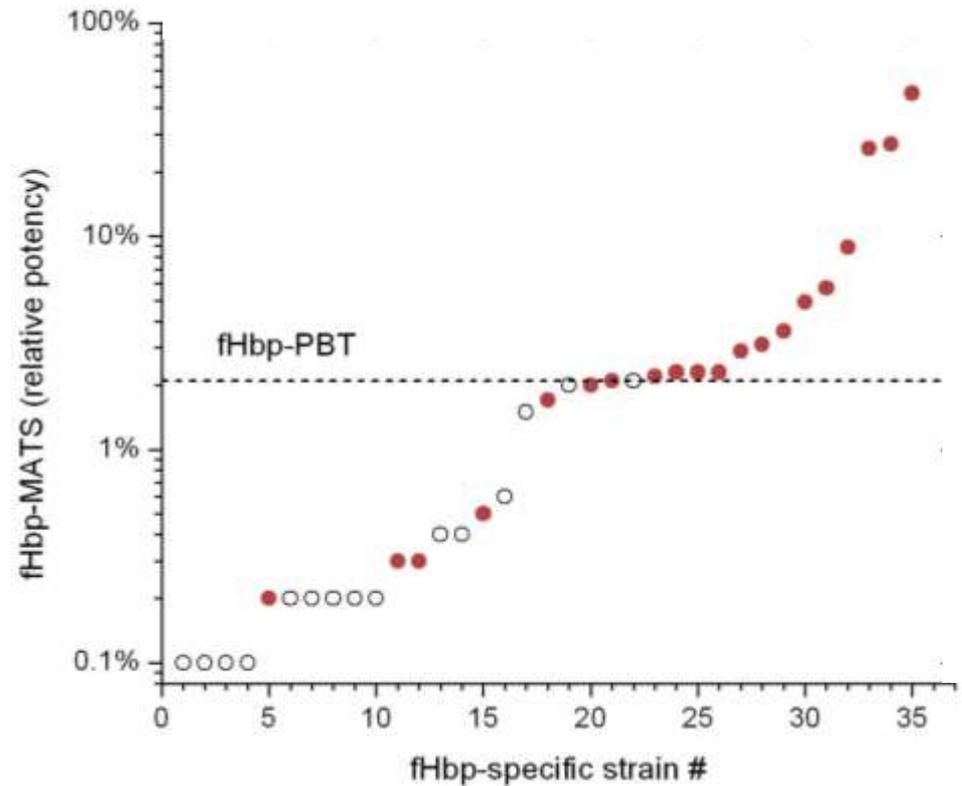
# Schematic Diagram of the MATS ELISA



# Using MATS to Predict Whether Strains are Covered by the Vaccine

## Positive Bactericidal Thresholds (PBT): Example - fHbp

- Serum pools from **13-month-olds** immunized with 4CMenB were tested in SBA against diverse MenB strains
- Shown are the 36 fHbp expressing strains in which NadA, NHBA and PorA are either absent or mismatched
- The PBT is defined as the value above which  $\geq 80\%$  strains are killed in SBA
- We assigned a separate PBT for each antigen based on corresponding subsets of strains with 3 of 4 antigens absent or mismatched

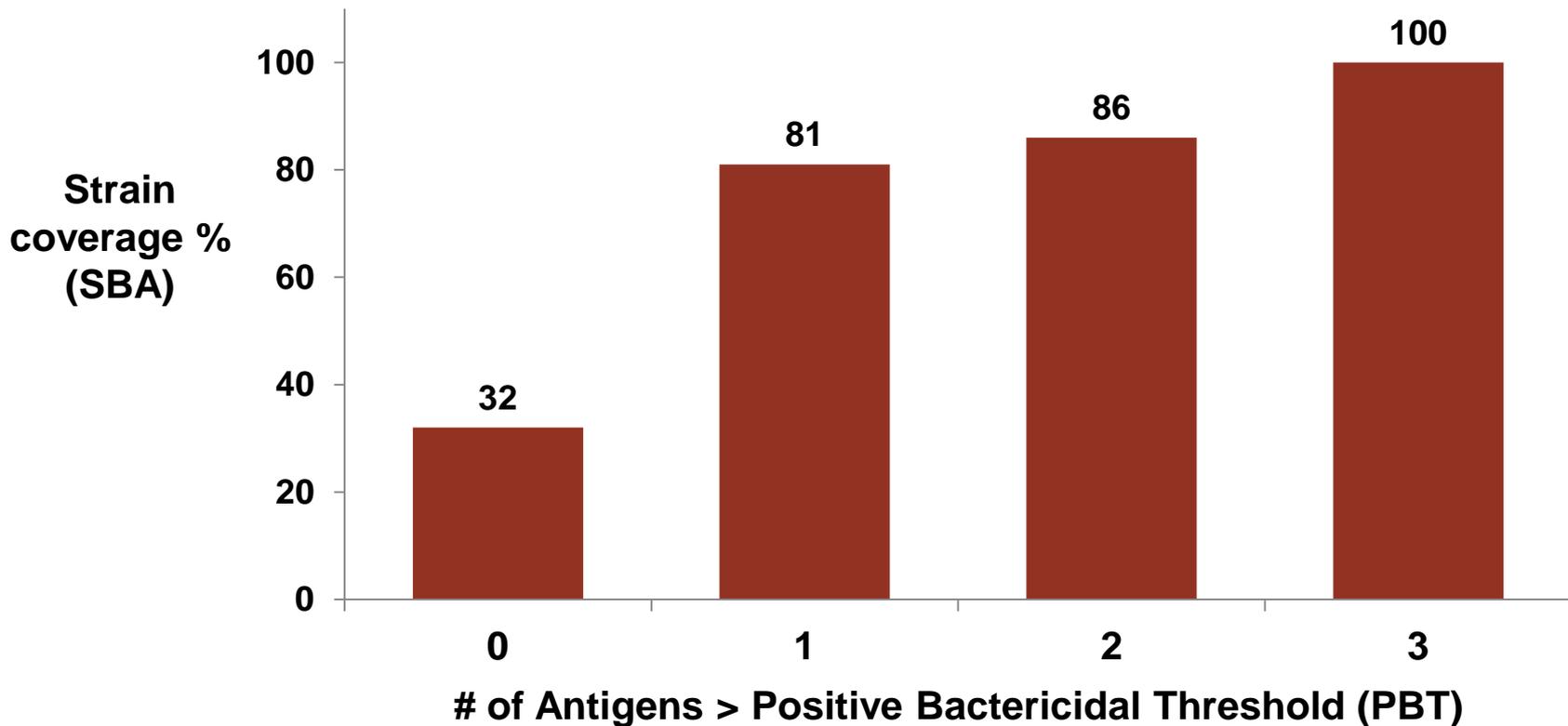


- Killed in SBA: infant serum pool titer  $\geq 1:8$
- Not killed in SBA

# MATS > PBT for one or More Antigens Predicts Killing in the SBA

*Strain coverage is increased with increased number of antigens >PBT*

SBA results for 93 MenB disease isolates tested in SBA against pooled immune sera from 146 infants post boost



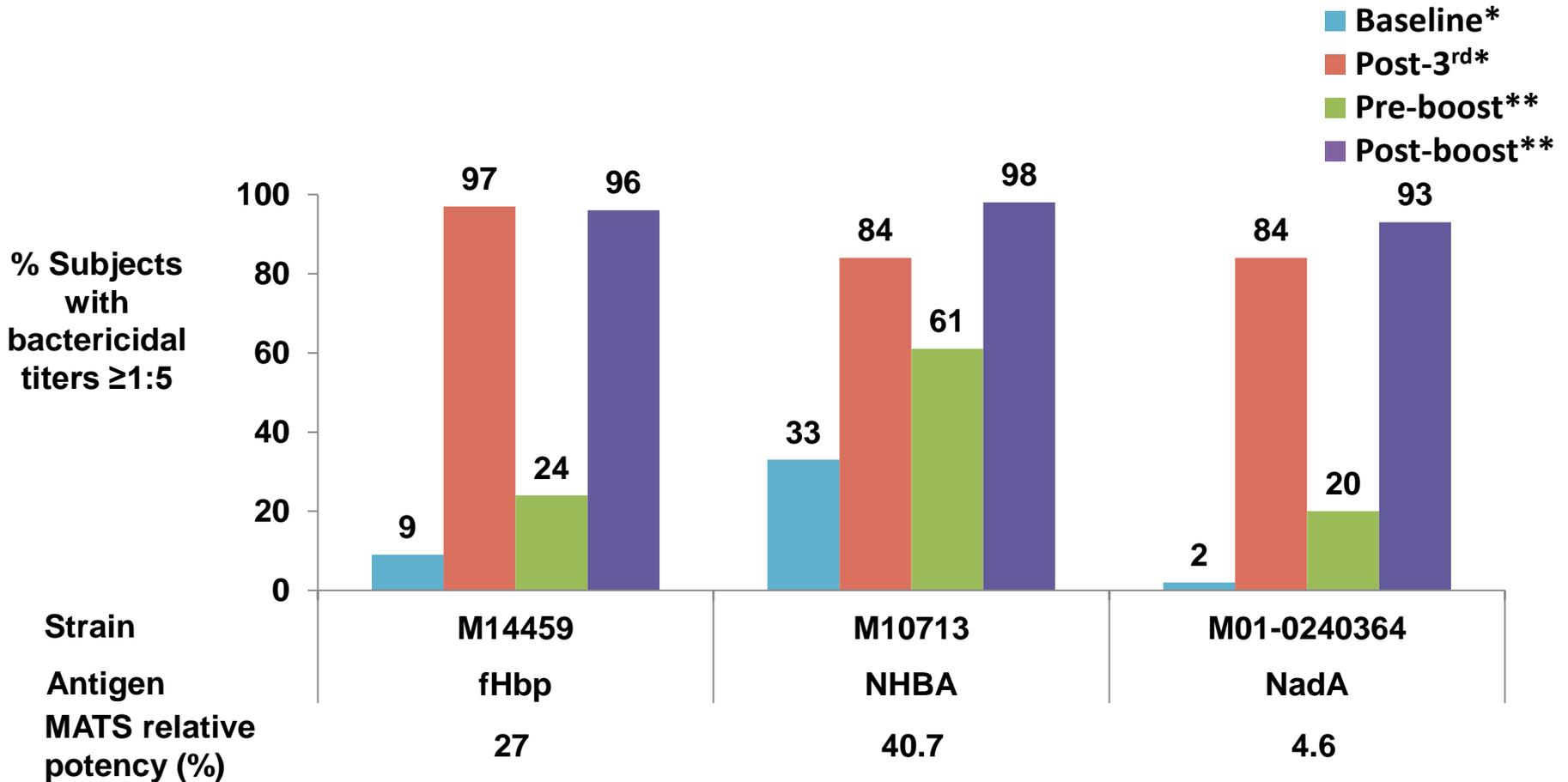
# Bridging MATS to Efficacy

*Compare MATS results with whether or not bacteria are killed by both pooled and individual immune sera in SBA*

- Level of MATS Relative Potency (above or below the PBT) is a ***property of the bacteria*** that predicts susceptibility of the bacteria to killing by vaccine induced antibodies
- Ability of MATS to predict strain coverage
  - MATS overall accuracy 80-86%
    - positive predictive value > negative predictive value indicates a conservative estimate
  - Proves principle that MATS can be used to predict killing in SBA
- Pooled sera vs. individual sera
  - Pooled sera: reflect average immune response – economical of specimen – screen large numbers of strains rapidly
  - Individual sera: reflect individual response rates – we selected strains near the PBT and tested them against 100's of individual sera

# 100 Individual SBA Responders Against Strains with MATS Near PBT for 1 Antigen and all Others < PBT

*Infants immunized at 2, 4, 6 and 12 months of age in European Ph III*



\* Titers at baseline (pre-dose 1) and post-dose 3 (2,4,6-month primary schedule) are from serum samples from the same 100 subjects from study V72P13, across all three strains.

\*\* Pre-boost and post-boost (at 12 months of age) samples were obtained from a different subset of 100 subjects from study V72P13E1, an extension study in which subjects from study V72P13 received a further immunization at 12 months of age

# Agenda

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**Conclusions**

**John Donnelly**

# Conclusions

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- The immune response to 4CMenB in infants can kill diverse MenB strains
- Targeting more antigens on the bacteria allows the vaccine to provide greater breadth of protection and minimize potential for escape mutants
- Bacterial antigen phenotype as defined by MATS predicts killing of the bacteria in the SBA by vaccine-induced antibodies
  - MATS is a conservative estimate of coverage
- MATS can be used for estimating strain coverage and monitoring changing epidemiology

# Path Forward

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- MATS was transferred and standardized in 8 national reference laboratories including US CDC
  - Results of interlaboratory standardization study to be published in collaboration with US CDC
- Continuing to survey large numbers of disease causing meningococcal isolates from different countries and regions to determine the proportion of endemic strains with 0, 1, 2, 3 or 4 antigens above the PBT
  - Ongoing projects in USA, Europe, Canada, and Australia to type large numbers of meningococcal strains
- MATS will be used to determine strain coverage rates and to monitor for the potential emergence of vaccine resistant strains after approval and routine use of the 4CMenB

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