Approaches towards new meningococcal vaccines

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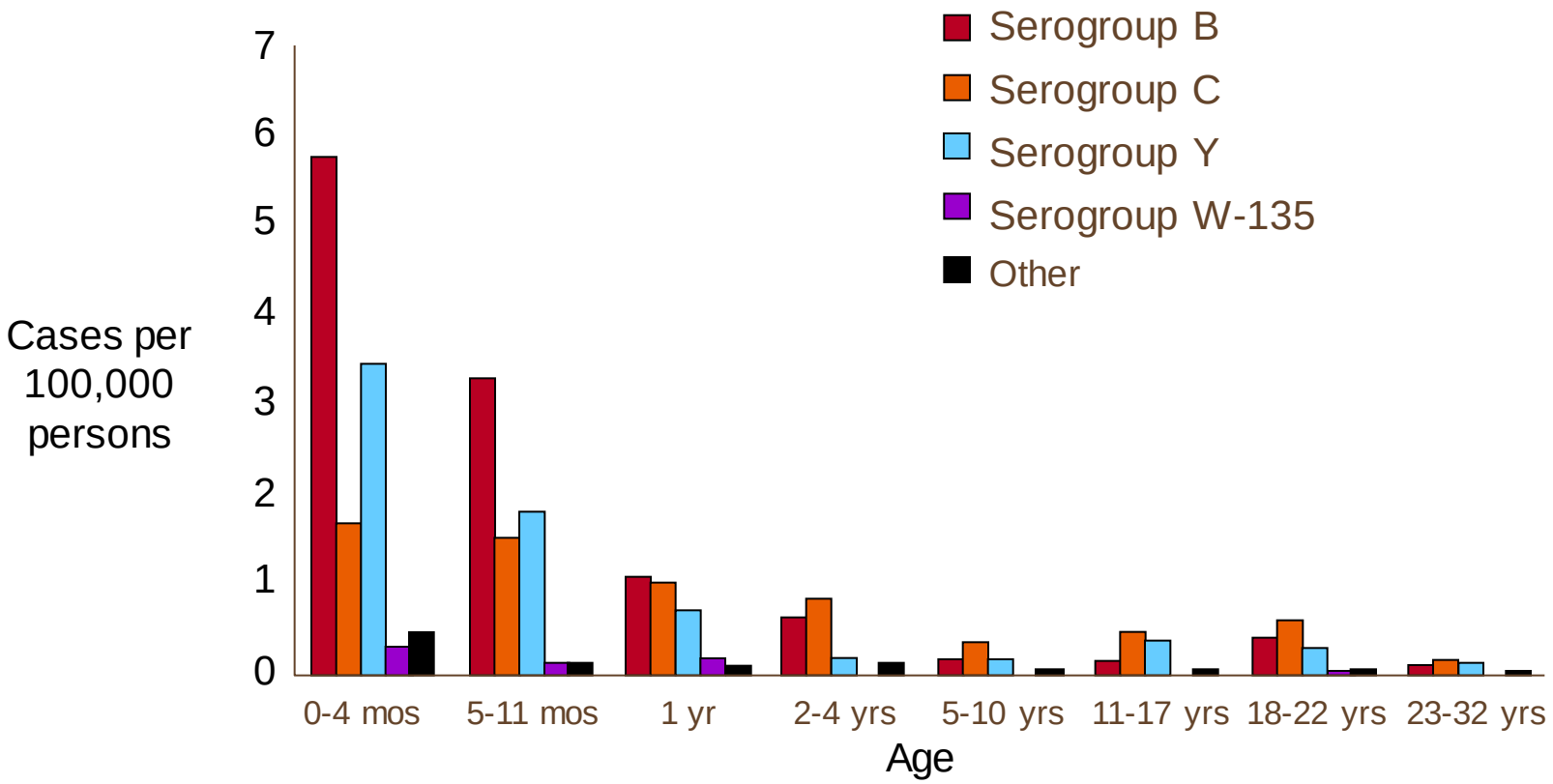
Age- and Serogroup-Specific Meningococcal Disease Incidence

United States, 1993–2002

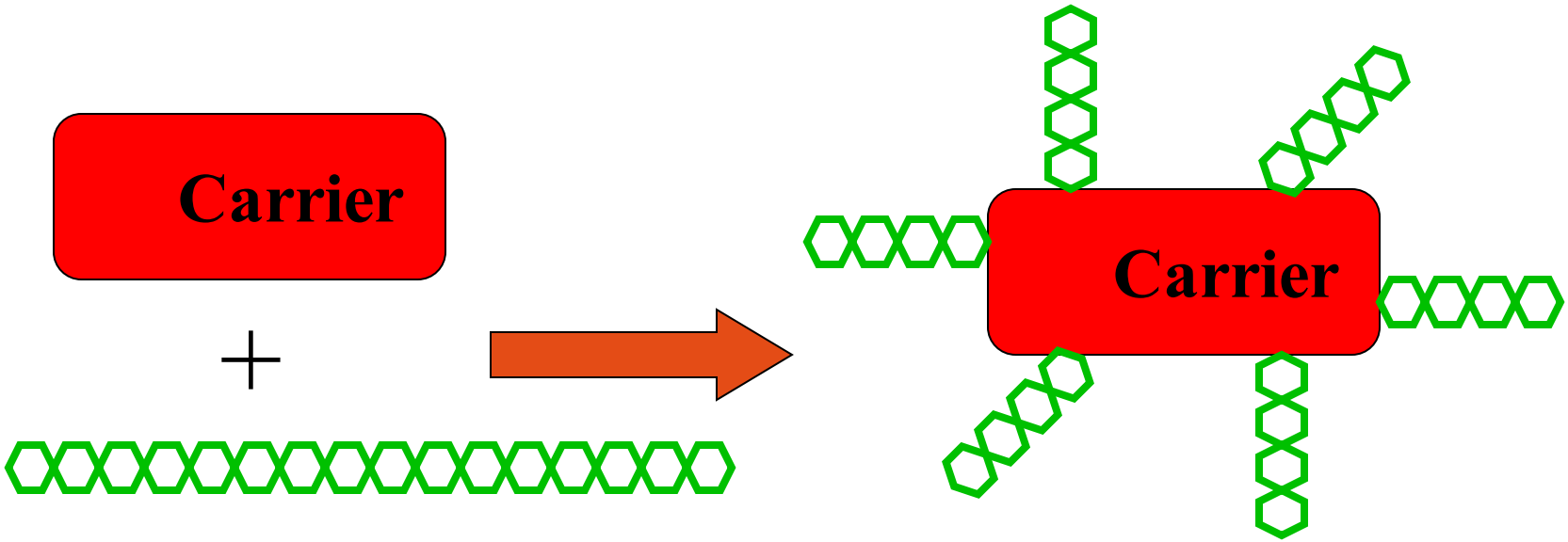


Invasive Meningicoccal Disease has serious consequences and impacts on highly vulnerable populations: infants and adolescents

- Mortality high despite treatment
- Sequelae in 11 - 19% of survivors (amputations, hearing loss, skin scarring)
- Bimodal pattern of disease
  - Peak incidence in infants < 6 months of age; mortality 8%
  - 2nd peak incidence in adolescents; mortality ~20%

Shepard CW, et al. Pediatrics. 2005;115:1220-1232.

Polysaccharides and conjugates



Plain capsular polysaccharide:

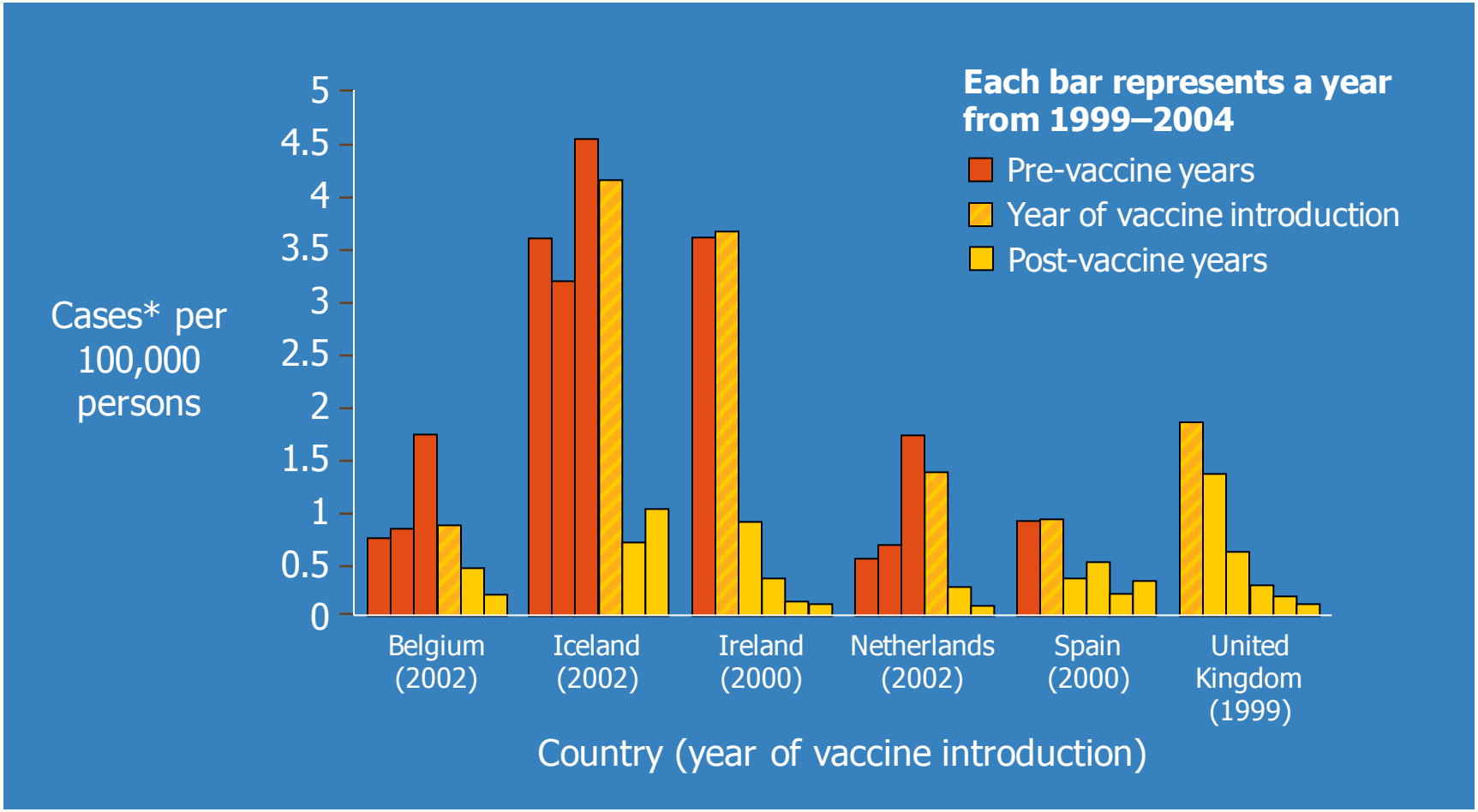
- ✓No response in < 18 mo-olds
- ✓No immunological memory
- ✓No boosting reponse

Conjugated vaccine:

- ✓Good response in infants
- ✓Good immunological memory
- ✓Good boosting response

Impact of an Immunization Campaign Using Serogroup C Meningococcal Conjugate Vaccine

Europe



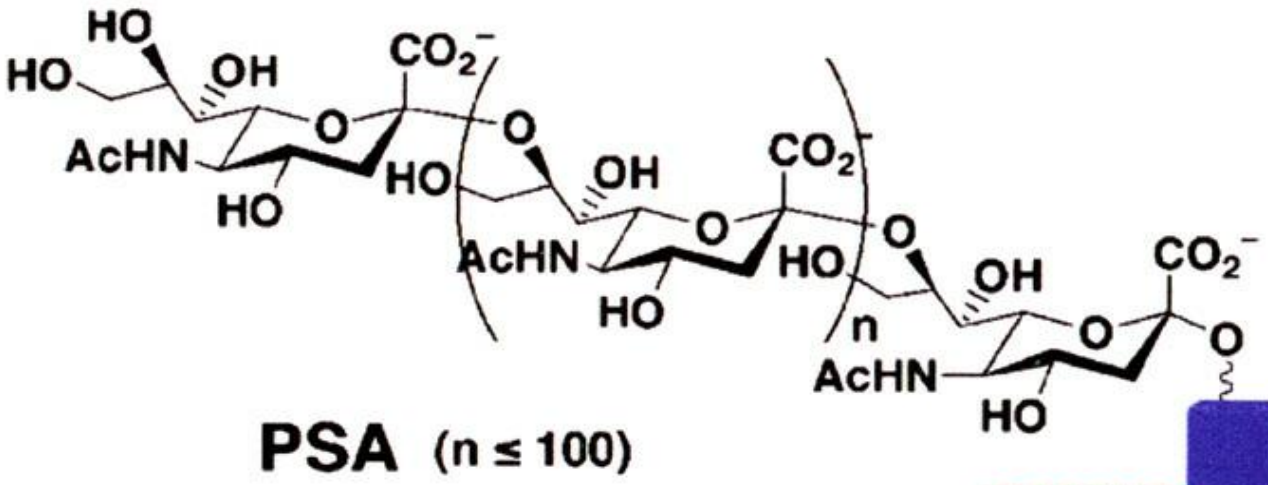
*Cases of meningococcal serogroup C.

Trotter CL, et al. *FEMS Microbiol Rev*. 2007;31:101-107.

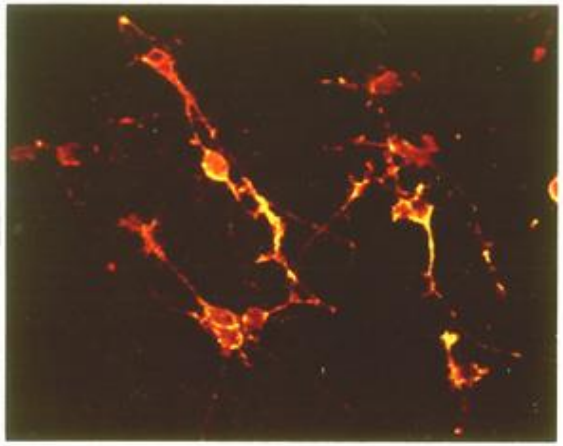
Status of the vaccines needed for elimination of bacterial meningitis

Pathogen	***Status of the vaccine***
Hib	Available
Pneumococcus	Available
ManA, MenC and MenCY	Available
MenA, Men C, MenY, MenW	Available
MenB	**Trials and tribulations !**

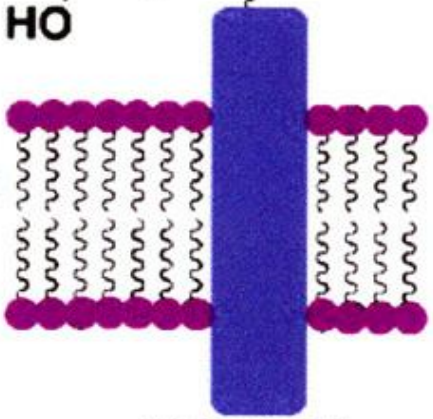
MenB capsular polysaccharide is a self antigen



PSA ($n \leq 100$)

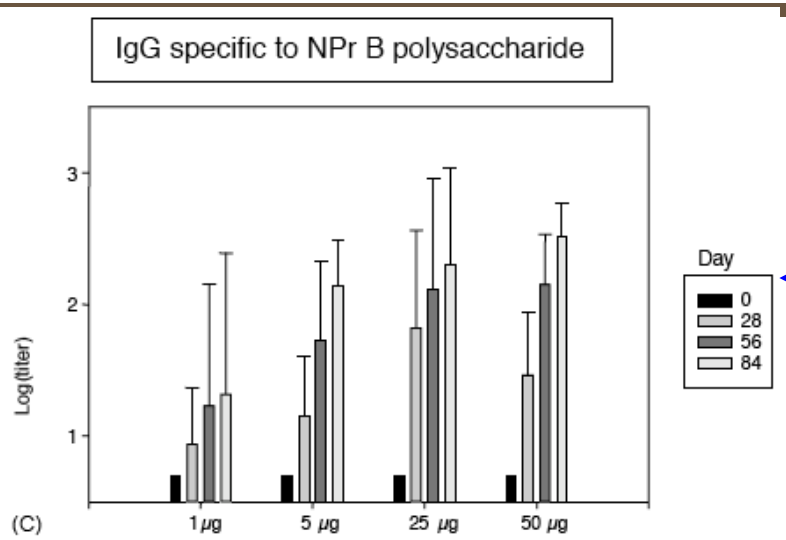


Neuron or tumor cell membrane



NCAM

Poor immunogenicity of NPr MenB PS in humans



N-Propionyl MenB PS conjugated to TT and given 3 x at 4 wks intervals at 1, 5, 25, 50 μg

IgG response

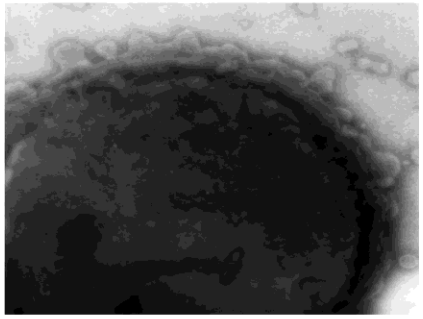
But not functional (bactericidal) antibodies

Participant number	Bactericidal titres[a]					
	M986 strain				H44/76 strain	
	With rabbit complement		With human complement		With human complement	
	Day 0	Day 84	Day 0	Day 84	Day 0	Day 84
112	2048	4096	<4	<4	<4	<4
113	8192	8192	<4	[4]	<4	[4]
114	4096	4096	[4][c]	[4]	[8]	[8]
115	4096	4096	<4	<4	<4	<4
116	4096	4096	[8]	<	<4	<4

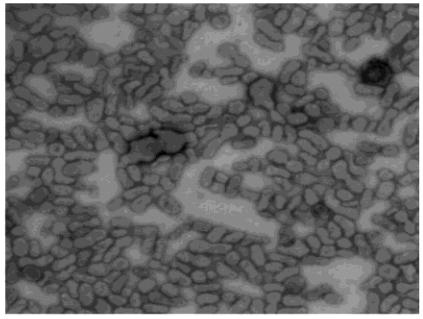
Bruge et al *Vaccine* **22**: 1087-96, 2004

OMV vaccine preparation

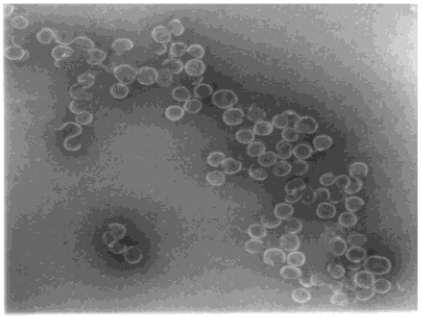
Bactericidal (= protective) antibody primarily ***directed at PorA strain-specific***



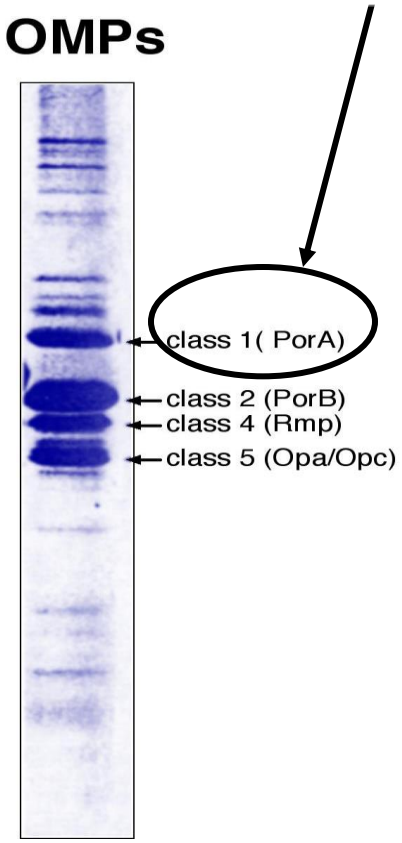
"blebbing" meningococcus



extracted OMV vesicles



purified LPS-depleted OMV



SDS PAGE of OMVs

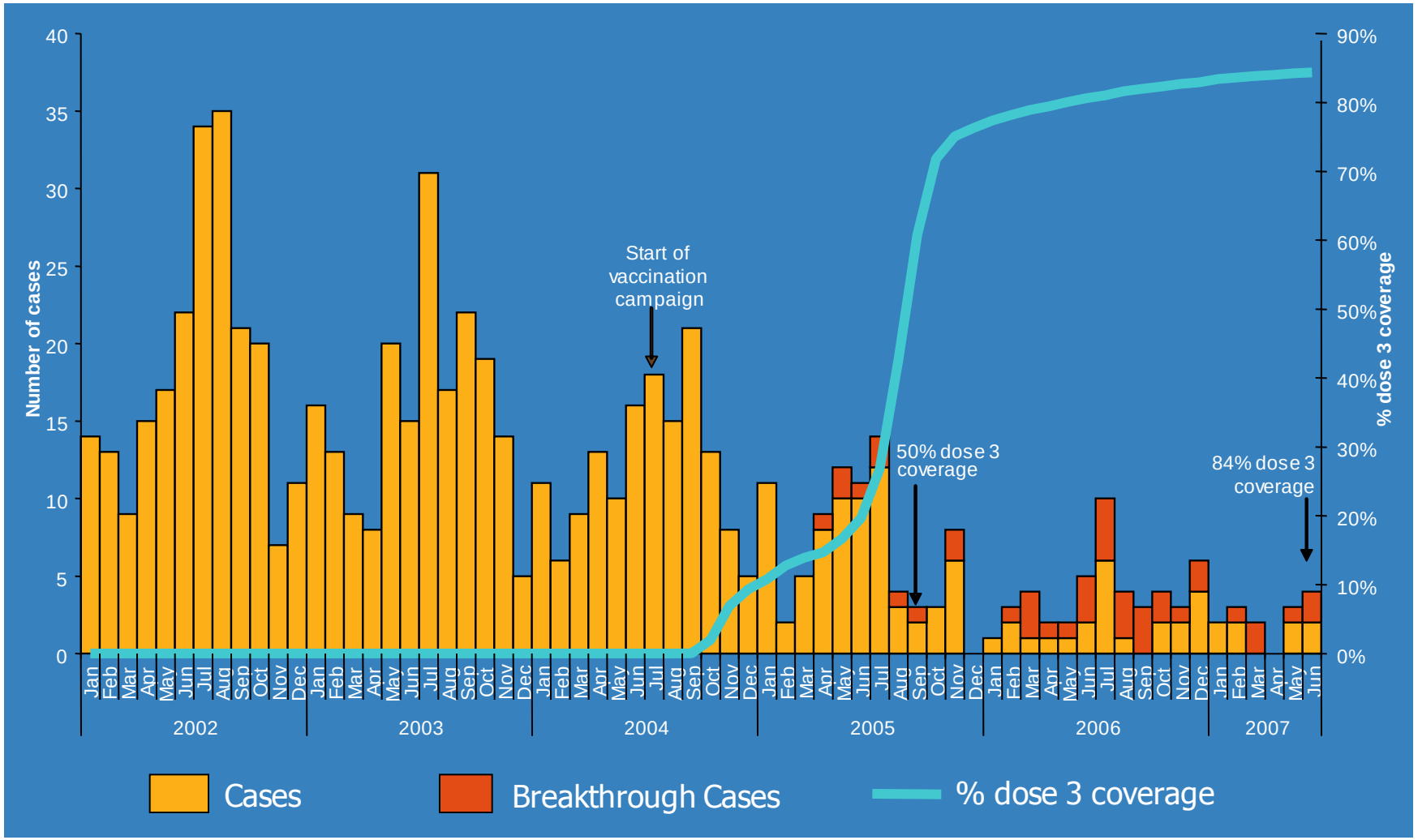
Three doses of OMV vaccines induce *good bactericidal titers against the homologous strain* at all ages. No or low titers against heterologous strain in infants and children.

Bactericidal responses (percentages)

Strain	***Norwegian vaccine***			***Cuban vaccine***		
	Infants	*Children*	*Adults*	*Infants*	*Children*	*Adults*
Chilean	12	35	60	10	31	37
Cuban	2	24	46	***90***	***78***	***67***
Norwegian	***98***	***98***	***96***	31	41	56

Tappero et al, *JAMA* **281**: 1502-1507, 1999

Successful program using PorA tailor made OMV vaccine against serogroup B meningococcal disease: *New Zealand*



Martin D, et al. The Epidemiology of Meningococcal Disease in New Zealand in 2006. Report prepared for the Ministry of Health by the Institute of Environmental Science and Research Limited (ESR). Wellington: Ministry of Health. Unpublished 2007 data.

NspA

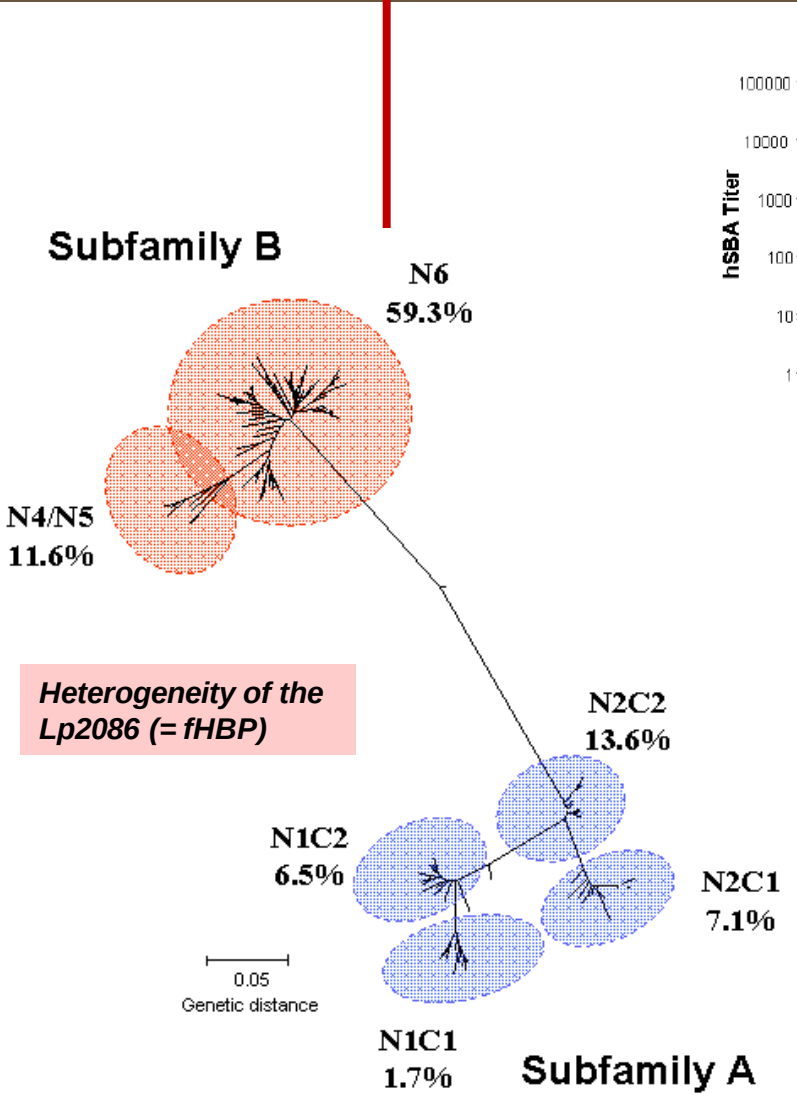
- Neisserial surface protein A (NspA) is a conserved, surface-exposed outer membrane protein of *Neisseria meningitidis* shown to induce a bactericidal antibody response in animals
- Healthy 18-50-year-old adults were assigned to receive, in a dose escalating manner, 3 doses of 1 of 5 formulations of an experimental, unfolded, recombinant NspA (rNspA) vaccine
- An antibody rise measured by enzyme immunoassay was elicited with a dose-related increase that reached a maximum with the 125 μg dose.
- ***No bactericidal antibodies were detected after any of the rNspA formulations***

Geometric mean anti-rNspA antibody after one dose of Menomune® or each of three doses of rNspA or placebo

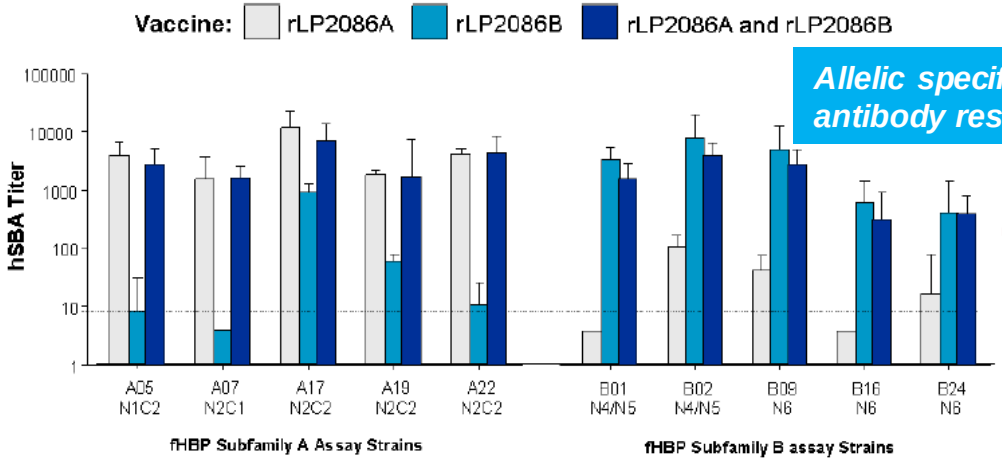
Study	Vaccine formulation	Geometric mean antibody level (95% confidence interval)			
		Pre-immunization	Post-dose 1	Post-dose 2	Post-dose 3
Bactericidal assay					
A	Menomune®	1.74 (0.73–4.15)[8]	1.74 (0.73–4.15)	–	–
	Placebo	1.23 (0.77–1.97)	–	–	1.23 (0.77–1.97)
	RNspA 7 μg	1.23 (0.77–1.97)	–	–	1.23 (0.77–1.97)
	RNspA 35 μg	1.49 (0.93–2.41)	–	–	1.67 (1.00–2.77)
	RNspA 105 μg	1.49 (0.93–2.41)	–	–	1.86 (1.09–3.17)
B	Placebo	2.11 (0.87–5.13)	–	–	1.76 (0.74–4.17)
	RNspA 125 μg	1.00 (1.00–1.00)	–	–	1.21 (0.92–1.59)
	RNspA 250 μg	1.00 (1.00–1.00)	–	–	1.09 (0.91–1.32)

Halperin et al, *Vaccine* **25**:450-457, 2007

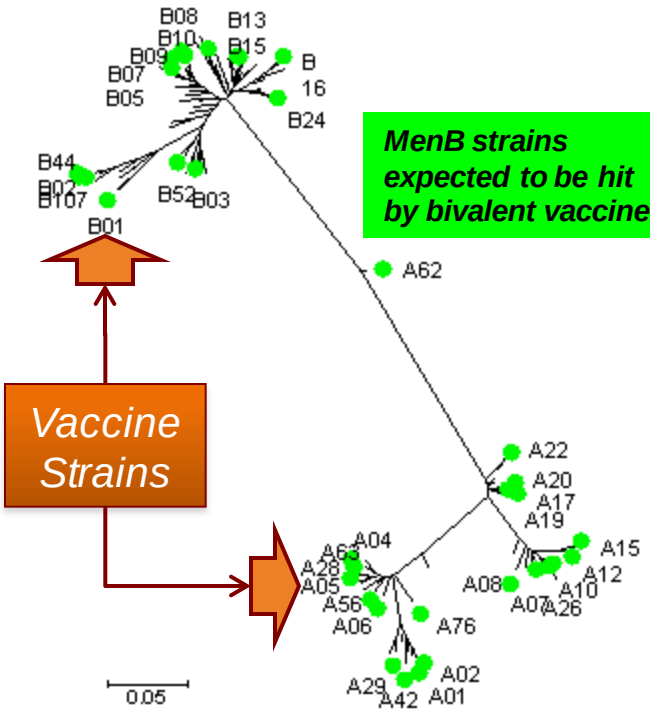
Lp2086 (= fHBP)



Heterogeneity of the Lp2086 (= fHBP)



Allelic specificity of antibody response



MenB strains expected to be hit by bivalent vaccine

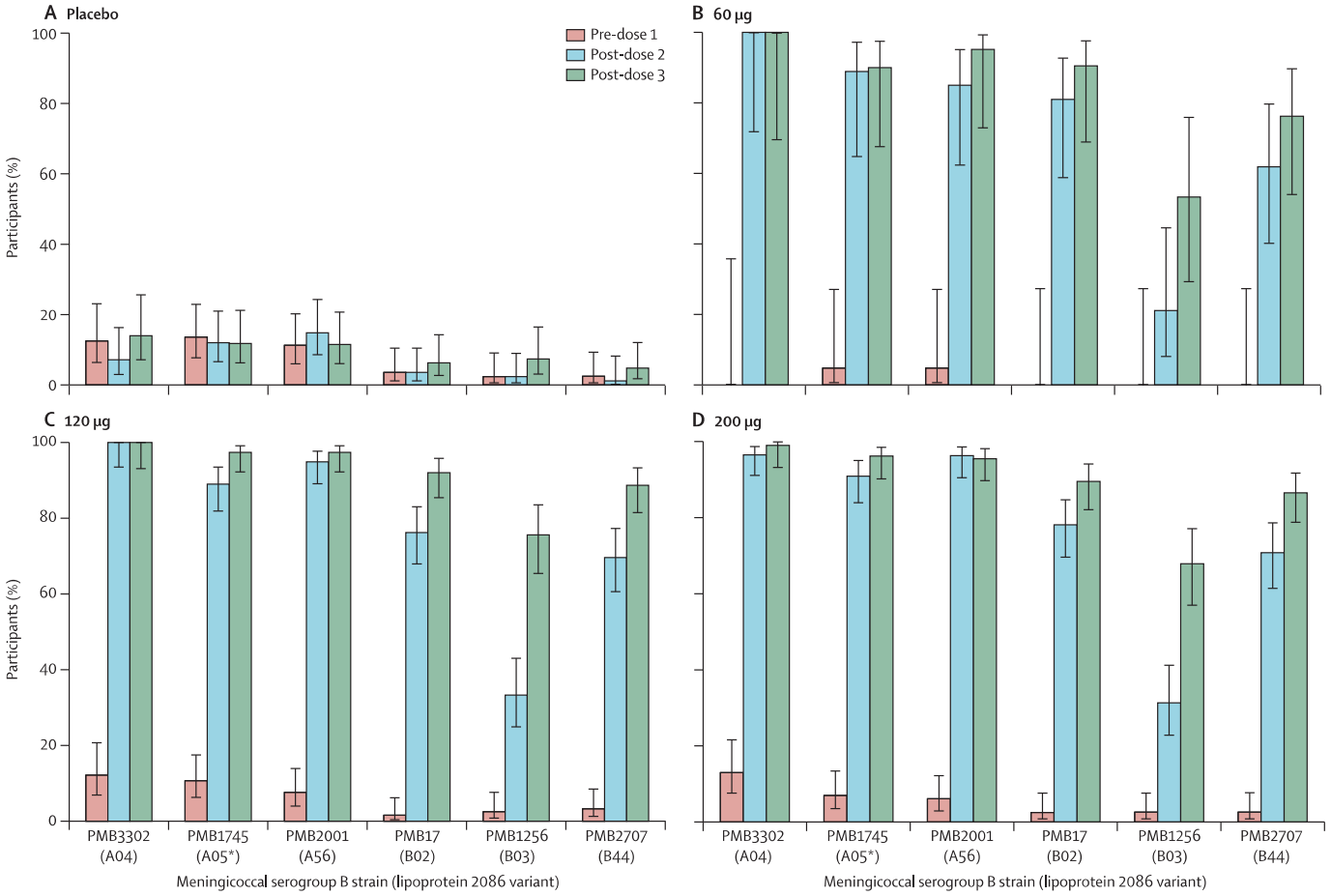
Vaccine Strains

FDA, VRBPAC Meeting, Gaithersburg, MD, 7 April 2011 |
HQ Jiang et al, Vaccine 28: 6086-6093, 2010

Immunogenicity of Lp2086 vaccine in adolescents

Percentage of subjects with detectable bactericidal antibodies

- Well conserved surface exposed lipoprotein. Two main alleles (A and B)
- Candidate vaccine: rec Lp2086 allele A and rec Lp2086 allele B with aluminium phosphate, three times IM (0, 1, and 6 months) to 18-25 years old subjects at dosages of 60 μg, 120 μg or 200 μg of each protein

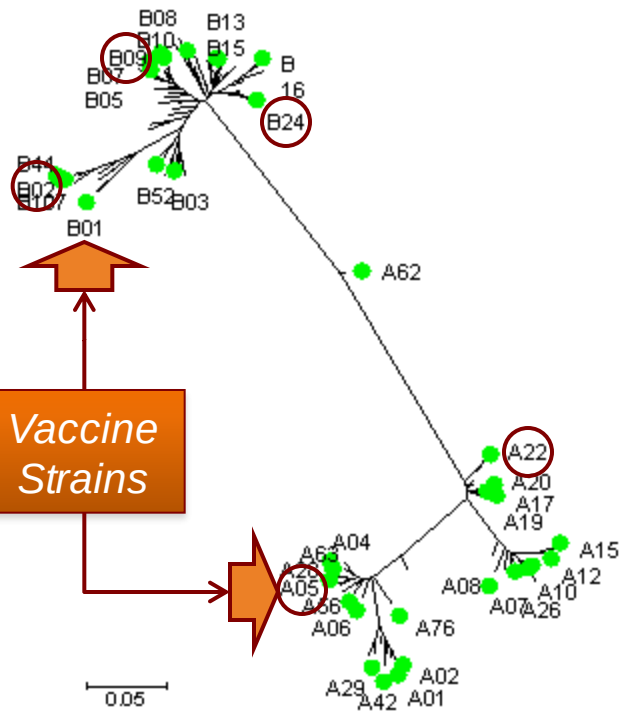


Richmond et al, *Lancet Infect Dis 2012; 12: 597-607*

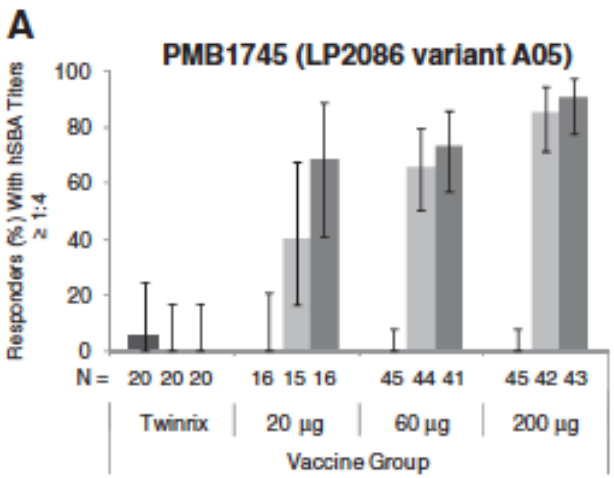
…and in 8-14 yr-old children

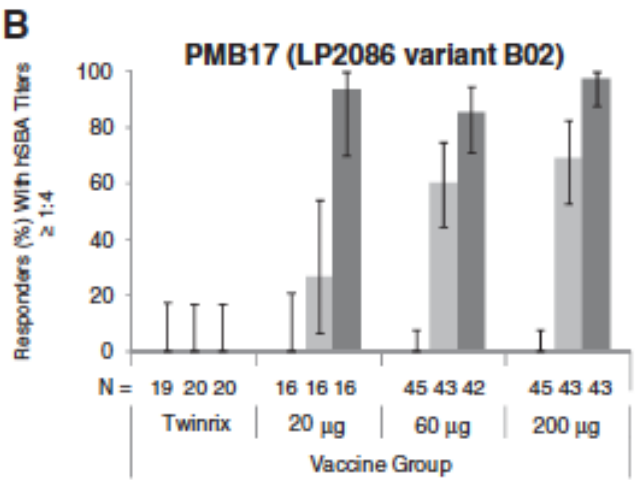
Randomized, observer-blinded phase I/II study

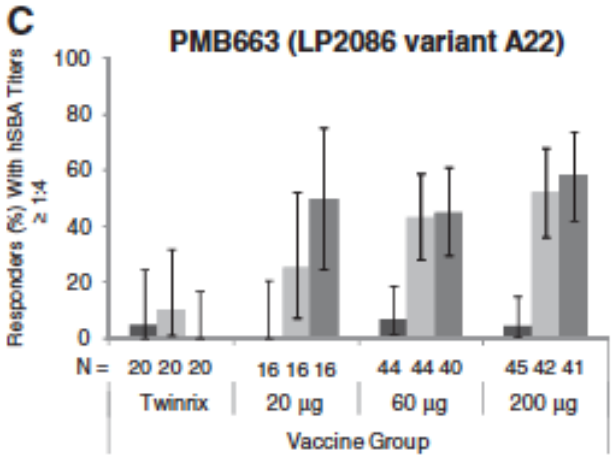
- 127 healthy 8-14 year-old children
- Vaccine (var. A05 + var. B01) given at 0, 1 and 6 months

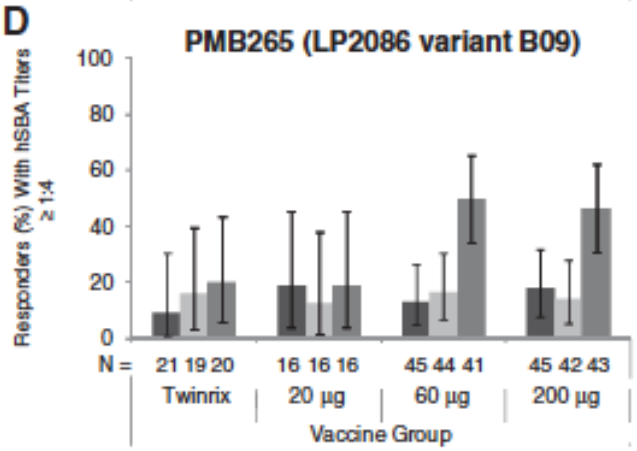


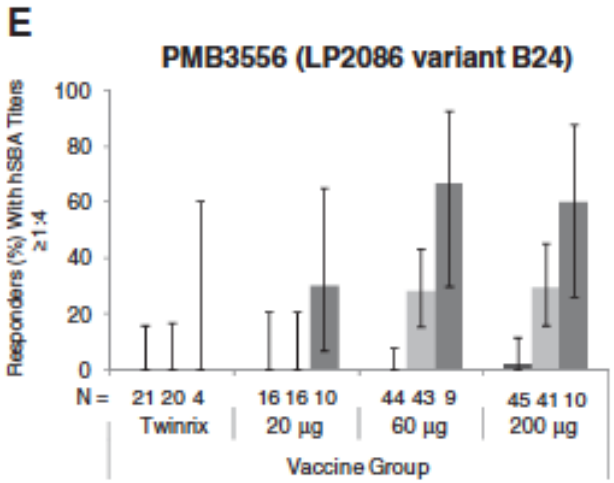
Nissen et al, Pediatr Infect Dis J 32: 364-371, 2013

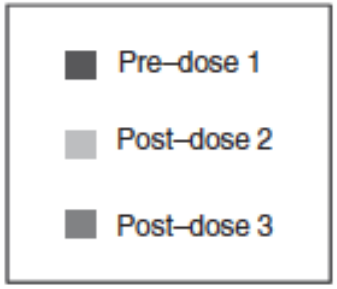






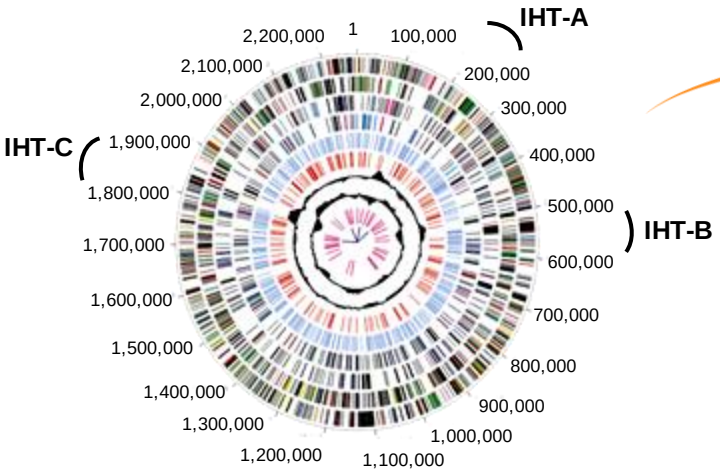






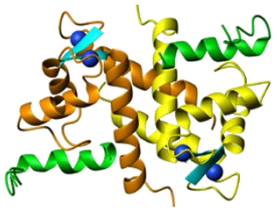
Novel Antigens Identified by Reverse Vaccinology: Example of MenB

Based on the genome sequence of MC58, **570** ORFs that potentially encoded novel surface exposed or exported proteins were identified



expression and purification

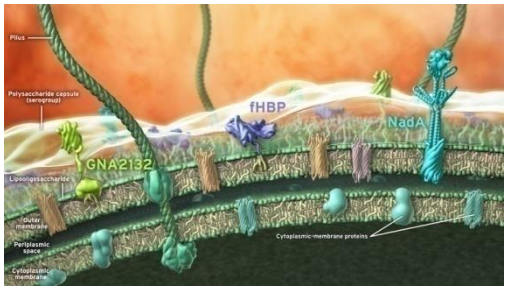
~350 proteins successfully expressed in *Escherichia coli*, purified, and used to immunize mice



purified proteins

immunizations

Sera used to confirm surface exposure of novel proteins



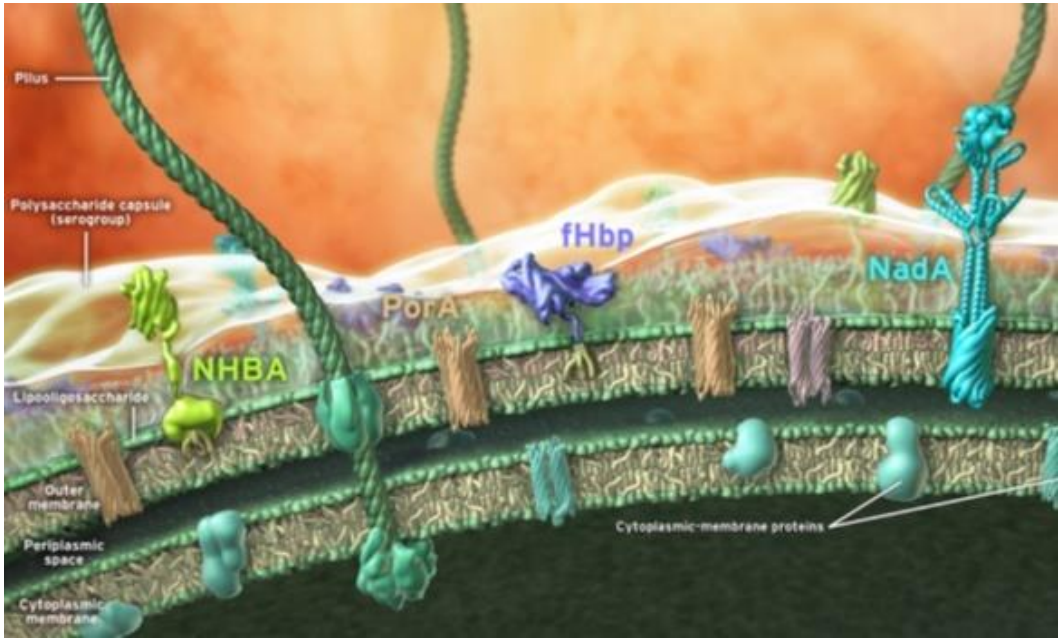
28 novel protein antigens with bactericidal activity were identified

ORF = open reading frame.

Based on Rappuoli R. Vaccine. 2001;19:2688-2691; Tettelin H, et al. Science. 2000; 287:1809-1815; Modified from Rosenstein NE, et al. N Engl J Med. 2001;344:1378-1388.

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.

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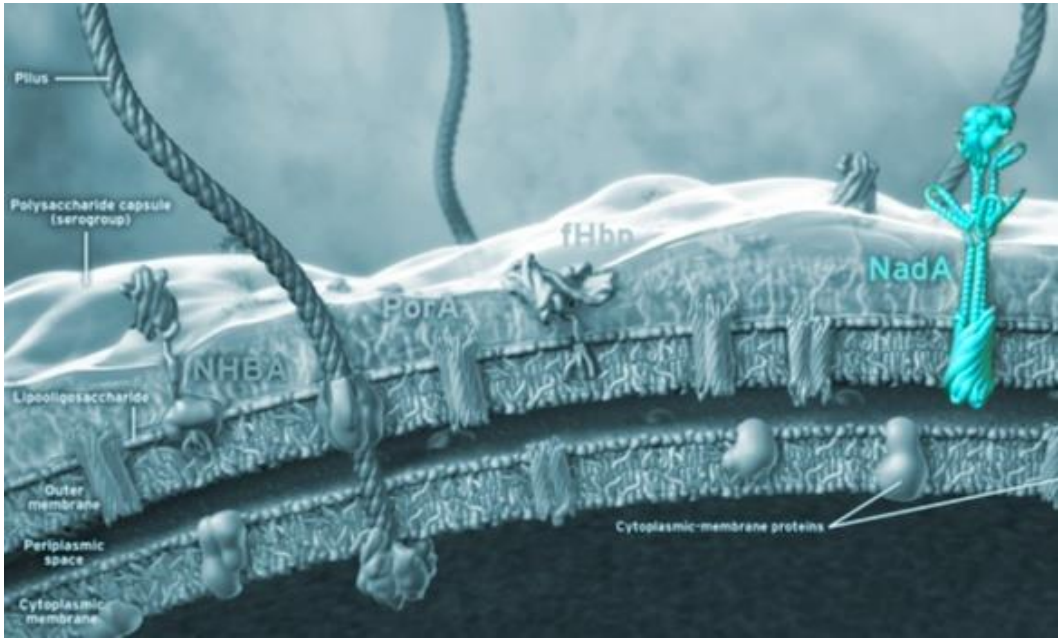
- **NadA: Neisserial adhesin A**
  - Promotes adherence to and invasion of human epithelial cells[1-3]
  - Possible importance in colonization



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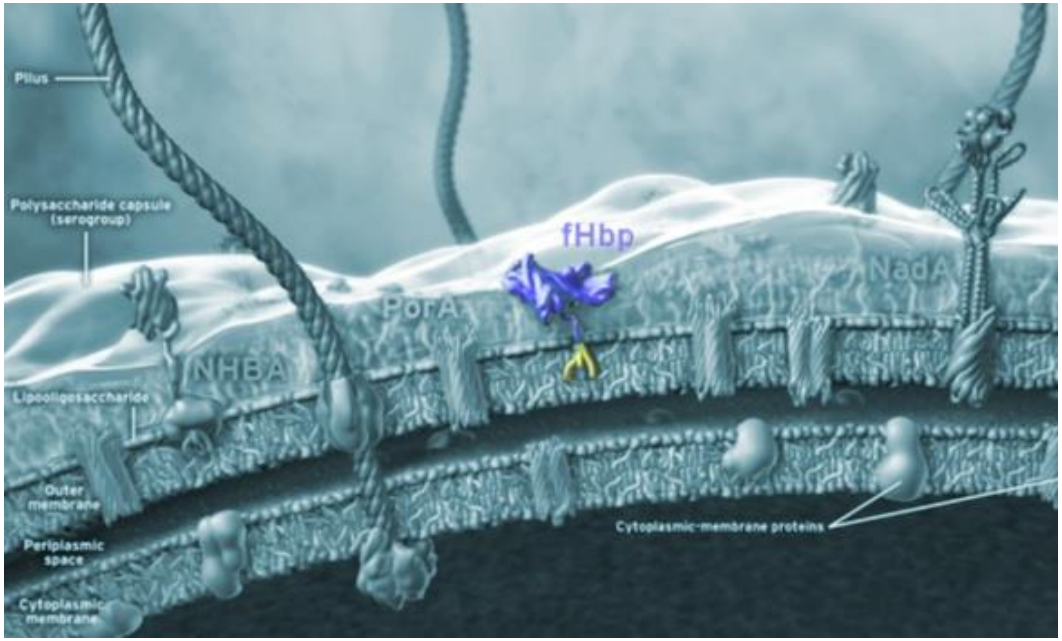
- **fHbp: factor H binding protein variant 1**
  - Binds factor H, which enables bacterial survival[5,6]

= Lp2086



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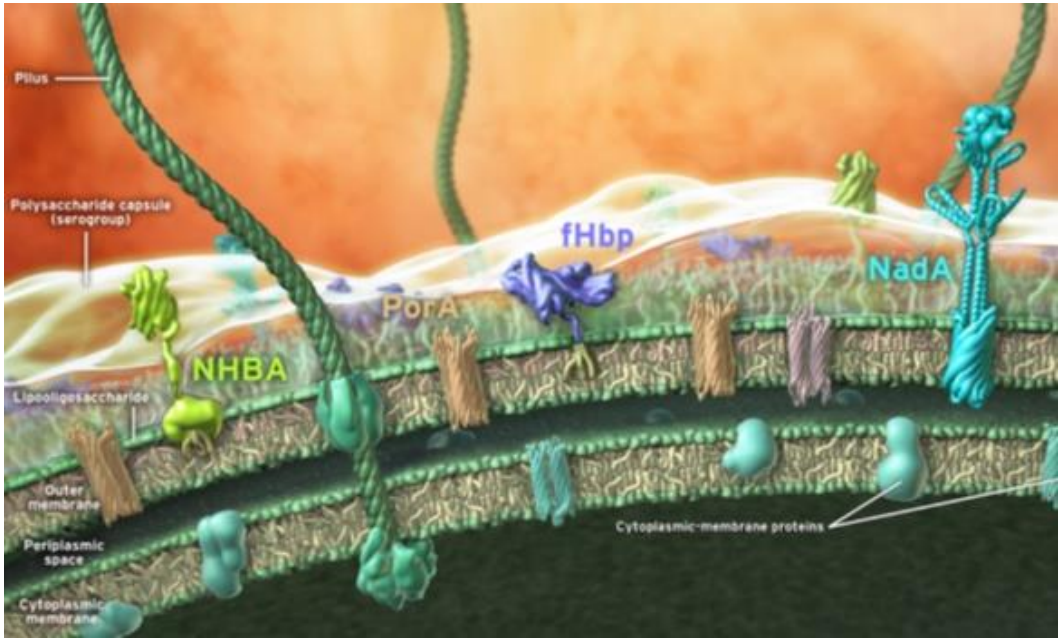
- **Utilizing multiple antigens**
  - Provides broad coverage
  - Maintains coverage against emergence of escape mutants



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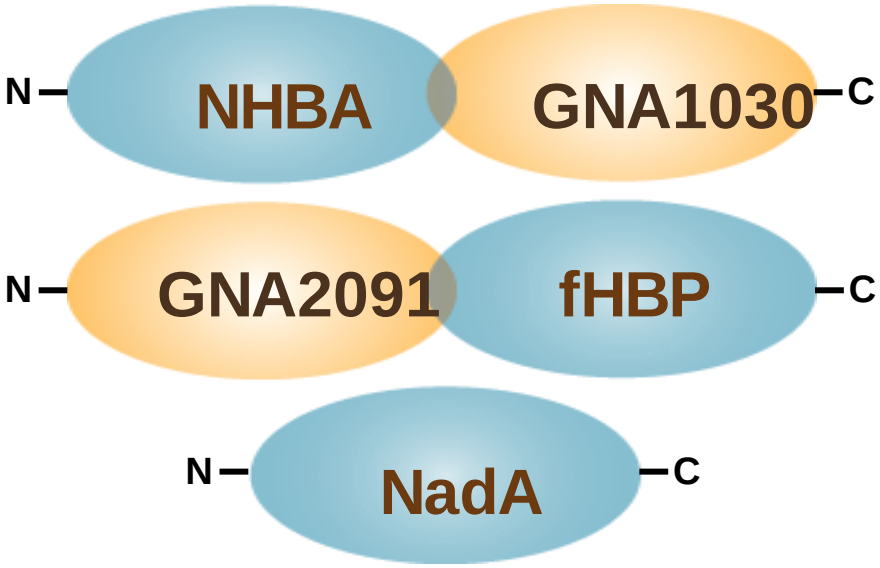
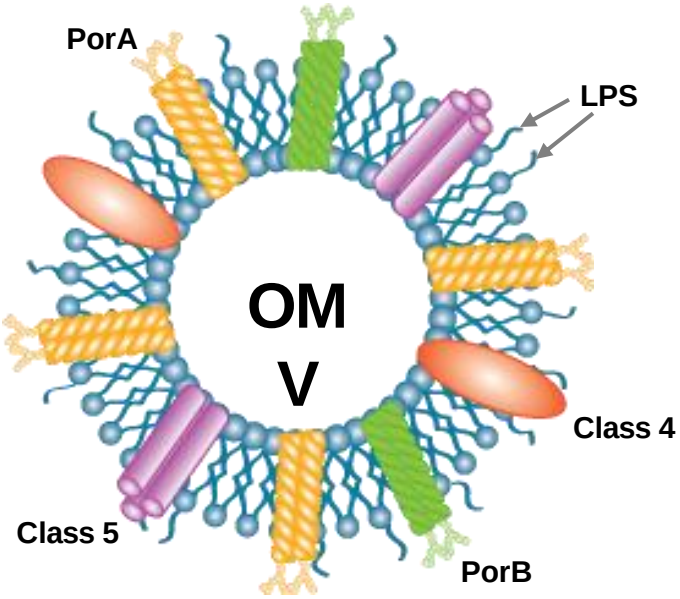
4CMenB Vaccine Composition

- 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^{3+}
0.5ml	50 μg	50 μg	50 μg	25 μg	0.5 mg

Rationale for Multicomponent 4CMenB Vaccine

- Provide broad coverage in all age groups
- Minimize potential for 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

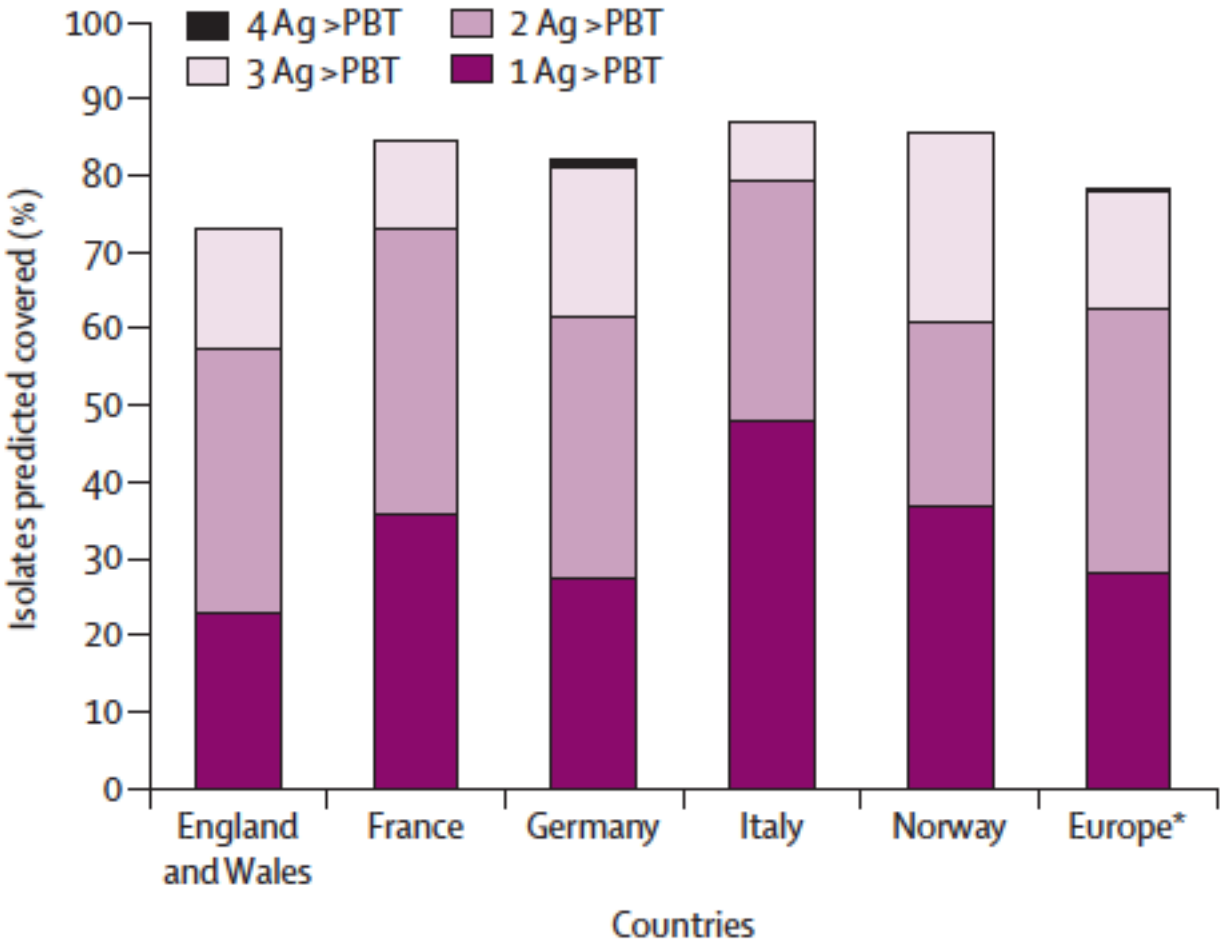
Predicted Serogroup B Strain Coverage of the 4CMenB Vaccine by Country

Country	Years	No. of strains	Predicted coverage (95% CI)
United States[1]	2000–2008†	442	91% (72%–96%)
Greece[2]	2008–2010	52	88% (60%–96%)
Italy[3]	2007/8*	54	87% (70%–93%)
Norway[3]	2007/8*	41	85% (76%–98%)
France[3]	2007/8*	200	85% (69%–93%)
Germany[3]	2007/8*	222	82% (69%–92%)
Brazil[4]	2010‡	99	81% (71%–95%)
Australia[5]	2007–2011	373	76% (63%–87%)
Czech Republic[3]	2007–2010	108	74% (58%–87%)
England & Wales[3]	2007/8*	535	73% (57%–87%)
Spain[3]	2008–2010	300	69% (48%–85%)
Canada[6]	2006–2009	157	66% (46%–78%)

*All invasive capsular group B isolates tested. †Downweighted with respect to outbreak strains from Oregon.
‡Represents about 53% of capsular group B cases.

1. Kim E, et al. Poster presented at: 18th International Pathogenic Neisseria Conference (IPNC) Meeting; September 9-14, 2012; Würzburg, Germany. Poster P270; 2. Data on file, Novartis Vaccines and Diagnostics; 3. Vogel U, et al. *Lancet Infect Dis*. 2012 [in press]; 4. Lemos AP, et al. Poster presented at: 18th International Pathogenic Neisseria Conference (IPNC) Meeting; September 9-14, 2012; Würzburg, Germany. Poster P272; 5. Nissen M, et al. Poster presented at: 18th International Pathogenic Neisseria Conference (IPNC) Meeting; September 9-14, 2012; Würzburg, Germany. Poster P269; 6. Bettinger J, et al, IMPACT Investigators. Poster presented at: 5th Vaccine and International Society for Vaccines (ISV) Annual Global Congress; October 2-4, 2011; Seattle, WA.

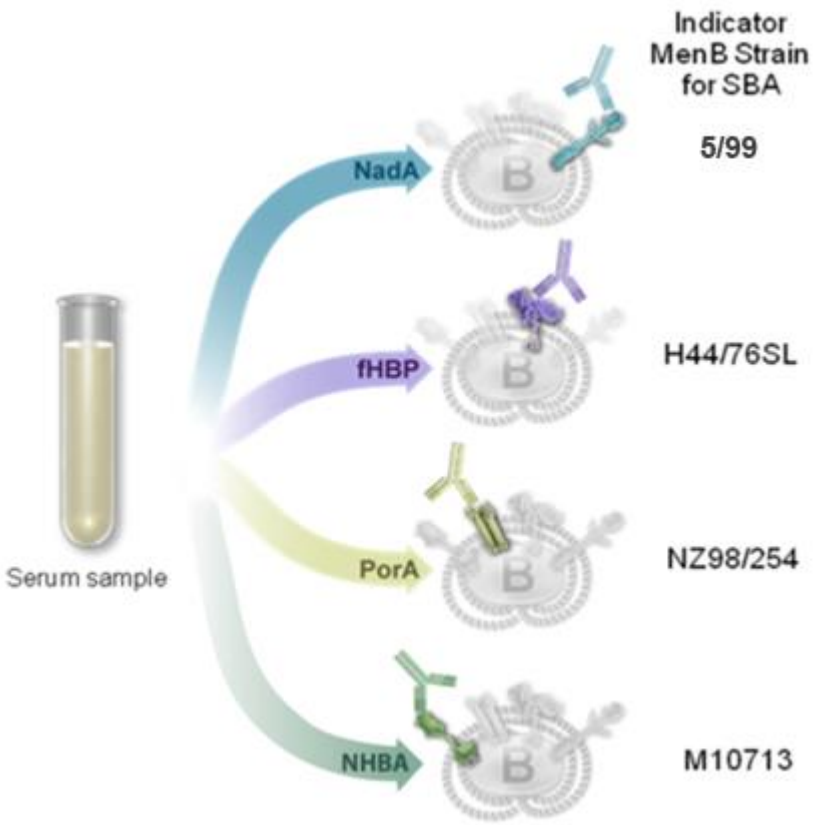
Percentage of strains predicted to be covered by no. of antigens and by country



Vogel et al, *Lancet Infect Dis* **13**: 416-425, 2013

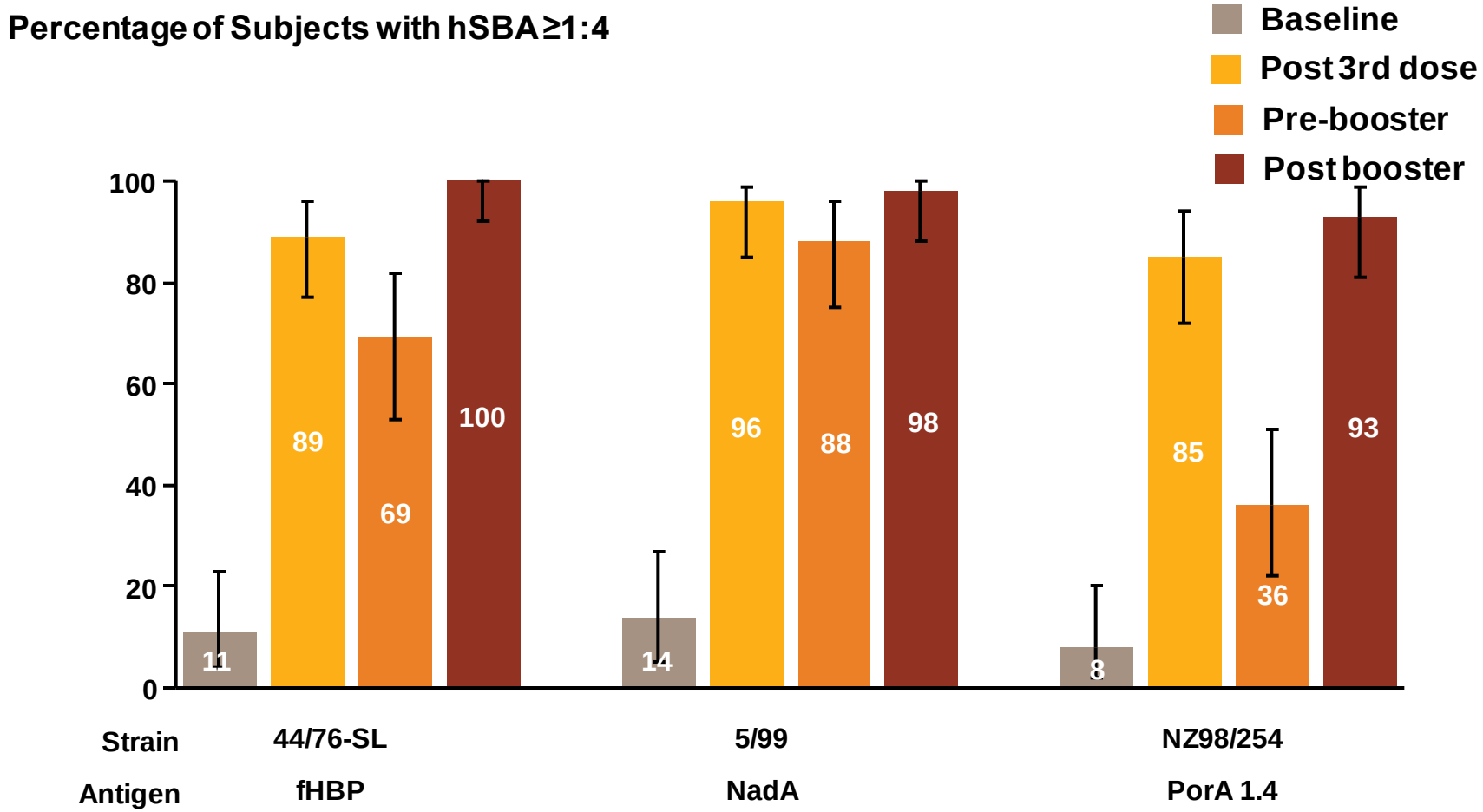
Strain Panel for Demonstrating Antigen-specific Bactericidal Responses

- **NadA:** 5/99, NadA allele 2
- **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)



hSBA Titers ≥1:4 After 3 Doses of Novartis MenB Vaccine and Persistence to 12 Months of Age

Phase II Immunogenicity in Infants

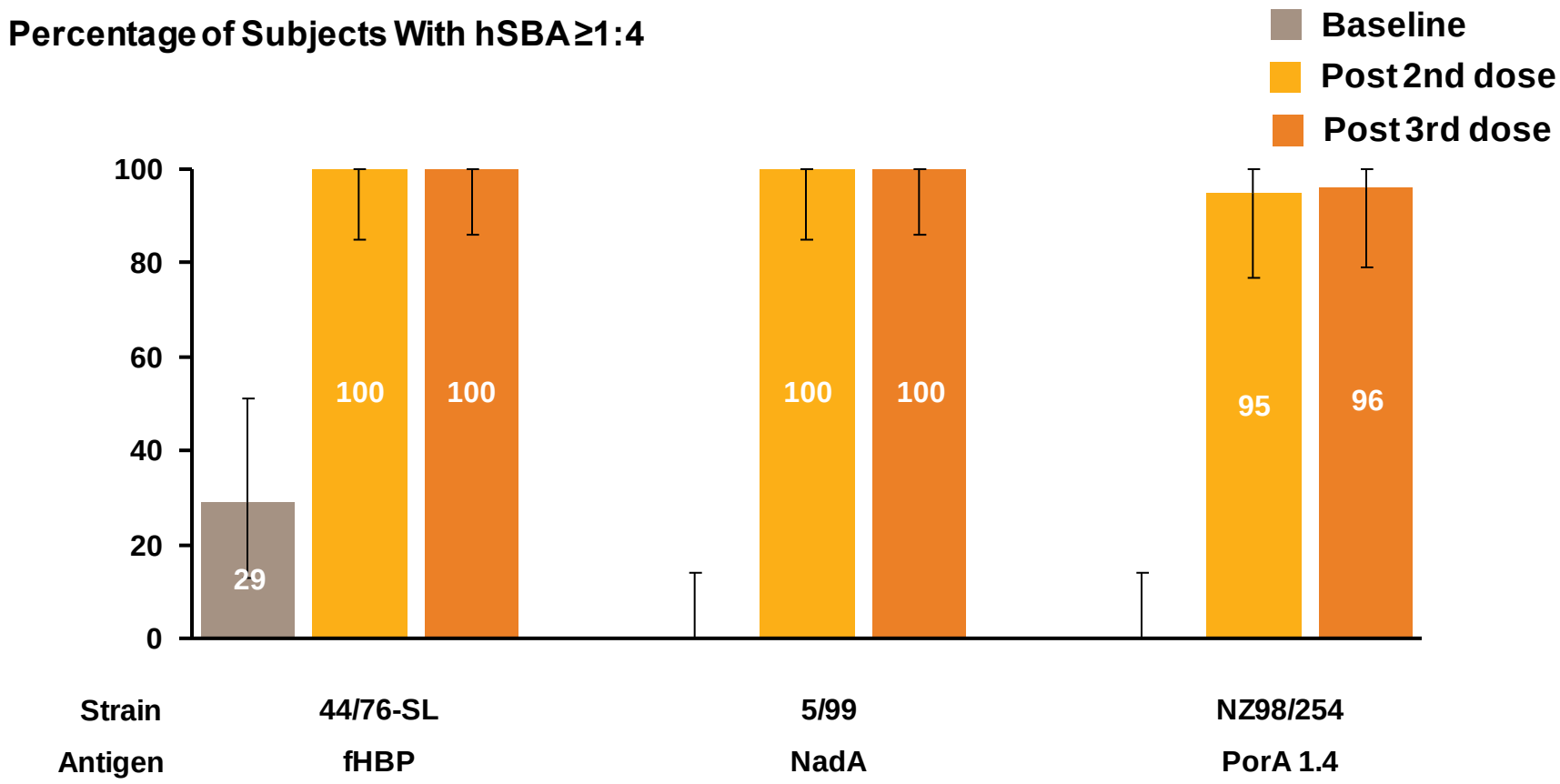


MenB vaccine = rMenB + OMV.

Findlow et al, Clin. Infect Dis 51: 1127-1137, 2010.

hSBA Titers ≥1:4 After 2nd and 3rd Doses of Novartis MenB Vaccine

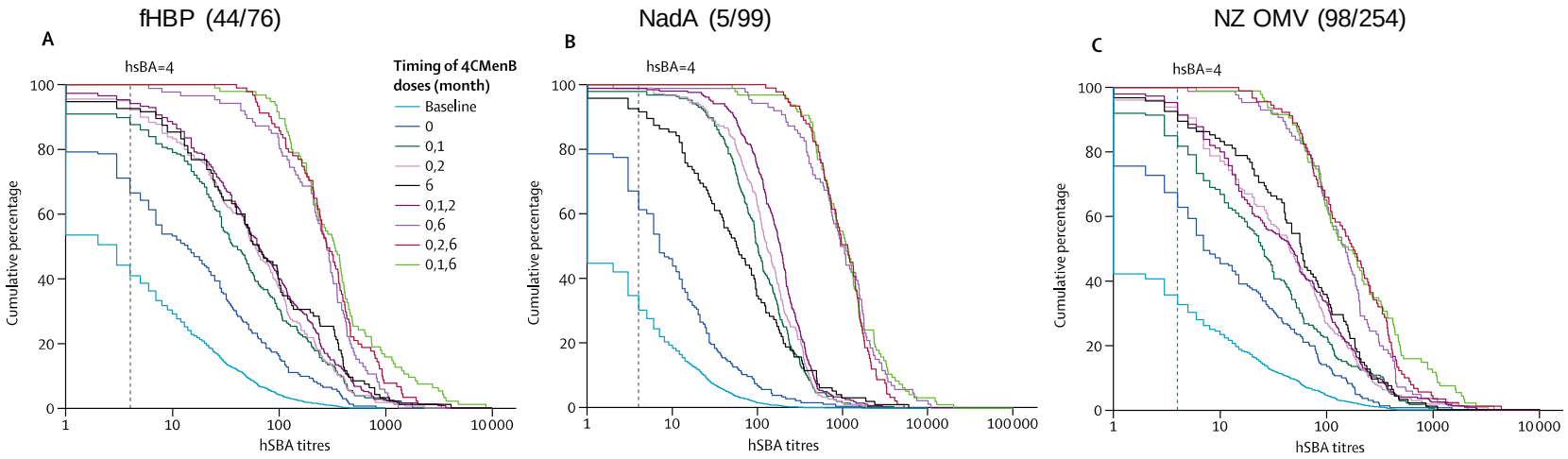
Phase II Immunogenicity in Infants 6-8 Months of Age



MenB vaccine = rMenB + OMV.

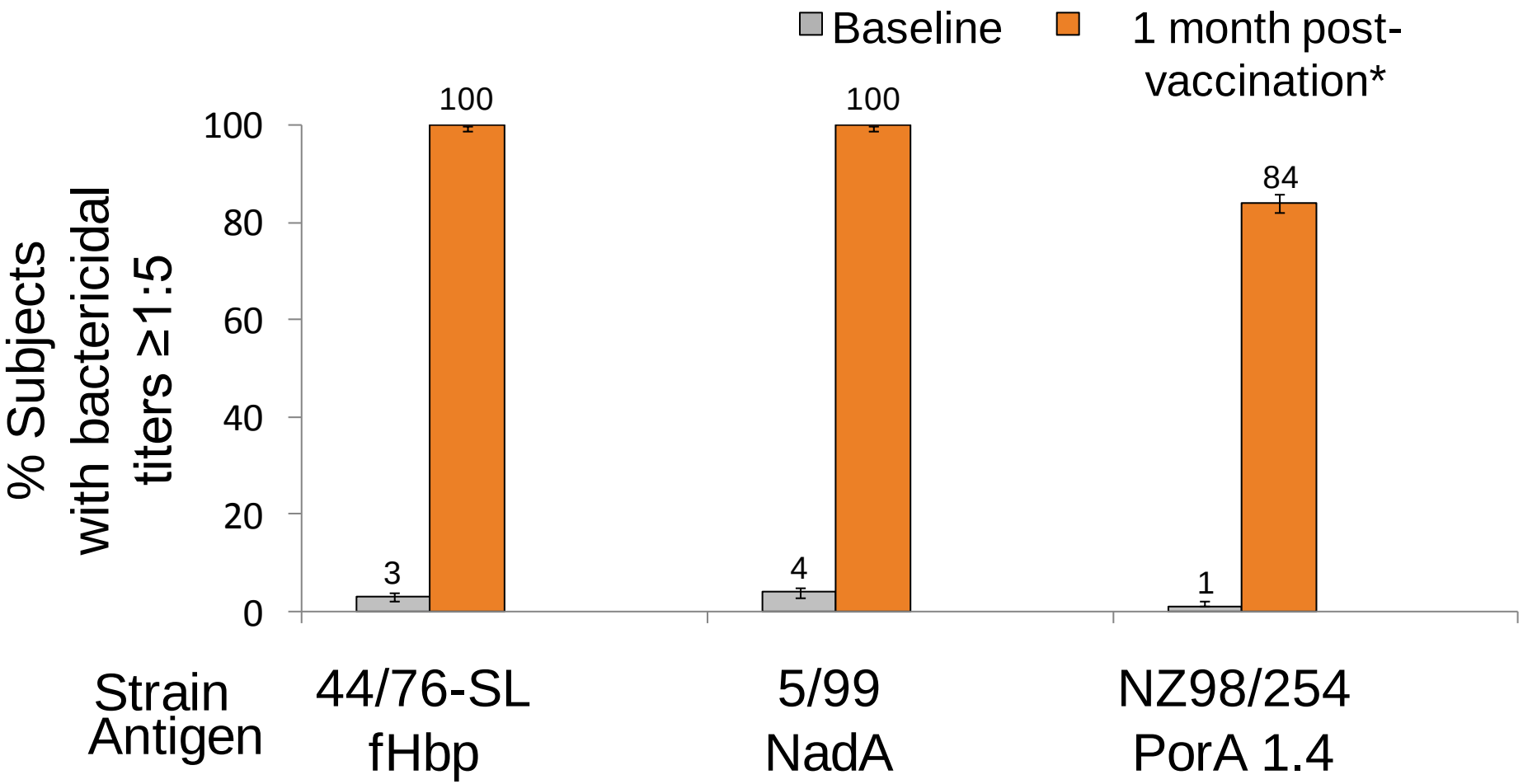
Snape et al, Pediatr Infect Dis J 29: e71-e79, 2010.

Immunogenicity of 4CMenB vaccine (Novartis) in adolescents. Bactericidal antibody responses



Santolaya et al, Lancet 379: 617-624, 2012

Percentage of Infants with Bactericidal Titers ≥1:5 After a Primary Series of 4CMenB* at 2, 4, and 6 Months of Age

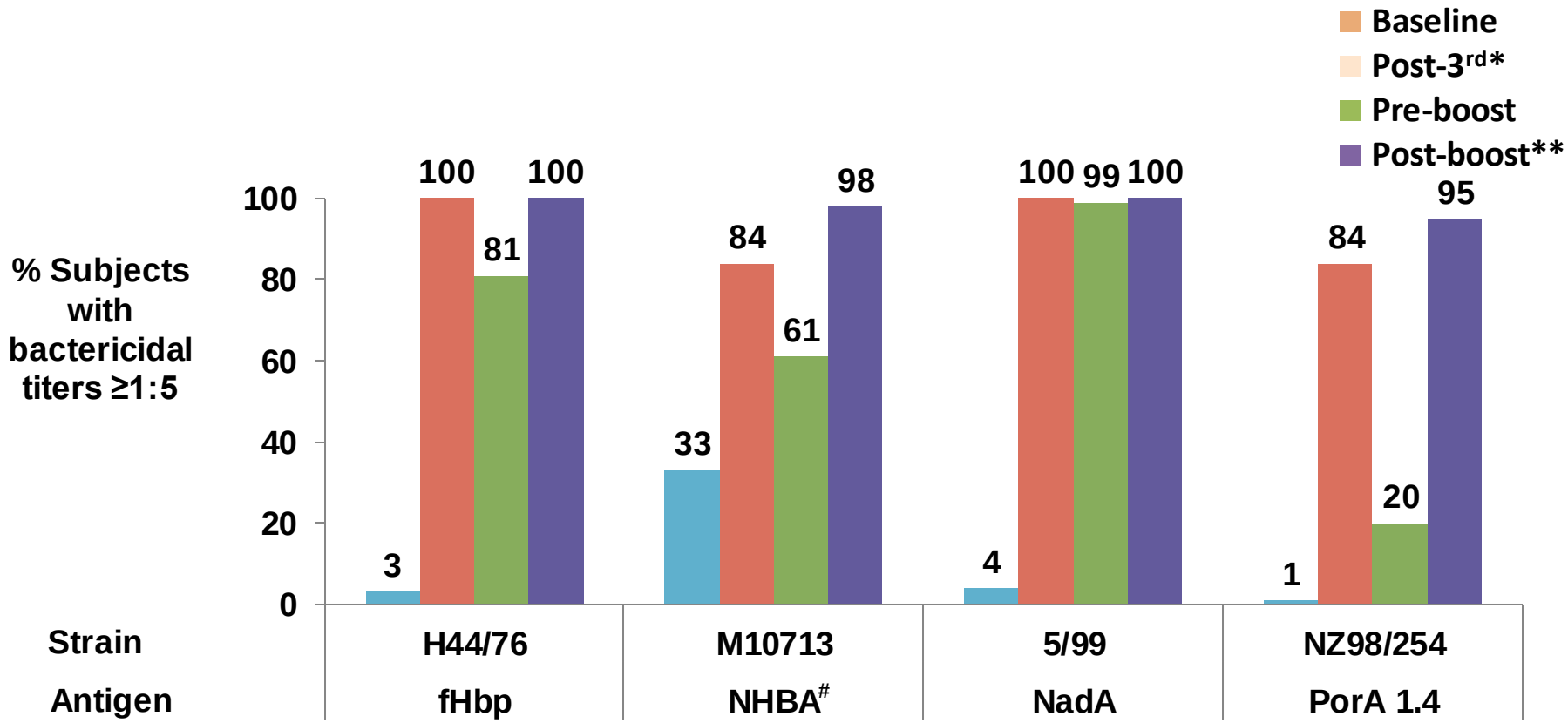


*Blood drawn at age 7 months, N=1149-1152; Coadministered with PCV7 and DTPa-HBV-IPV/Hib

Vesikari et al, Lancet 381: 825-835, 2013

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

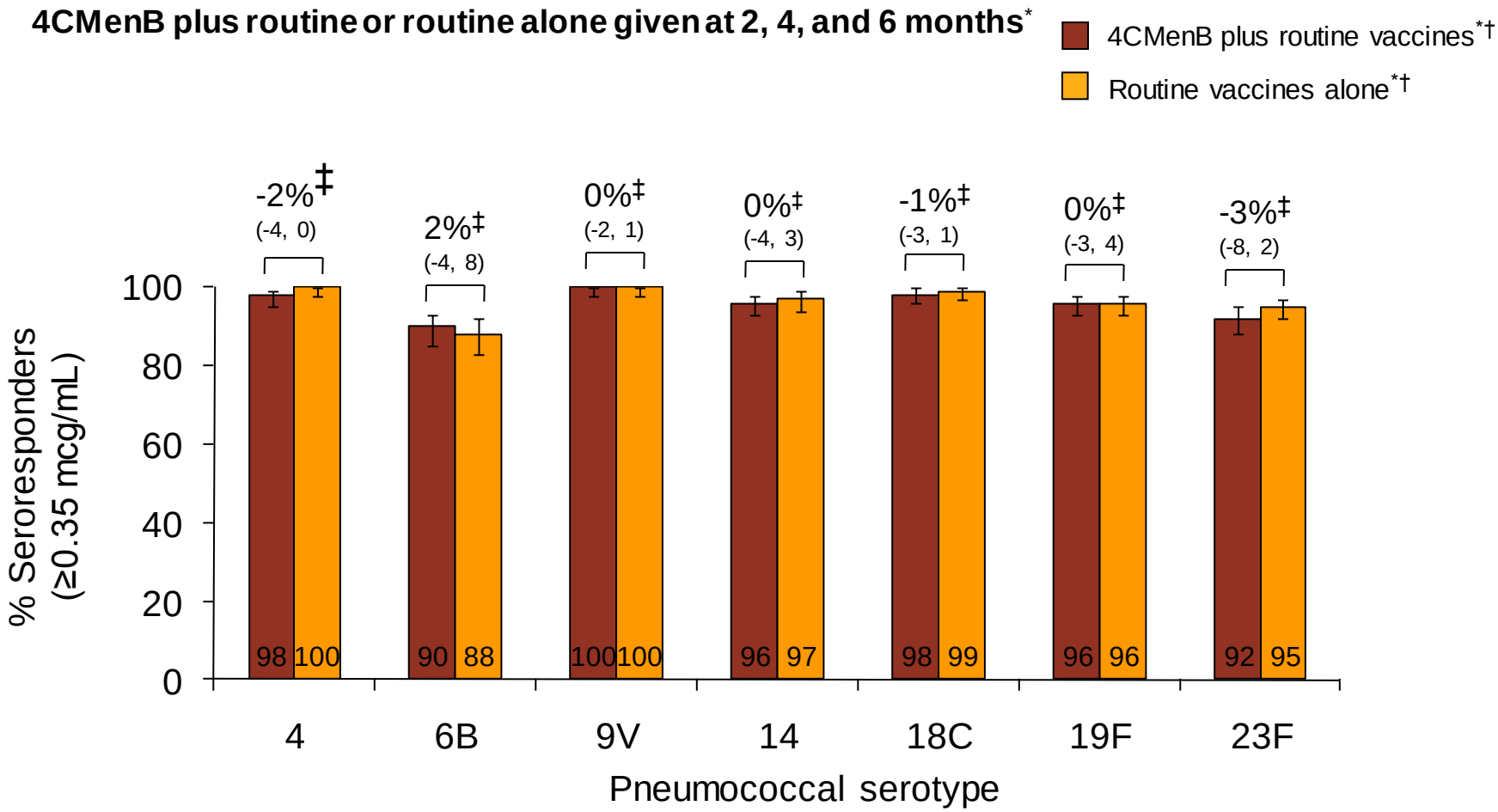
N=100

Vesikari et al, Lancet 381: 825-835, 2013

Phase III Study in Infants

Pneumococcal Seroresponse After Routine Vaccines Coadministered With 4CMenB or Routine Vaccines Alone in Infants

4CMenB plus routine or routine alone given at 2, 4, and 6 months*



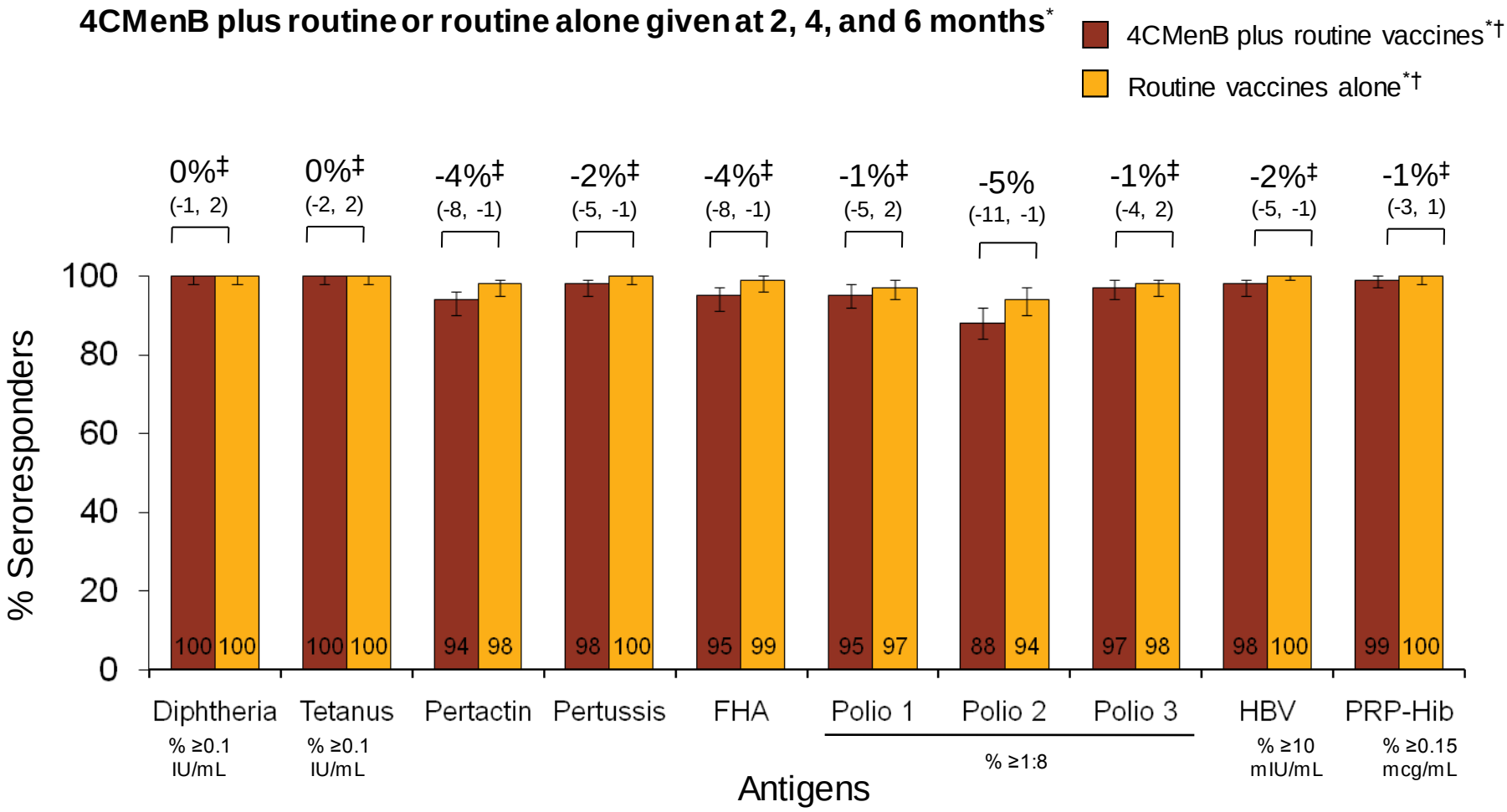
* Routine vaccines: Infanrix-Hexa™; Prevenar™.

†n=242-243.

‡Criteria met for LL 95% CI > -10% for difference in percent of responders. Blood drawn at 7 months.

Gossger et al, JAMA 307: 573-582, 2012

Immunogenicity of Routine Infant Vaccines Given With or Without 4CMenB



* Routine vaccines: Infanrix-Hexa™; Prevenar™.

†n=238-248.

‡Criteria met for LL 95% CI for difference in seroresponders > -10%.

Blood drawn at 7 months.

Gossger et al, JAMA 307: 573-582, 2012

NOVARTIS

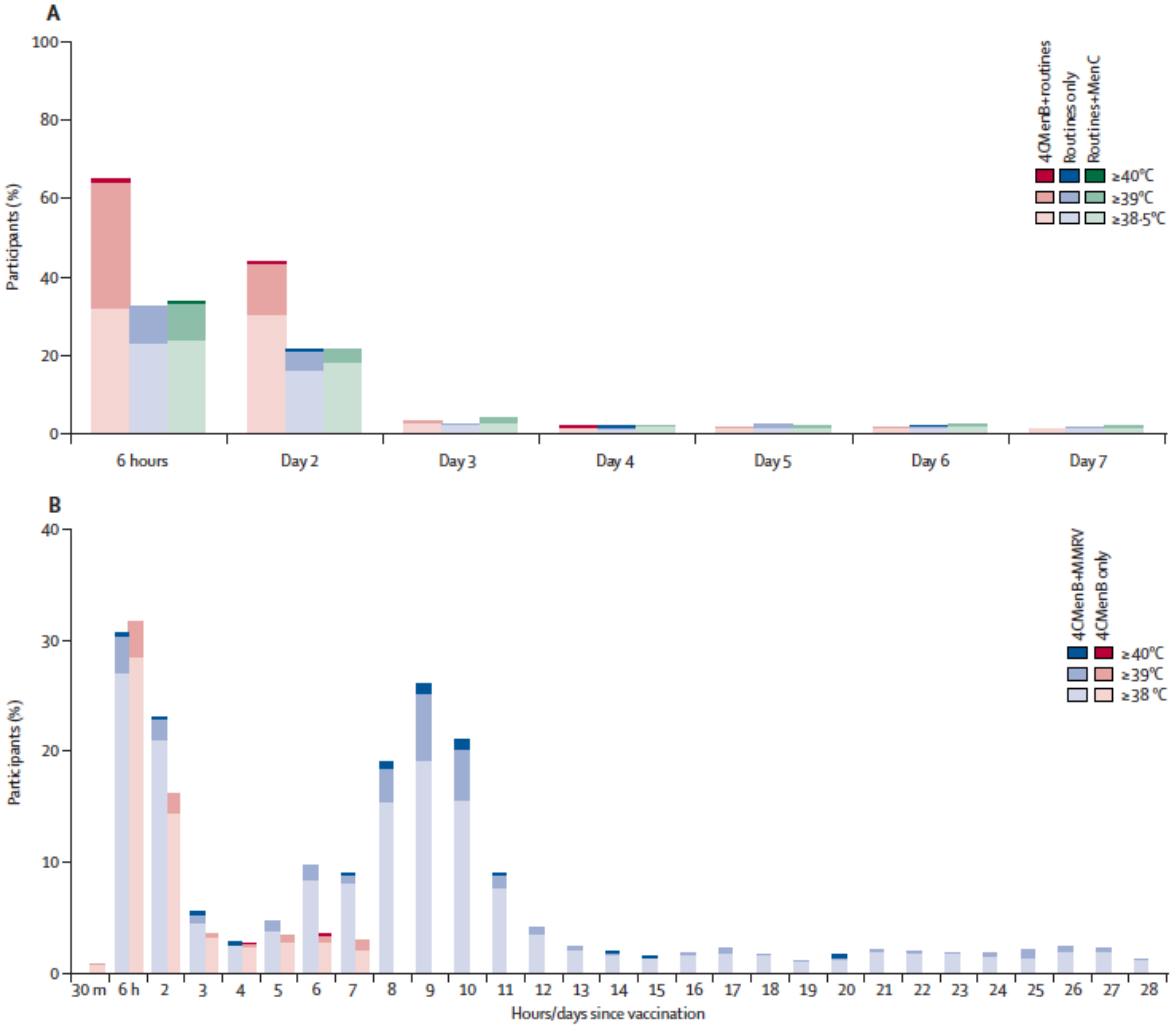
Serious Adverse Events and Adverse Events After Any Vaccination

	4CMenB+Routine (N=2480)	Routine Vaccines (N=658)	MenC+Routine Vaccines (N=488)
Serious Adverse Events	**8%**	**8%**	**6%**
Adverse Events	**87%**	**83%**	**73%**

*Routine vaccines: PCV7 and DTPa-HPV-IPV/Hib

Vesikari et al, Lancet 381: 825-835, 2013

Fever rates after 4CMenB vaccine given without or without routine vaccines



Vesikari et al, Lancet 381: 825-835, 2013

In summary

- ***Conventional approaches*** for MenB vaccine development have consistently ***failed***: conjugates not feasible; proteins variable and not immunogenic (no bactericidal antibodies induced)
- A ***tailor-made approach*** does work (e.g. OMV in New Zealand), but it has ***limited geographical impact***.
- The genome-based approach has allowed the identification of a large number of potential vaccine candidates which are now in clinical trials
- Data from these clearly show that a ***protein-based vaccine against MenB offering a broaden coverage*** against circulating strains is a reality at all ages, including infants
- ***This has led to the approval of the first vaccine against MenB able to confer broad protection starting from 2 months of life***

Conclusions. Positive opinion granted by CHMP on 12 November 2012 for use starting from the age of 2 months

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 November 2012
EMA/CHMP/669278/2012
Committee for Medicinal Products for Human Use (CHMP)

On 15 November 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Bexsero, suspension for injection intended for the prophylaxis against invasive disease caused by *N. meningitidis* group B strains. The applicant for this medicinal product is Novartis Vaccines and

The approved indication is: "Bexsero is indicated for active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B. The impact of invasive disease in different age groups as well as the variability of antigen epidemiology for group B strains in different geographical areas should be considered when vaccinating. See section 5.1 of SmPC for information on protection against specific group B strains. The use of this vaccine should be in accordance with official recommendations." It is proposed that Bexsero be prescribed by physicians experienced in the disease caused by *Neisseria meningitidis* group B.

Authored article

MenB vaccine should join childhood vaccination programme

Organisation: Department of Health
Written on: 21 March 2014
Page history: Published 21 March 2014
Policy: Giving all children a healthy start in life
Topics: Public health, + 2 others
Writer: Deputy Chief Medical Officer John Watson

Deputy Chief Medical Officer John Watson welcomes JCVI's recommendation for a new meningococcal B (MenB) immunisation programme.

Today marks an important step forward in tackling meningococcal B (MenB) disease, which can have a devastating and distressing impact, particularly for babies and young children. MenB is a disease that many parents of young children fear.

Our expert advisers on vaccination and immunisation, the Joint Committee on Vaccination and Immunisation (JCVI), have recommended that a recently licensed MenB vaccine is added to the childhood immunisation programme. The committee recommended that MenB immunisation should be offered to infants starting at 2 months of age, subject to the vaccine being obtained from the manufacturer at a cost-effective price which represents good value -for-money to the NHS.

The Department of Health, which requested JCVI's advice on MenB vaccine, has accepted this recommendation and will work to introduce the programme as quickly as possible. This timing will depend on being able to purchase a sufficient and continuing supply of vaccine at an appropriate

Bexsero recommendations for regional & national vaccination programs

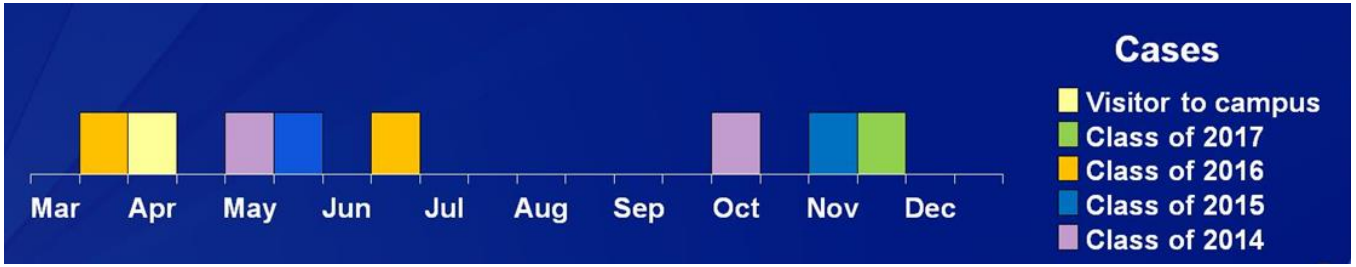
Country	National	Regional	Funding	Infant	Children	Adolescent	High Risk	Note
UK	👍		👍	👍			👍	JCVI: Infants 2-4 moa, 2+1 schedule
Germany	👍*	👍*	see note	👍	👍	👍	👍	Saxony: 2moa-18 yoa Ped Assoc.: all children Voluntary reimbursement by 40+ Sick Funds
France	👍*		👍**				👍	High risk, outbreak, epidemic, hyperendemic
Italy	👍*	👍	👍	👍				Basilicata: infants, 3+1 Med Societies: all infants
Australia	👍*			👍	👍	👍	👍	ATAGI: young children, esp.<2 yoa; 15-19 yoa
Austria	👍*		see note				👍	High risk reimbursable by regional insurance
Czech Rep	👍*			👍	👍	👍	👍	Vaccinology Society: 2 moa-10 yoa, 13-15 yoa
Poland	👍*			👍	👍	👍		From 2moa, no upper age limit

* clinical recommendation, not linked to funding

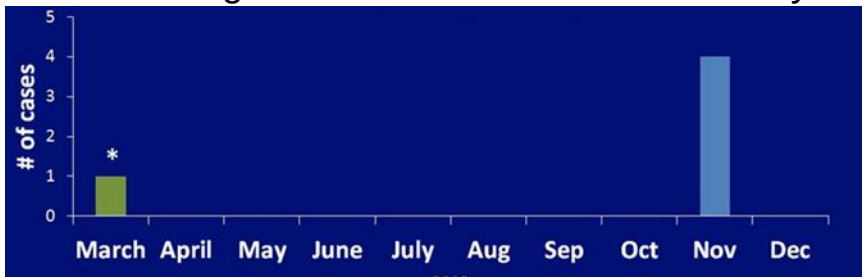
** currently for outbreak only, reimbursement for high risk groups under review

Serogroup B meningococcal disease outbreaks in the US: Princeton University and University of California, Santa Barbara (UCSB)

- 8 cases at Princeton University from March to November 2013
  - Students or persons with links to the university
  - No fatalities; 2 cases with sequelae
  - Attack rate 134/100,000 among undergraduates



- 5 cases at UCSB from March to November 2013
  - Undergraduates (age 18-22 years): no epi-links
  - 4 recovered, 1 case with sequelae (bilateral foot amputation)
  - Attack rate of 21.1/100,000 among UCSB 17-22 year olds
    - 234-fold higher than incidence rate for 17-21 year olds in general US population



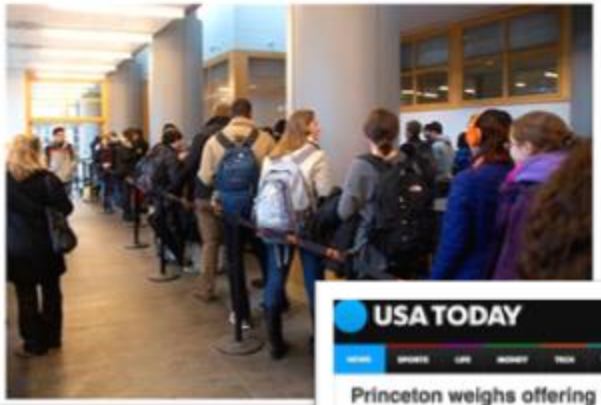
*Source: Outbreaks of Serogroup B Meningococcal Disease on University Campuses – 2013, Manisha Patel, MD MSc

US Adolescents vaccinated under expanded access treatment IND (CDC) (1/2)

Chronology

- CDC approached FDA to explore the use of Bexsero in outbreak setting under an expanded access Investigational New Drug (IND) Protocol – August 2013
- Princeton Institutional Review Board approval and FDA Safe-to-Proceed letter issued – November 2013
- Vaccination campaign in Princeton started in December 2013
- CDC-sponsored expanded access IND approved by FDA for use in UCSB outbreak in January 2014
- Vaccination campaign at UCSB started in February 2013
  - Second dose in April 2014

Bexsero: Princeton and UCSB



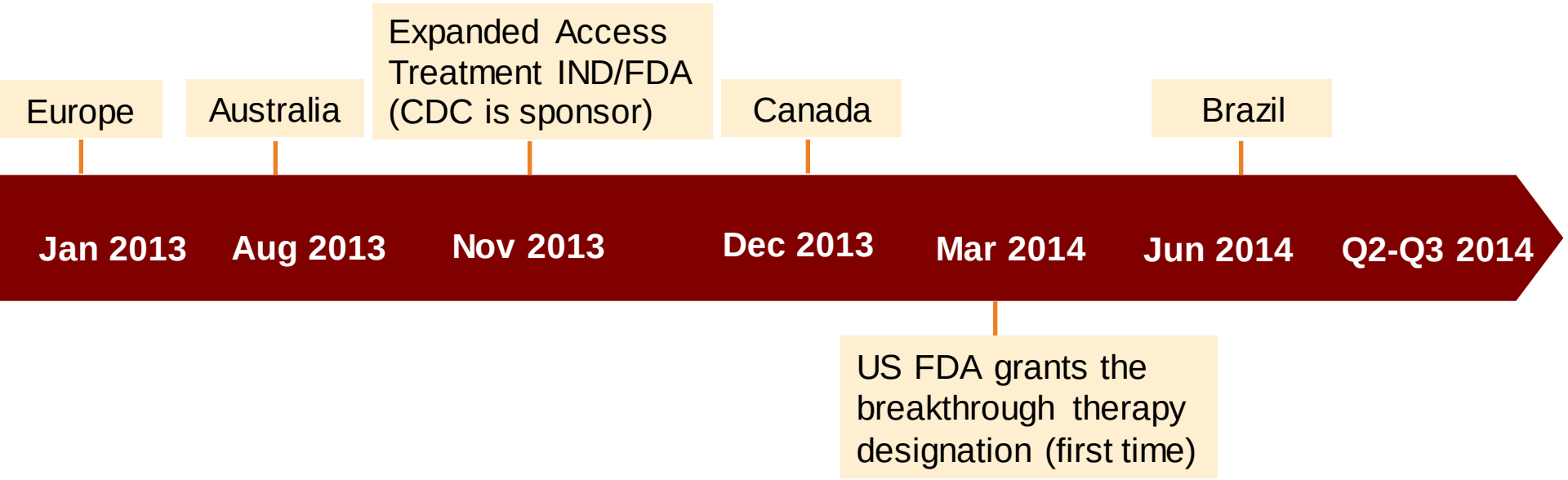
US Adolescents vaccinated under expanded access treatment IND (CDC) (2/2)

Safety follow-up

- More than 14000 subjects were vaccinated with Bexsero as of end March 2014
- Mandatory reporting of all serious adverse events (SAEs) to FDA including expedited reporting for related events
- Additional collection including pregnancy exposures, vaccine failure (none to date) and non-serious adverse events screened by CDC Vaccine Safety group and summarized
- Preliminary data from Princeton vaccination campaign (more than 5000 exposed students)
  - Rate of SAEs reported is 2.0/1,000 vaccinees in first dose recipients and 0.2/1,000 vaccinees in second dose recipients
  - Consistent with clinical trial safety profile

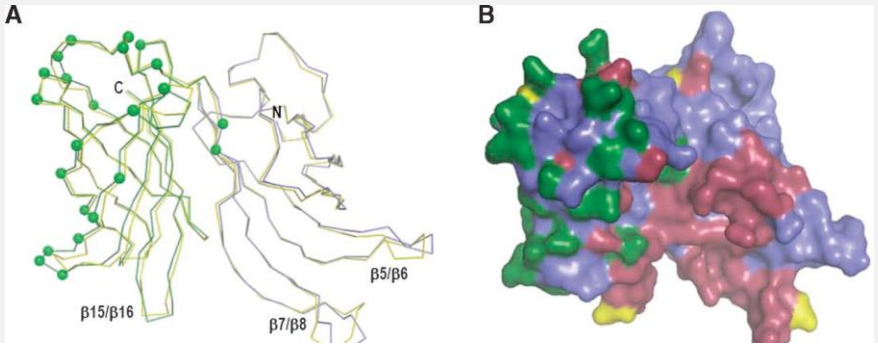
Bexsero: 2013-14 approvals and submissions

Approvals



Submissions

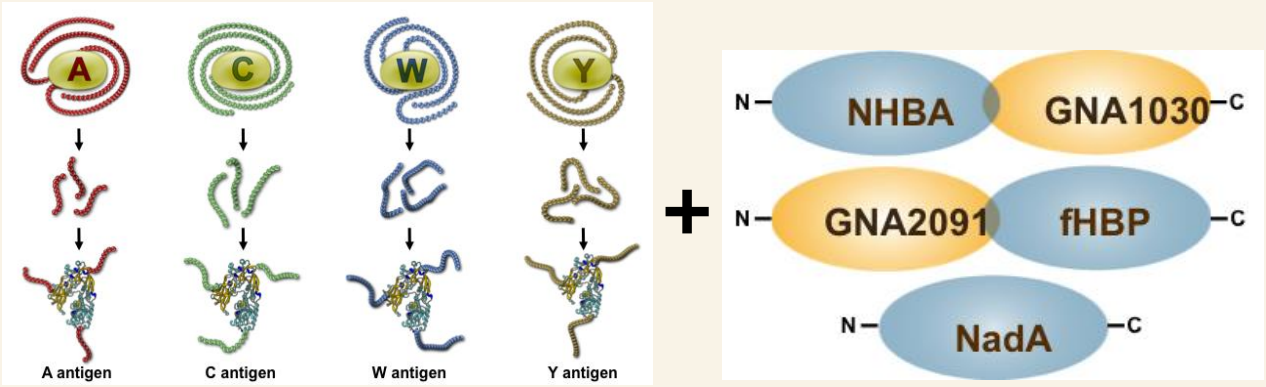
Future perspectives



	MC58	UK149	M4030	UK185	NZ98/254	961-5945	M3153	C11	M6208†	M1239
	1.1	1.4	1.12	1.10	1.14	2.1	2.4	2.7	2.10	3.1
Antigen										
fHBP var.1.1 wt	**2048**	**256**	**512**	**16**	**128**	<8	<8	<8	<8	<8
fHBP var.2.1 wt	<8	<8	<8	<8	<8	**64**	<8	<8	**128**	<8
GNA2091-G1-G1	**1024**	**512**	**>512**	**256**	**256**	**64**	**256**	**256**	**512**	**256**
Homologs	**2048**	**>1024**	**512‡**	**>1024**	**>1024**	**256**	**128**	**128**	**512**	**1024**

Molecular surgery
Construct molecules containing all variants for broader responses

Scarselli et al, *Science Transl Med* 3: 91ra62, 2011

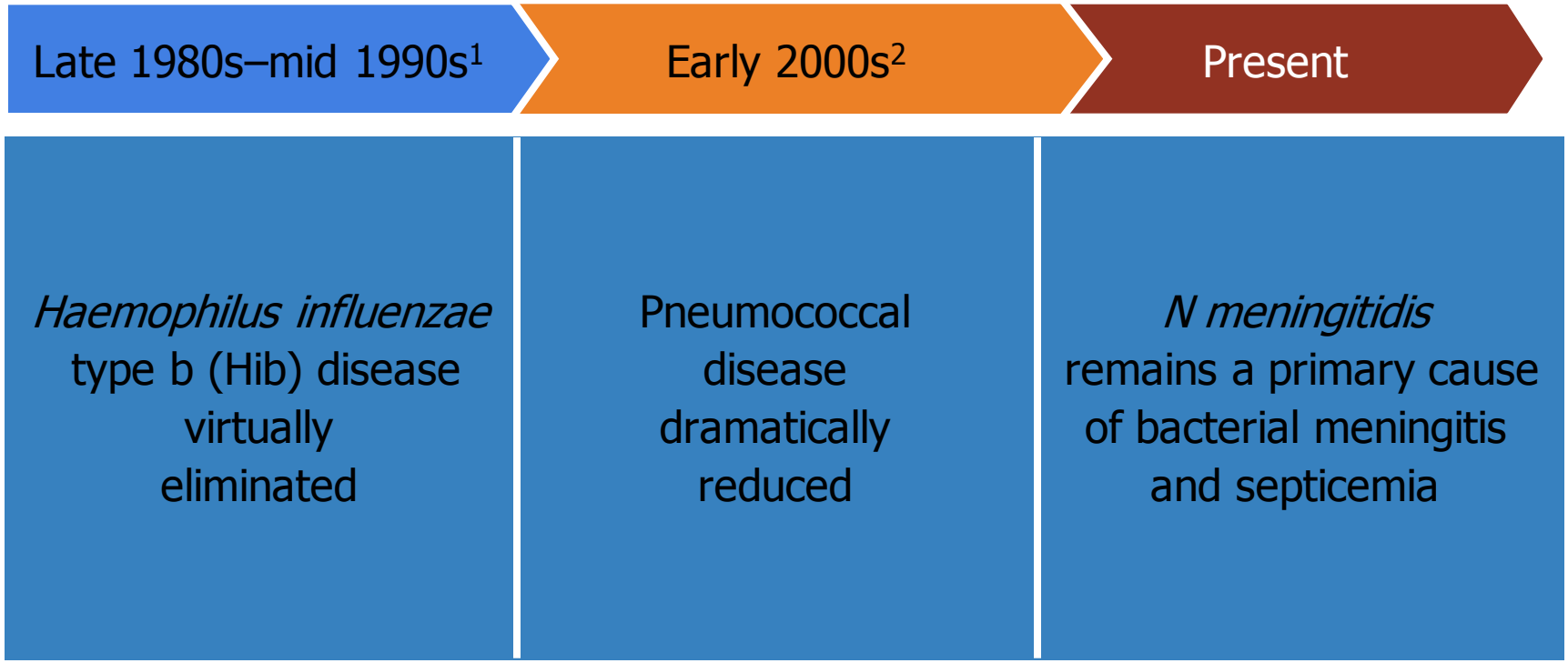


Vaccine blending
Blend together conjugates of MenA, MenC, MenW, MenY and proteins of MenB

Acknowledgements

- Rino Rappuoli
  - …and Mariagrazia Pizza and the large Men and MenB team at the Research Center of Novartis Vaccines
- Richard Moxon
- Craig Venter
- Clinical Development Team at Novartis Vaccines
- The Clinical investigators throughout the world
- The volunteers and the parents of the children participating in the trials

Neisseria meningitidis: Next Target for Vaccine Prevention of Pediatric Bacterial Meningitis and Septicemia



1. Watt JP, et al. *J Pediatr.* 2003;143(6 suppl):S163–S187; 2. Black S, et al. *Pediatr Infect Dis J.* 2007;26:771-777.

TABLE 1. FUNCTION AND CLASSIFICATION OF THE OUTER-MEMBRANE COMPONENTS OF *NEISSERIA MENINGITIDIS*.

COMPONENT	FUNCTION	CLASSIFICATION
Capsule	Protects against host-mediated, complement-dependent bacteriolysis and phagocytosis	13 Serogroups (A, B, C, E-29, H, I, K, L, M, W-135, X, Y, Z)
Outer-membrane proteins		
Porins	Create pores through which small hydrophilic solutes pass, cation-selective or anion-selective	
PorA		Class 1 outer-membrane protein (serosubtyping)
PorB		Class 2 or 3 outer-membrane protein (serotyping)
Opacity-associated proteins		
Opa	Promotes adherence to host cells and leukocytes	Class 5 outer-membrane proteins
Opc	Promotes adherence to host cells	
Reduction-modifiable protein	Unknown	Class 4 outer-membrane protein
Lipooligosaccharide	Has potent endotoxic activity	13 Immunotypes*
Pili	Promote initial adherence to epithelial and endothelial cells and erythrocytes	Class I and II*

*The classification is based on differences in antigenicity.

From Rosenstein et al, N. Engl. J. Med. 344: 1378-1388, 2001

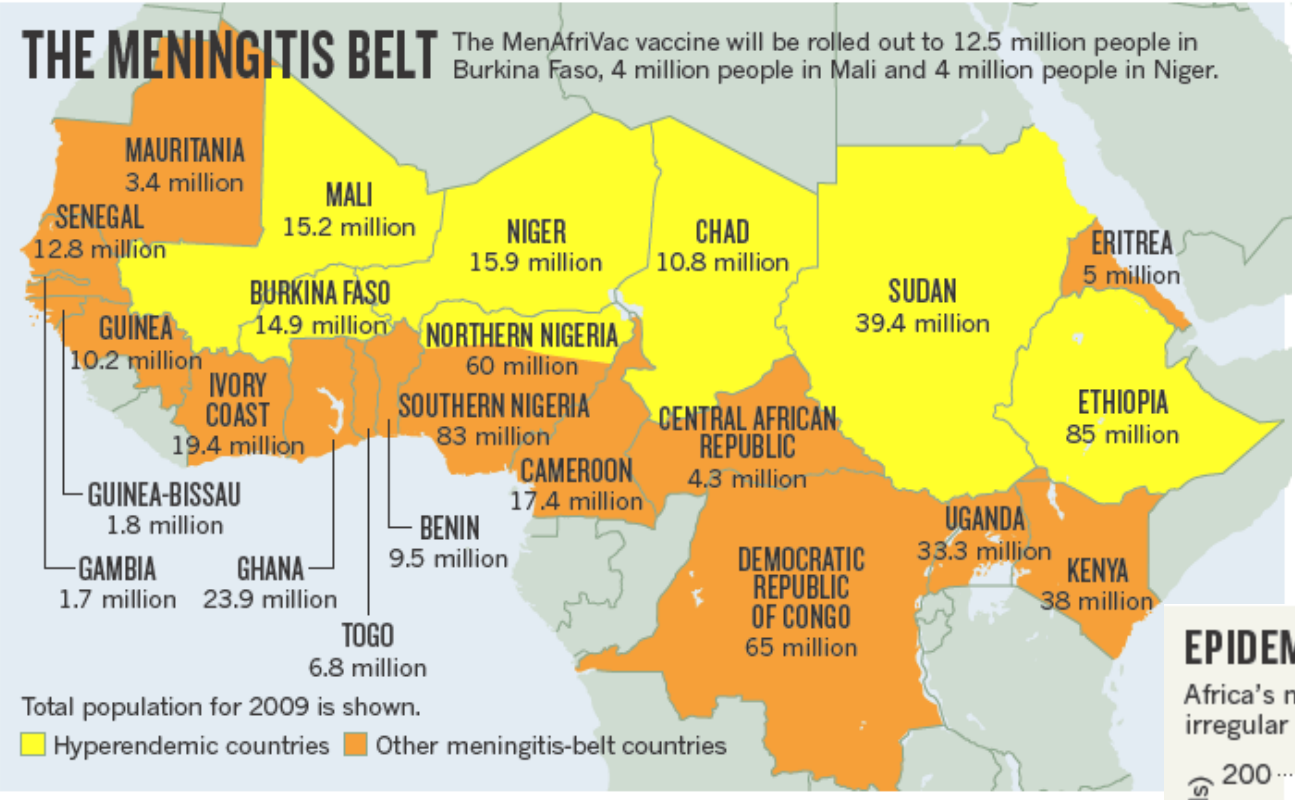
Development of MenA conjugated vaccine

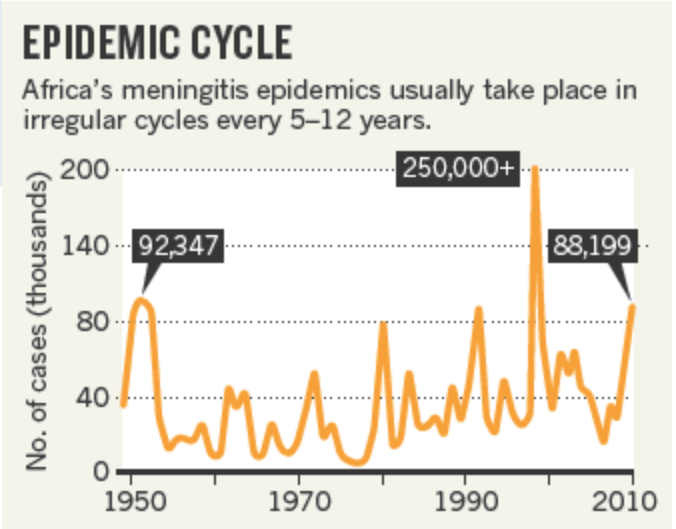
Tetanus toxoid as carrier protein

Immune response and antibody persistence to PsA-TT and PsA + C vaccines

	Vaccine group		
	Ps-ATT conjugate vaccine (24[a])	PsA + C vaccine (25[a])	TT vaccine (25[a])
Proportion of subjects with MenA SBA titer ≥8			
Baseline			
% (95%CI) [*N*]	88 (68–97) [21]	92 (74–99) [23]	88 (69–98) [22]
4 weeks			
% (95%CI) [*N*]	100 (86–100) [24]	100 (86–100) [25]	80 (59–93) [20]
6 months			
% (95%CI) [*N*]	100 (86–100) [24]	100 (86–100) [24]	88 (69–98) [22]
1 year			
% (95%CI) [*N*]	100 (86–100) [24]	100 (86–100) [24]	76 (55–91)[19]
Proportion of subjects with four-fold increase in MenA SBA pre to post-vaccination			
4 weeks			
% (95%CI) [*N*]	83 (63–95) [20]	72 (51–88) [18]	12 (2–31) [3]
6 months			
% (95%CI) [*N*]	83 (63–95) [20]	64 (42–82)[16]	4 (0–20)[1]
1 year			
% (95%CI) [*N*]	83 (63–95) [20]	56 (35–76)[14]	0 (0–14)[0]
MenA SBA GMT			
Baseline			
% (95%CI) [*N*]	228 (84–617)	422 (191–929)	347 (140–861)
4 weeks			
% (95%CI) [*N*]	8192 (5221–12,885)	5257 (2798–9878)	217 (73–644)
6 months			
% (95%CI) [*N*]	6339 (4973–8023)	4096 (2798–5997)	458 (178–1176)
1 year			
% (95%CI) [*N*]	4211** (3517–5078)	2226** (1552–3191)	256 (78–837)

N. Kshirsagar et al. / Vaccine 25S (2007) A101–A107





11 NOVEMBER 2010 | VOL 468 | NATURE | 143

Comparison of immune responses 1 month post-vaccination with either 3 doses of HibMenCY-TT at 2, 4, and 6 months of age or 1 dose of MPSV4 at 3 to 5 years of age

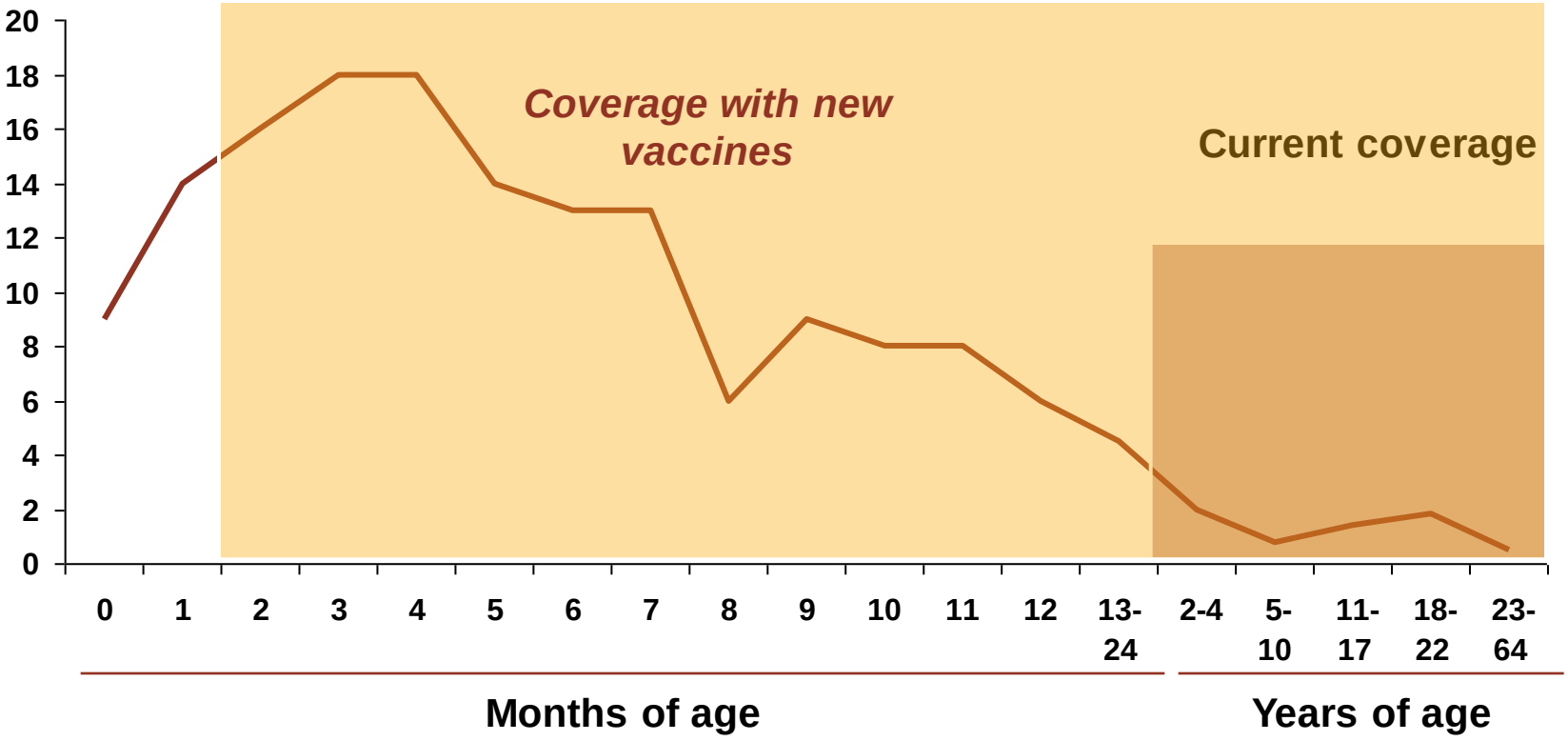
Antibody	Group	N	n	%	95% CI	n	%	95% CI	GMC or GMT*	95% CI
***N. meningitidis* serogroup C**										
hSBA				**≥1:4**			**≥ 1:8**			
	HibMenCY-TT	121	118	97.5*	[92.9; 99.5]	116	95.9*	[90.6; 98.6]	523.0*	[398.8; 686.0]
	MPSV4	53	20	37.7*	[24.8; 52.1]	16	30.2*	[18.3; 44.3]	6.4*	[3.6; 11.5]
rSBA				**≥1:8**			**≥ 1:128**			
	HibMenCY-TT	177	173	97.7*	[94.3; 99.4]	171	96.6*	[92.8; 98.7]	1096.5*	[896.5; 1341.1]
	MPSV4	136	126	92.6*	[86.9; 96.4]	105	77.2*	[69.2; 84]	284.2*	[210.1; 384.3]
	Hib-TT	194	7	3.6	[1.5; 7.3]	2	1.0	[0.1; 3.7]	4.4	[4.1; 4.8]
***N. meningitidis* serogroup Y**										
hSBA				**≥1:4**			**≥ 1:8**			
	HibMenCY-TT	141	129	91.5*	[85.6; 95.5]	126	89.4*	[83.1; 93.9]	139.8*	[102.6; 190.5]
	MPSV4	61	30	49.2*	[36.1; 62.3]	29	47.5*	[34.6; 60.7]	9.1*	[5.8; 14.2]
rSBA				**≥1:8**			**≥ 1:128**			
	HibMenCY-TT	174	171	98.3	[95.0; 99.6]	154	88.5	[82.8; 92.8]	495.3*	[409.2; 599.6]
	MPSV4	139	134	96.4	[91.8; 98.8]	131	94.2	[89.0; 97.5]	685.1*	[540.3; 868.7]
	Hib-TT	186	35	18.8	[13.5; 25.2]	6	3.2	[1.2; 6.9]	6.8	[5.8; 8.1]

N=number of subjects with available results; n=number of subjects with concentration/titer above the specified cut-off; *Statistically significant difference between HibMenCY-TT and MPSV4 groups

Marchant et al, *Pediatr Infect Dis J* **29**: 48-52, 2010

Coverage with tetravalent MenA,C,W,Y conjugated meningococcal vaccines: Today & Tomorrow

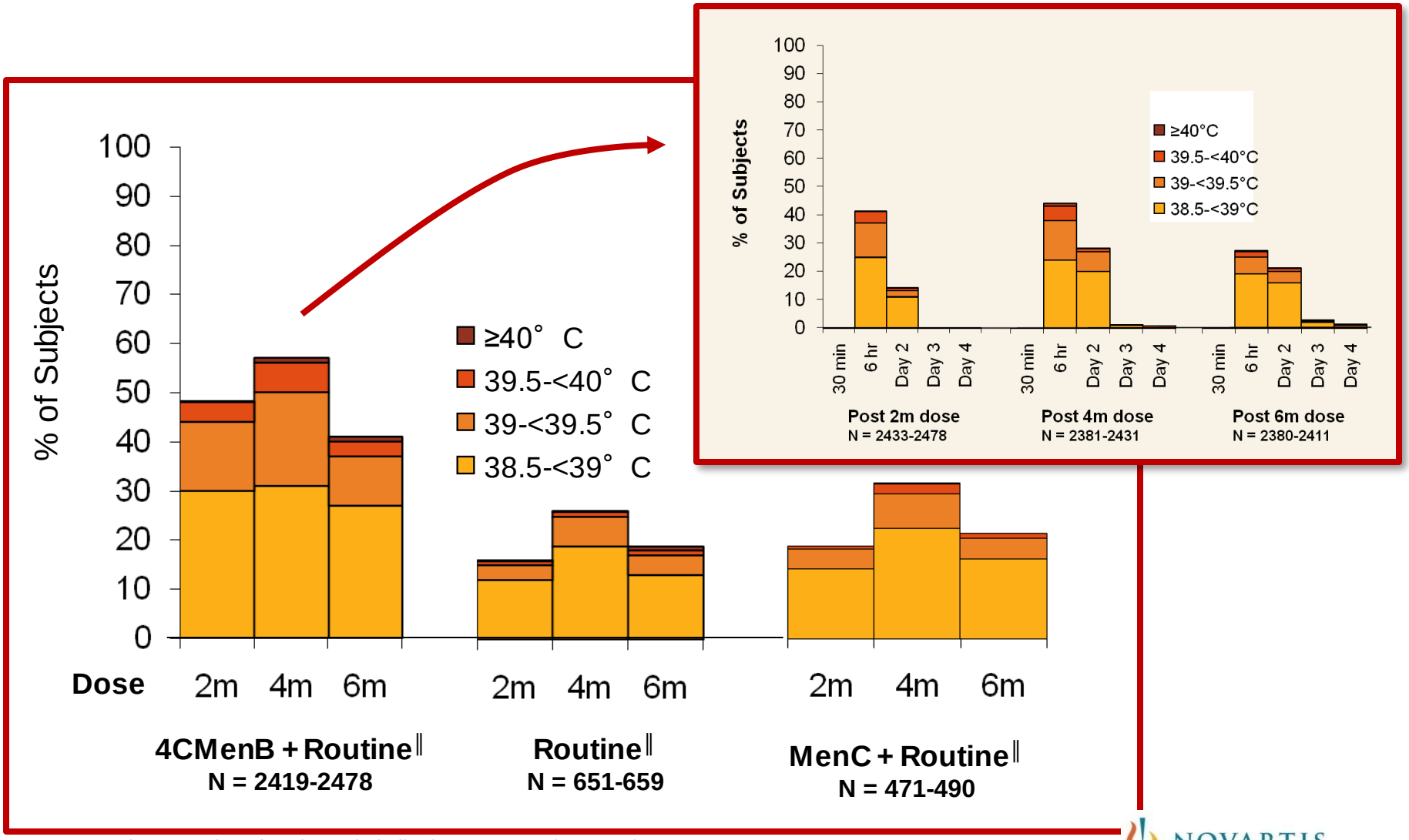
Incidence of culture confirmed meningococcal disease,
Cases per 100 000 population



Source: Shepard et al., Pediatr Infect Dis J. 2003 May;22(5):418-22.; Lingappa et al., Vaccine. 2001 Aug 14;19(31):4566-75
Note: No vaccines currently available for serogroup B disease for any age group

Phase III Study in Infants

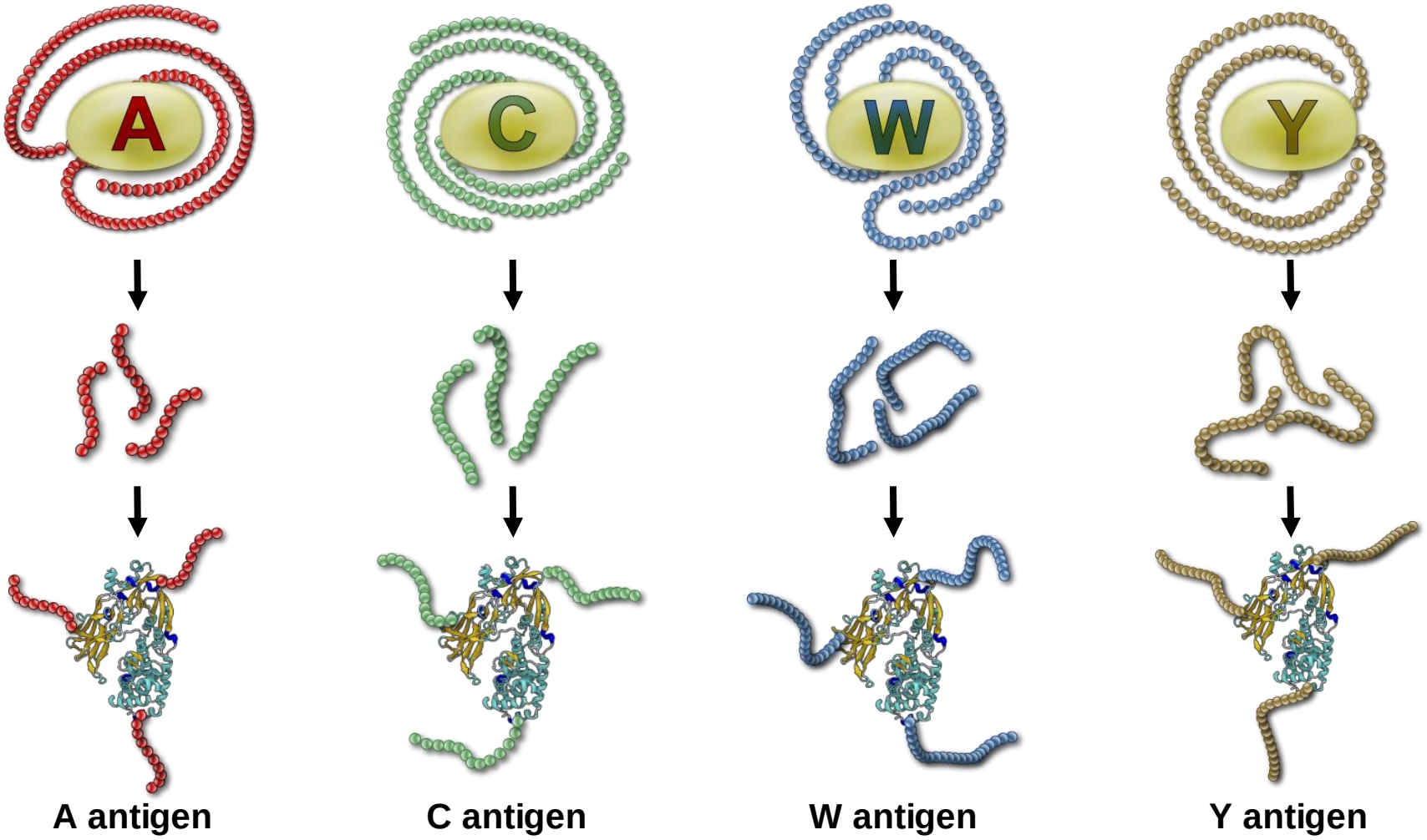
Fever Rates by Dose for 4CMenB + Routine Vaccines vs. Routine Vaccines Alone vs. MenC + Routine Vaccines



‖ Routine vaccines: Infanrix-Hexa™; Prevenar™.

NOVARTIS

Meningococcal glycoconjugates



Current Conjugated Meningococcal Vaccines

- Menomune®, an ACWY polysaccharide vaccine (MPSV4) licensed in 1981[1]
- Monovalent MenC, various companies, licensed in various countries
- Menactra®, an ACWY conjugate vaccine with diphtheria toxoid as the protein carrier, licensed in the United States in 2005[4]
- Menveo®, an ACWY conjugate vaccine with CRM-197 as the protein carrier, licensed in Europe and in the United States in 2010
- Other approaches
  - Monovalent MenA (MenAfriVac®)
  - Bivalent MenC-MenY (± Hib)

1. Harrison LH. *Clin Infect Dis*. 2000;30:648-651; 2. CDC. *MMWR Recomm Rep*. 2000;49(RR-7):11-20; 3. Harrison LH. *Clin Microbiol Rev*. 2006;19:142-164; 4. Bilukha OO, et al. *MMWR Recomm Rep*. 2005;54:1-21; 5. CDC. *MMWR Morb Mortal Wkly Rep*. 2007;56:794-795.