

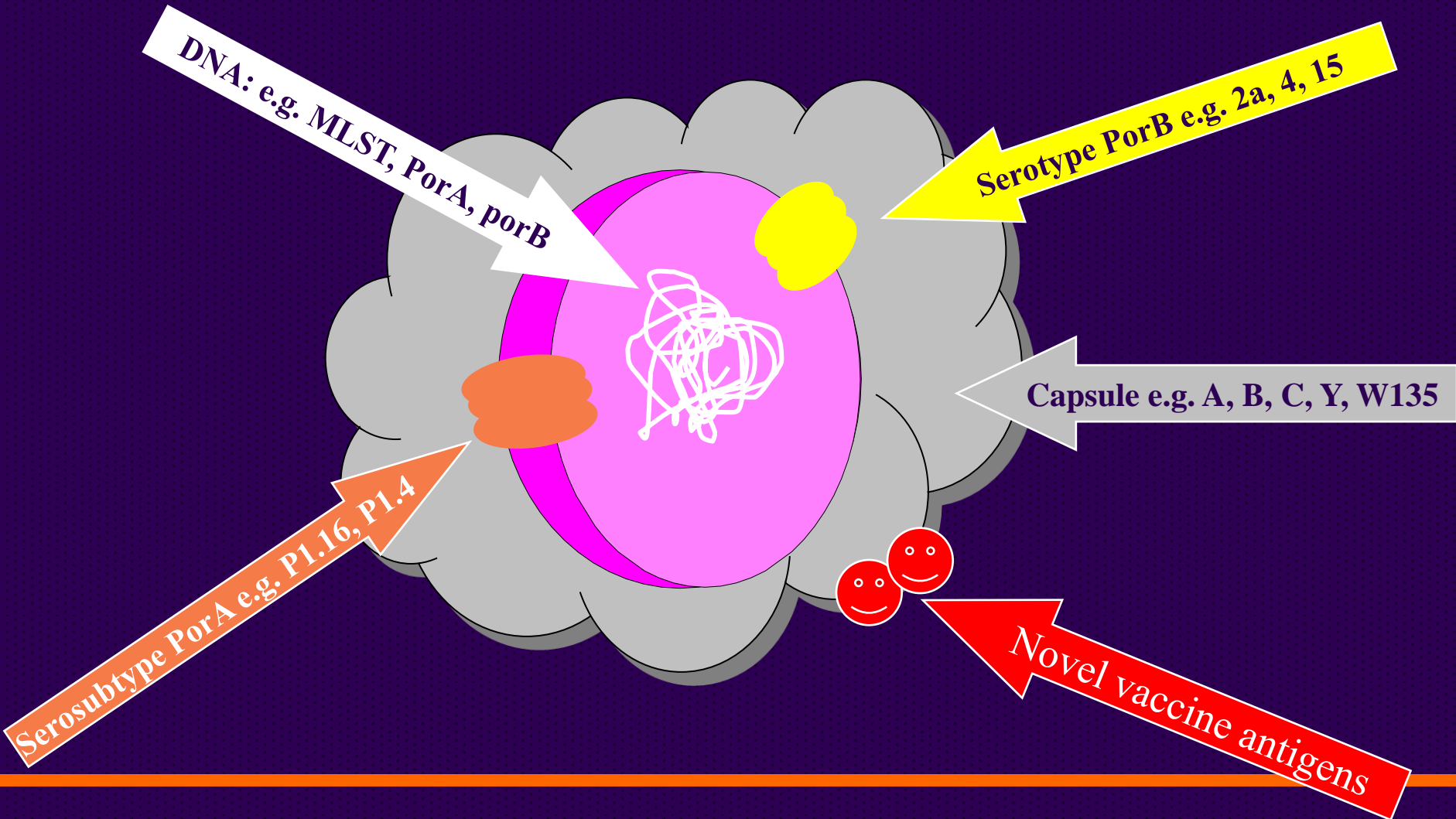
Meningococcal disease and vaccination in the UK

Ray Borrow

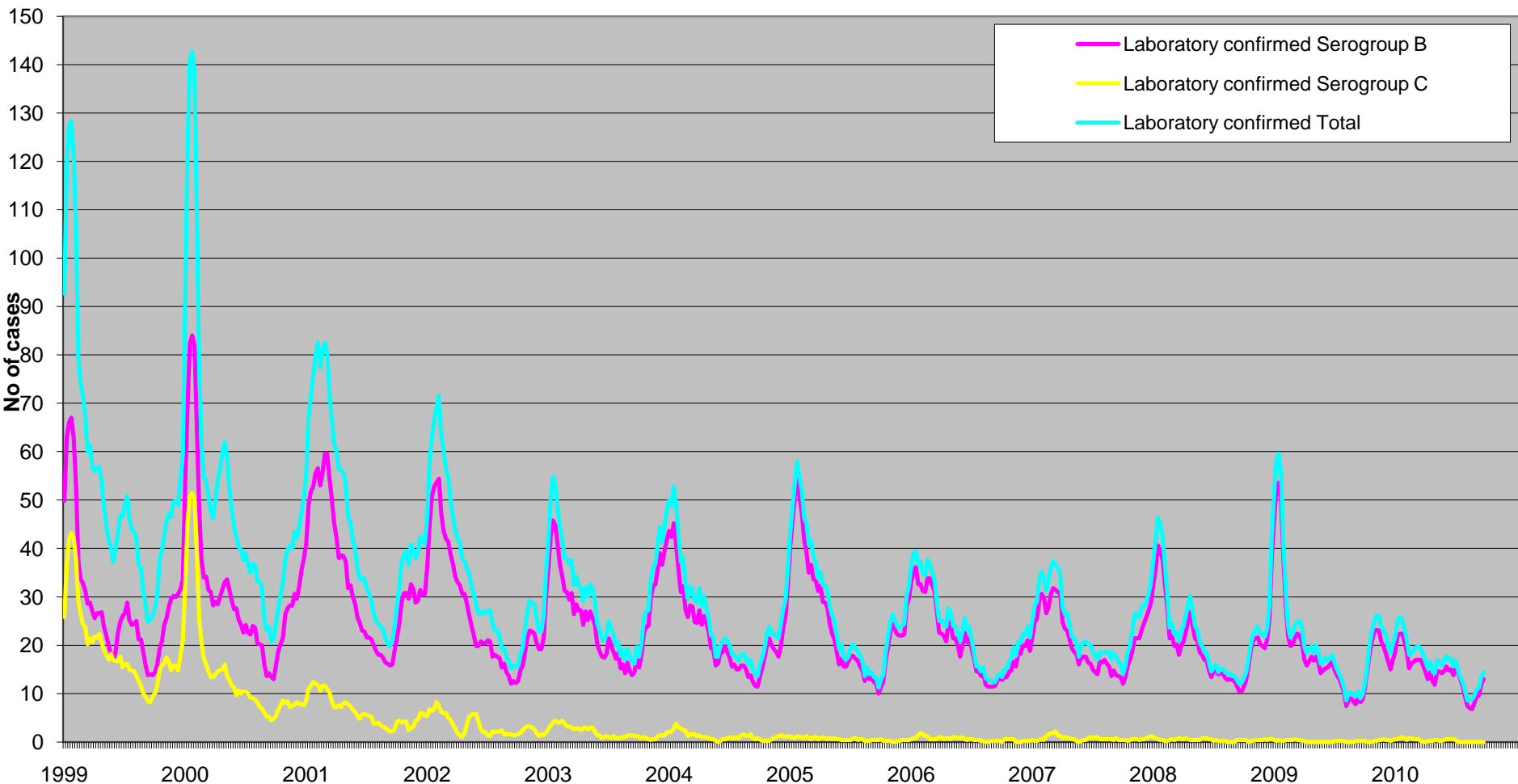
**Professor of Vaccine Preventable Diseases,
Vaccine Evaluation Unit, Health Protection Agency,
Manchester Royal Infirmary, Manchester, U.K.**

ray.borrow@hpa.org.uk

Classification



Laboratory confirmed cases of meningococcal disease England & Wales Five Weekly Moving Averages: 1997 to 2010 (up to Oct 5th 2010)



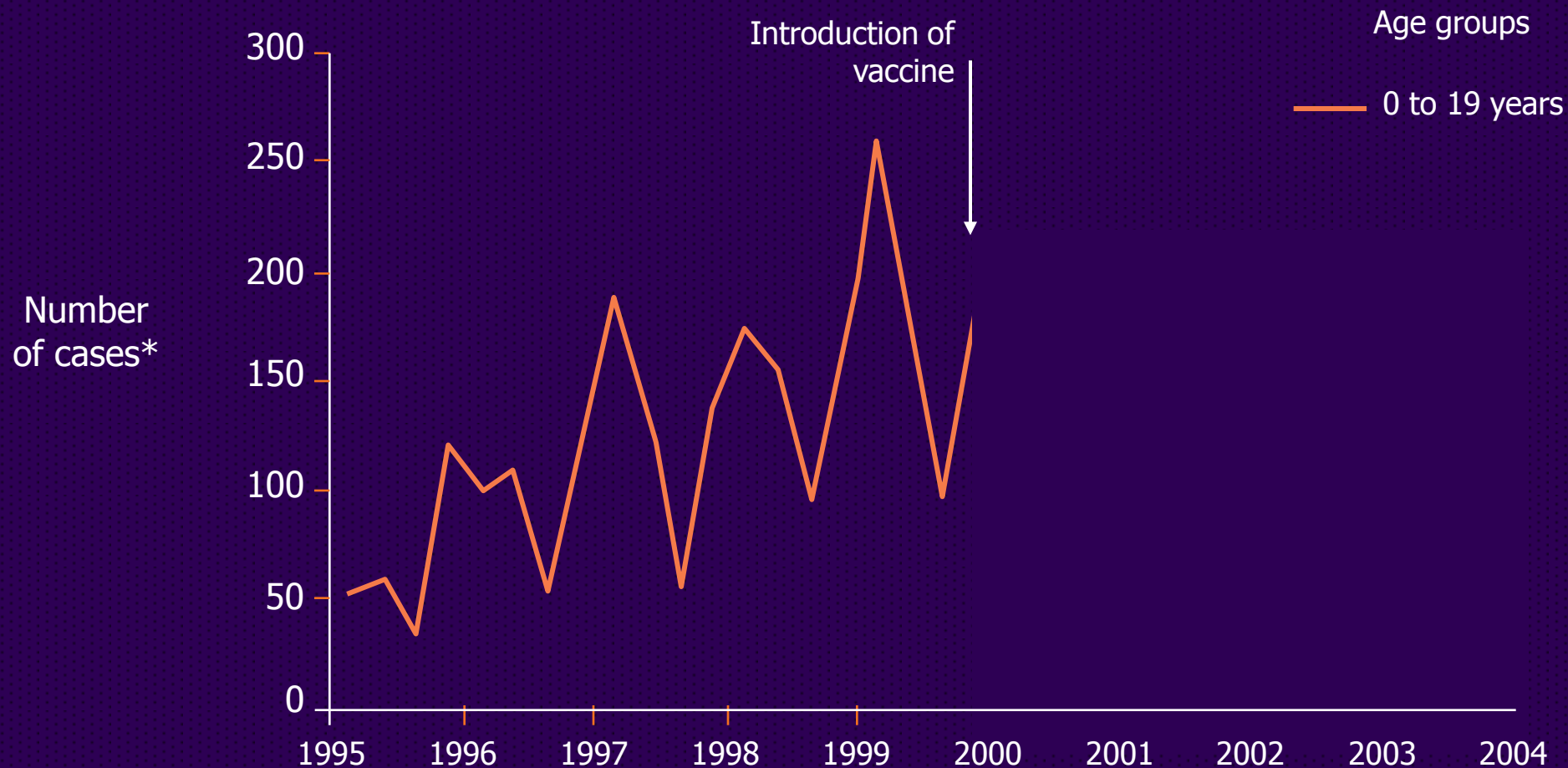
Introduction - MenC



- In 1999, the UK introduced meningococcal serogroup C conjugate (MCC) vaccines into the primary immunisation schedule at 2, 3 and 4 months of age.
- A catch up to 18 years of age was also performed.
- Three MCC vaccines were licensed.

Vaccine	Manufacturer	Carrier protein
NeisVac-C	Baxter	Tetanus toxoid
Meningitec	Wyeth (Pfizer)	CRM ₁₉₇
Menjugate	Novartis	CRM ₁₉₇

Confirmed cases of MenC disease pre- and post-introduction of MCC vaccines



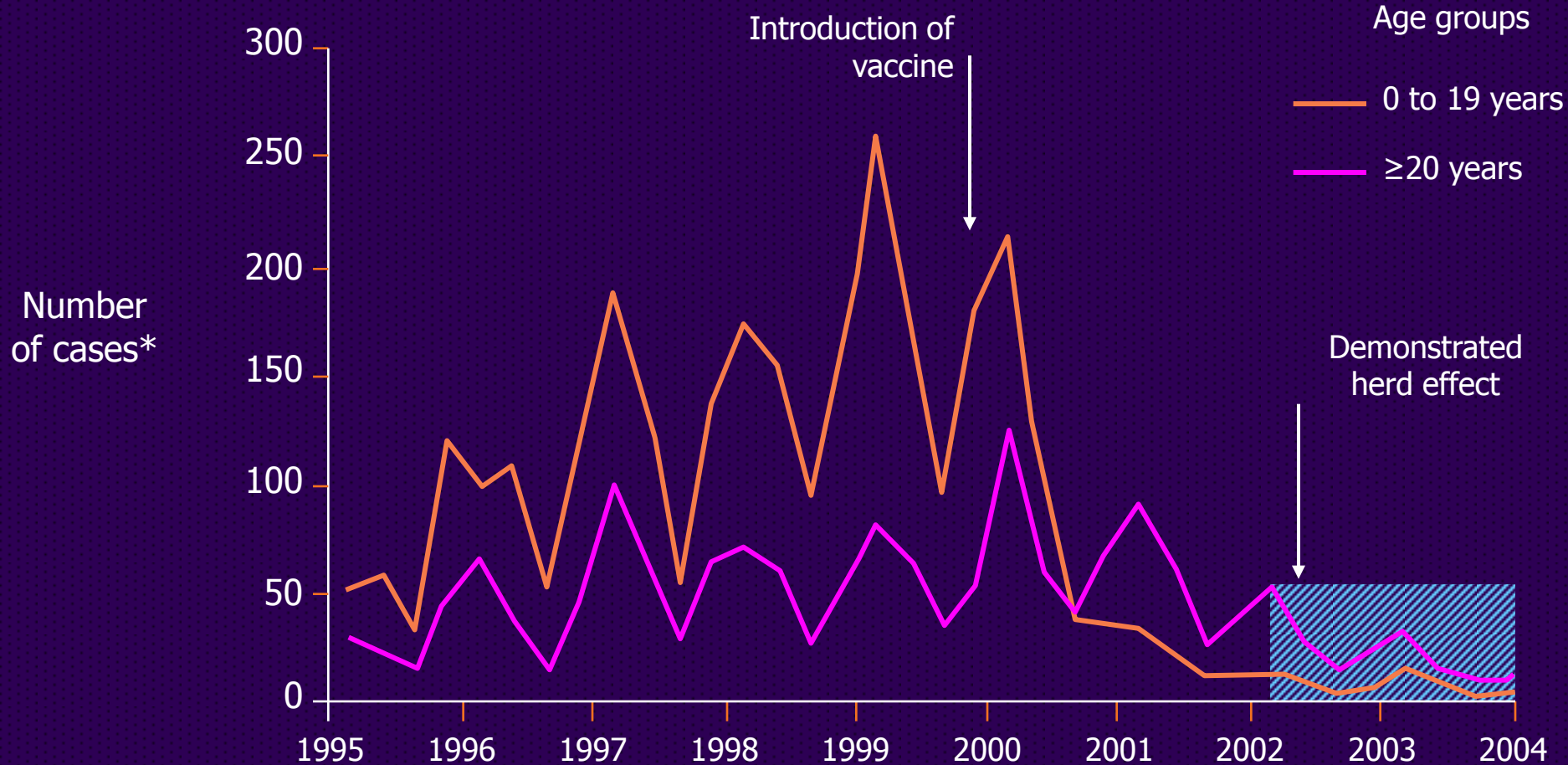
*Confirmed cases.

Trotter *et al.*, *Lancet*. 2004

Reduction in MenC carriage following introduction of MCC vaccines



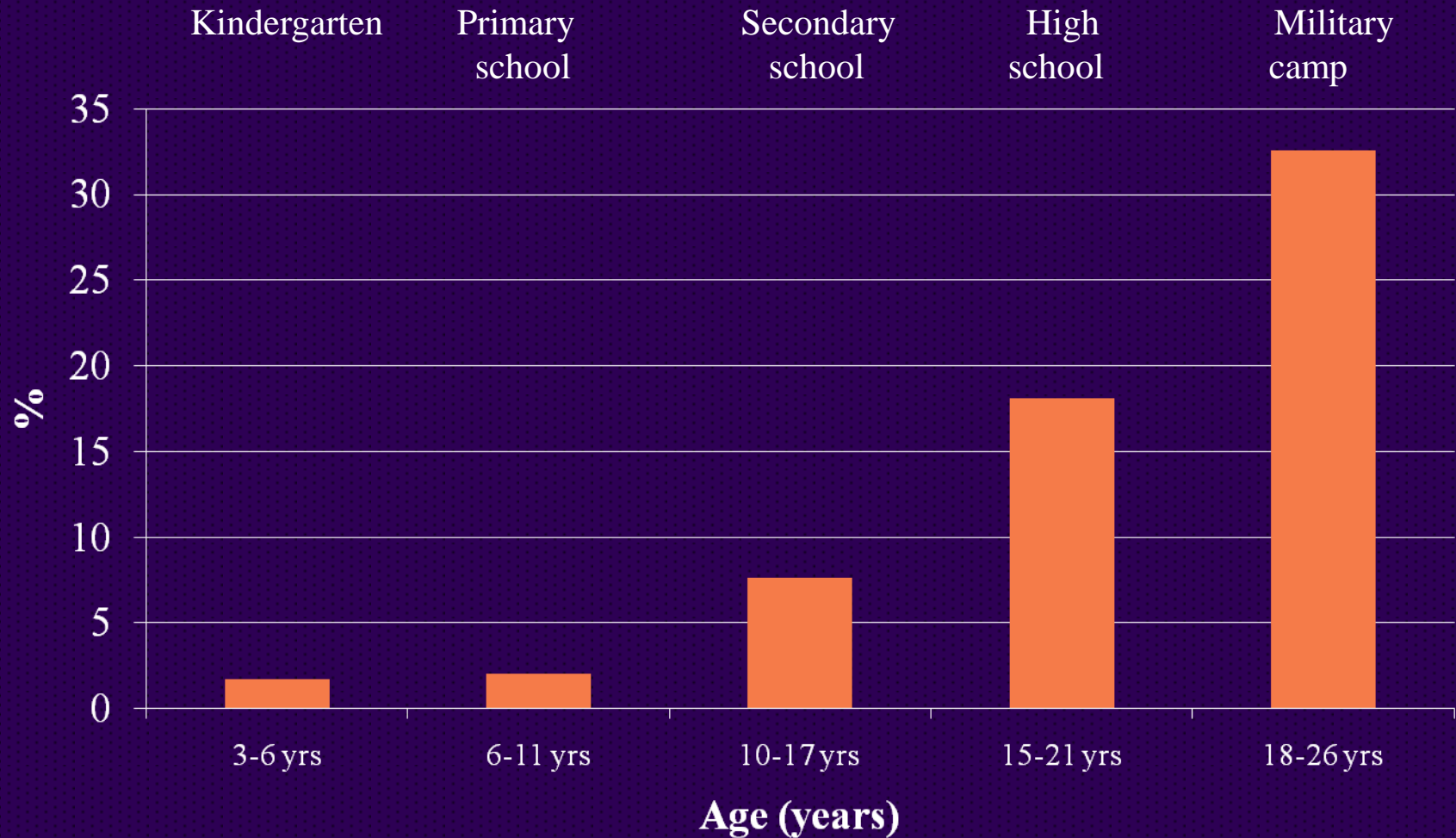
Confirmed cases of MenC disease pre- and post-introduction of MCC vaccines



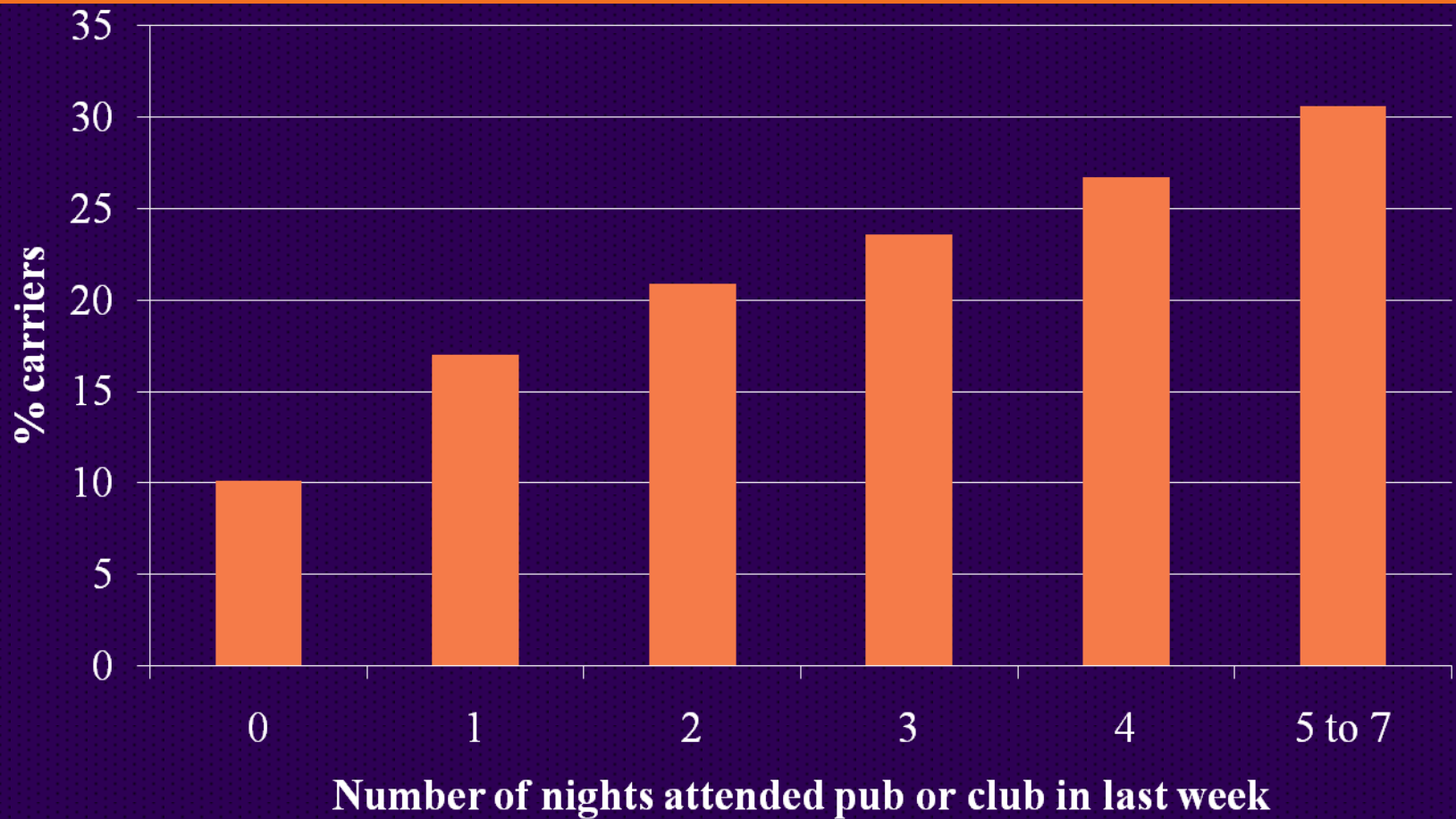
*Confirmed cases.

Trotter *et al.*, *Lancet*. 2004

Carriage rates of *N. meningitidis* at different ages and different institutions, Bavaria, Germany, 1999 to 2000



Risk factors for meningococcal carriage in British teenagers: Number of nights attended pub or club in last week



Risk factors for carriage



Smoking



Bar patronage



Passive smoking



Discotheque visits



Kissing



Over crowding



Military recruits

Enhanced surveillance post-MCC vaccine introduction



- Despite excellent efficacy being reported up to 1 year following infant vaccination, efficacy > 1 year was significantly lower (Trotter *et al.*, 2004; Campbell *et al.*, 2010).
- Studies had shown a rapid waning of antibody levels following infant vaccination but had confirmed the induction of immunological memory (Borrow *et al.*, 2002, Richmond *et al.*, 1999).
- However, comparison of convalescent sera from vaccine failures and controls demonstrated the vaccine failures were primed for immunological memory.
- Immunological memory alone is not sufficient to protect against meningococcal disease.

Summary of MenC



- Maintenance of protective levels of circulatory anti-MenC antibody are crucial for protection from invasive disease.

The Solution?

- Introduce a booster dose of MenC vaccine?
- Could the primary series of MenC be reduced?

We therefore, undertook a study to answer these questions.

Change of infant schedule?



CLINICAL AND VACCINE IMMUNOLOGY, Feb. 2009, p. 194–199
1556-6811/09/\$08.00+0 doi:10.1128/CVI.00420-08
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Vol. 16, No. 2

Immunogenicity of a Reduced Schedule of Meningococcal Group C Conjugate Vaccine Given Concomitantly with the Prevenar and Pediacel Vaccines in Healthy Infants in the United Kingdom[∇]

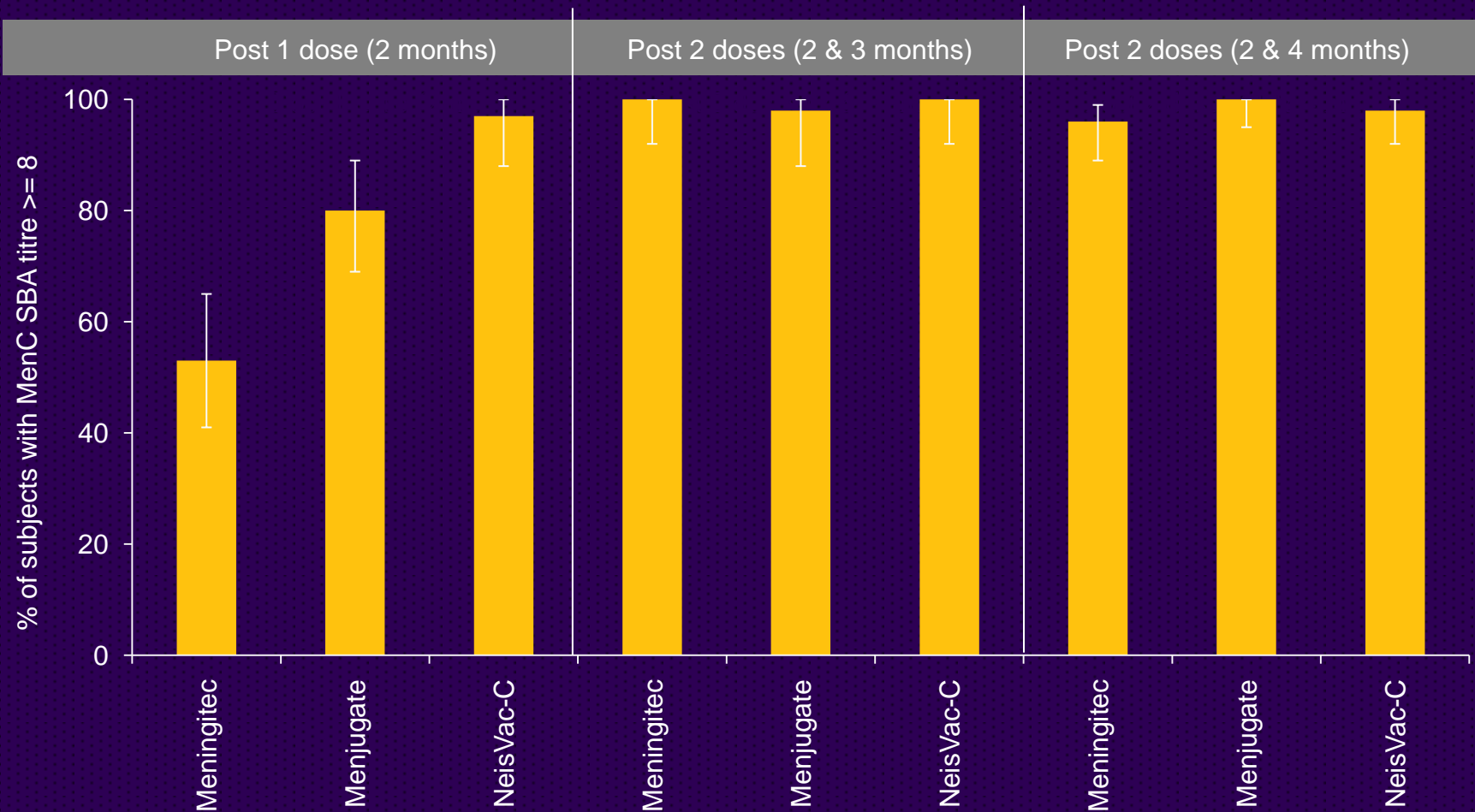
Jo Southern,¹ Ray Borrow,^{2*} Nick Andrews,³ Rhonwen Morris,⁴ Pauline Waight,¹ Michael Hudson,⁵ Paul Balmer,² Helen Findlow,² Jamie Findlow,² and Elizabeth Miller¹

Methods

- Comparison of Meningitec, Menjugate and NeisVac-C

Number of doses	Schedule
2	2 & 3 months
2	2 & 4 months

Proportions of subjects with SBA titres ≥ 8 by primary vaccination schedule and MCC vaccine



UK infant immunisation schedule; 2006 onwards

2 months	DTaP/IPV/Hib + pneumococcal
3 months	DTaP/IPV/Hib + MenC
4 months	DTaP/IPV/Hib + MenC + pneumococcal (MenC can be given at 5 months)
12 months	Hib/ Men C
13 months	MMR + pneumococcal

Antibody persistence following change of infant schedule



CLINICAL AND VACCINE IMMUNOLOGY, Jan. 2010, p. 154–159
1556-6811/10/\$12.00 doi:10.1128/CVI.00384-09
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Vol. 17, No. 1

Kinetics of Antibody Persistence following Administration of a Combination Meningococcal Serogroup C and *Haemophilus influenzae* Type b Conjugate Vaccine in Healthy Infants in the United Kingdom Primed with a Monovalent Meningococcal Serogroup C Vaccine[∇]

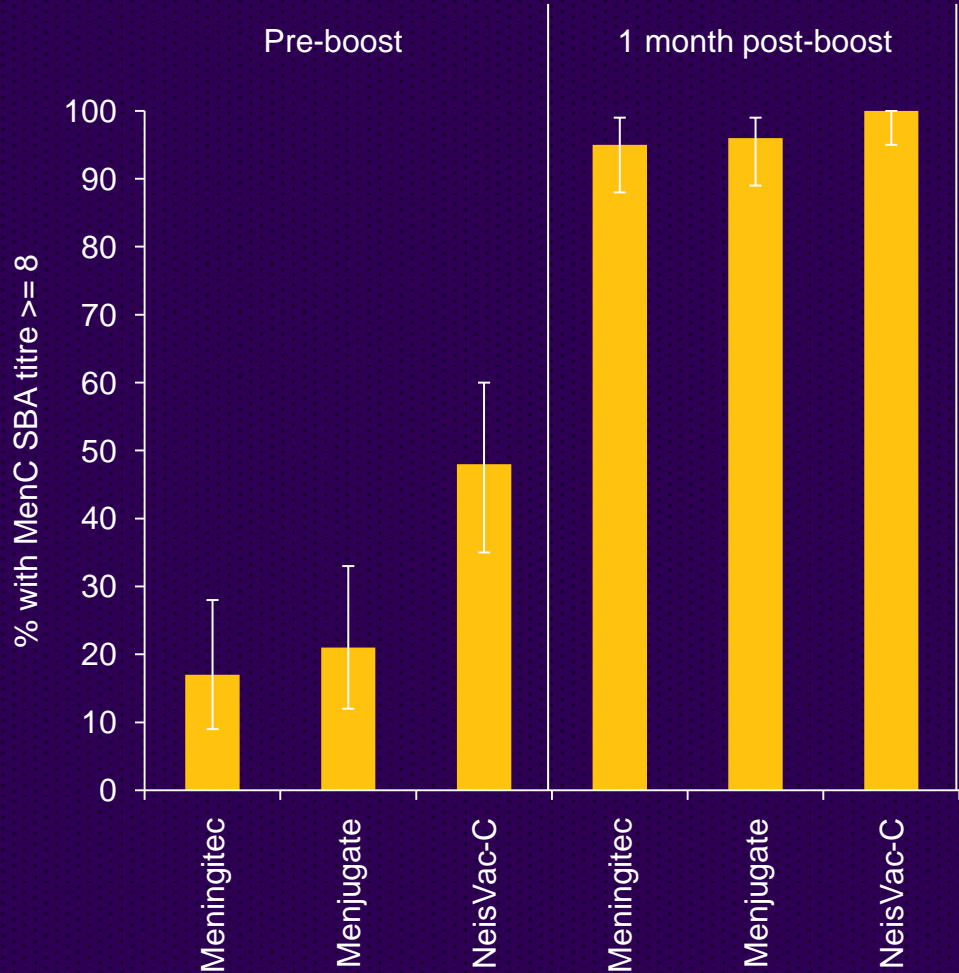
Ray Borrow,^{1*} Nick Andrews,² Helen Findlow,¹ Pauline Waight,³ Joanna Southern,³
Annette Crowley-Luke,⁴ Lorraine Stapley,⁴ Anna England,⁴ Jamie Findlow,¹
and Elizabeth Miller³

Methods

Primary series	Booster
2 x Meningitec	Menitorix
2 x Menjugate	Menitorix
2 x NeisVac-C	Menitorix

- Antibody persistence determined at 1 month, 2 months, 1 year and 2 years post-booster.

Proportions of subjects with SBA titre ≥ 8 , by primary MCC vaccine and time since Menitorix booster



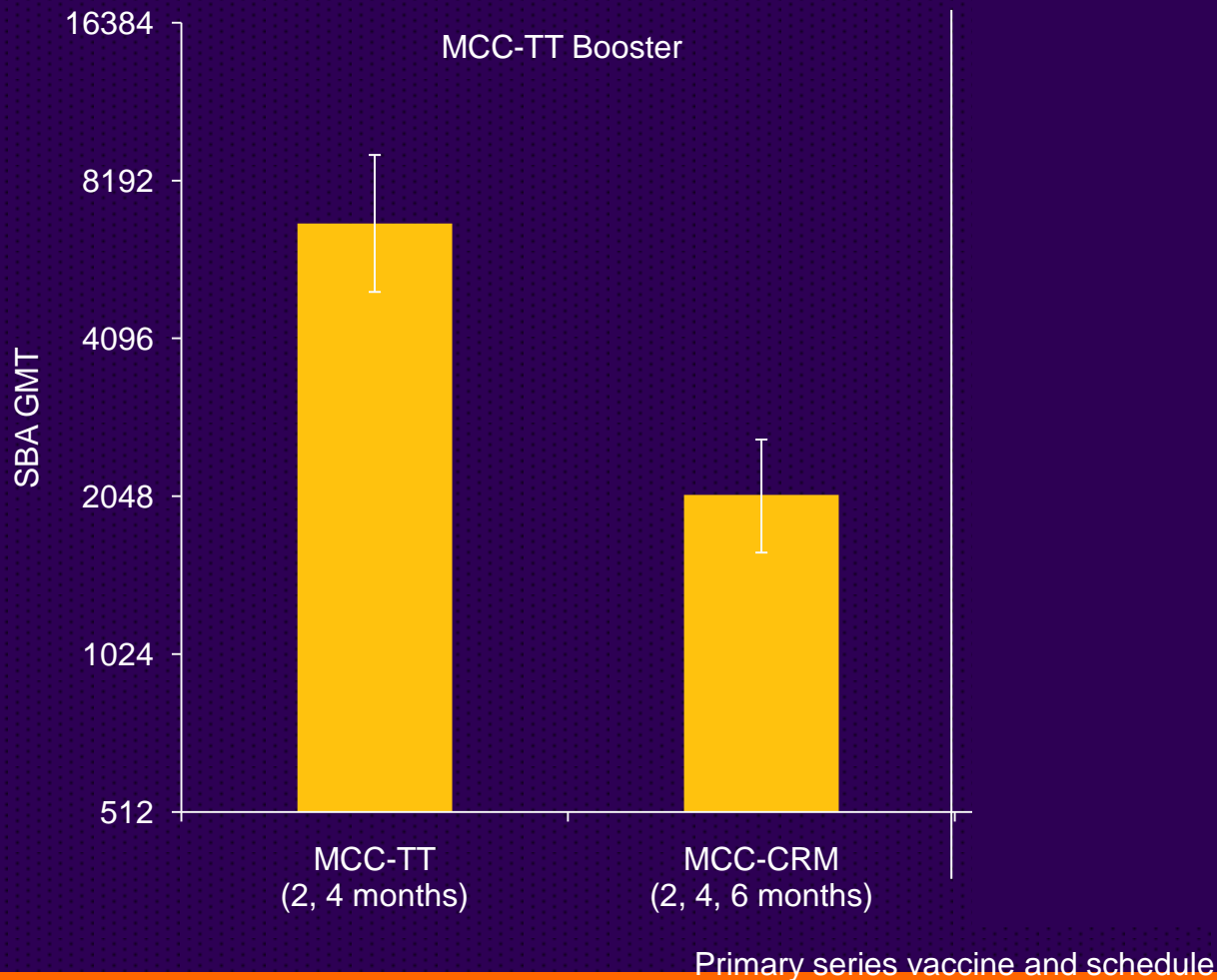
Why is there a difference in response and antibody persistence following a booster dose?



- Priming vaccine?
- Booster vaccine?
- Carrier protein(s)?
- Schedule/number of doses?

Data are beginning to emerge.....

SBA GMTs one month following MCC-TT or MCC-CRM boosting by primary vaccination schedule and MCC vaccine



Susceptible population?

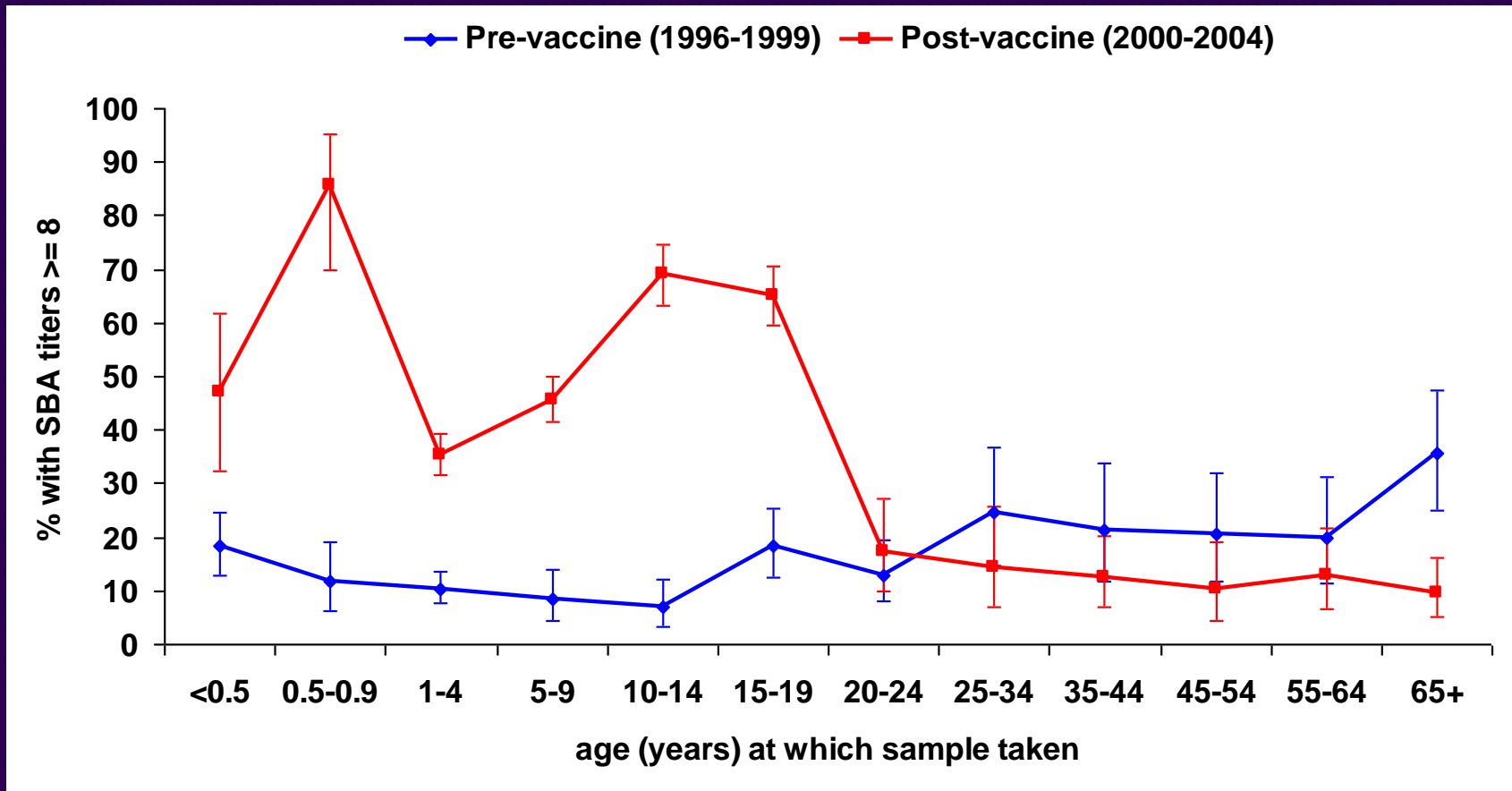


- The proportion of UK infants/toddlers with protective SBA titres declines rapidly following both primary and booster vaccination.
- Therefore, these infants/toddlers can be considered to be susceptible to MenC disease.
- Similar trends following infant schedules have been reported in Greece, the Netherlands and Spain.

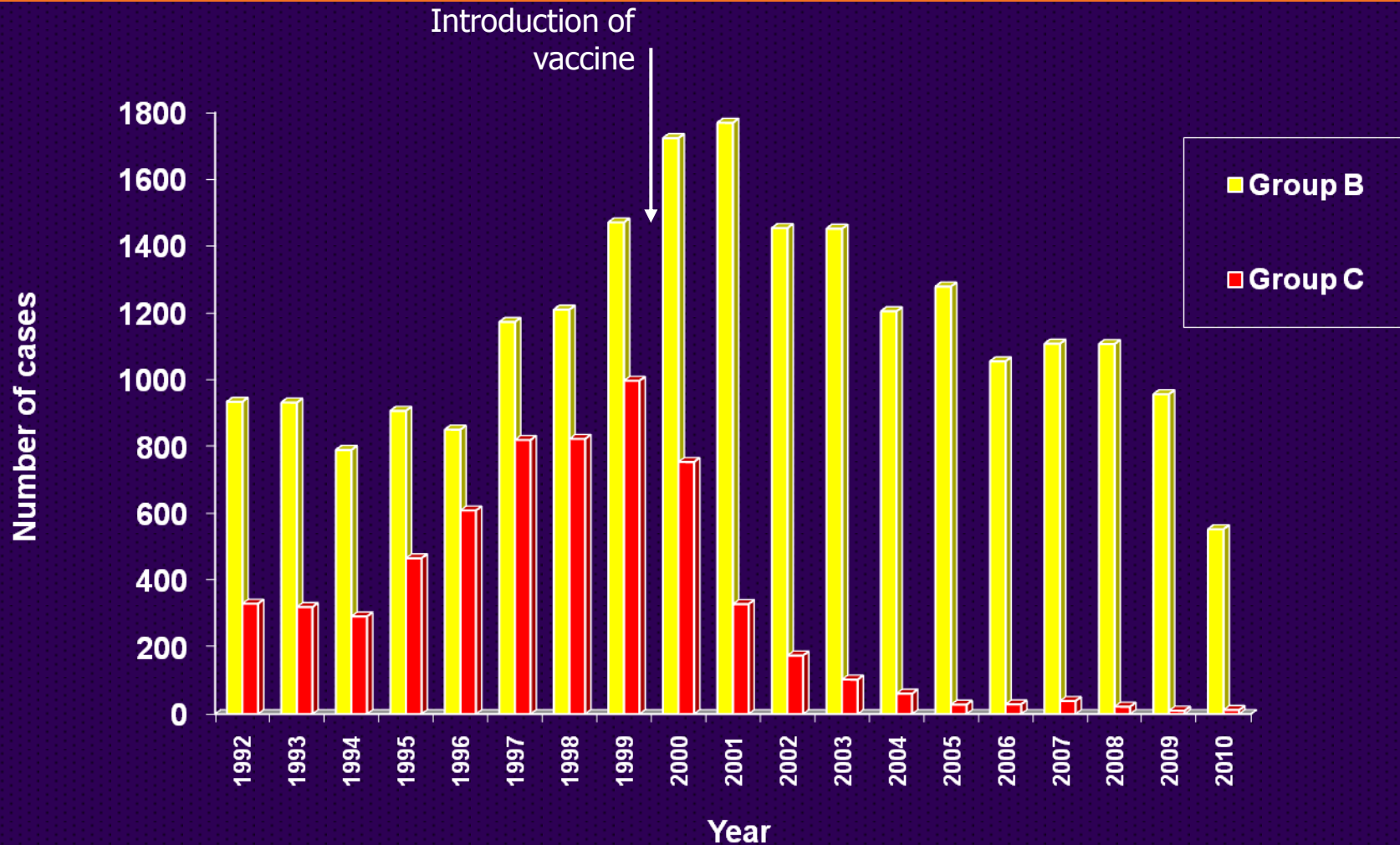
Therefore, is this growing population of susceptible individuals in the UK matched by an increase in MenC disease?

Prevalence of SBA ≥ 8 in the post-vaccine era

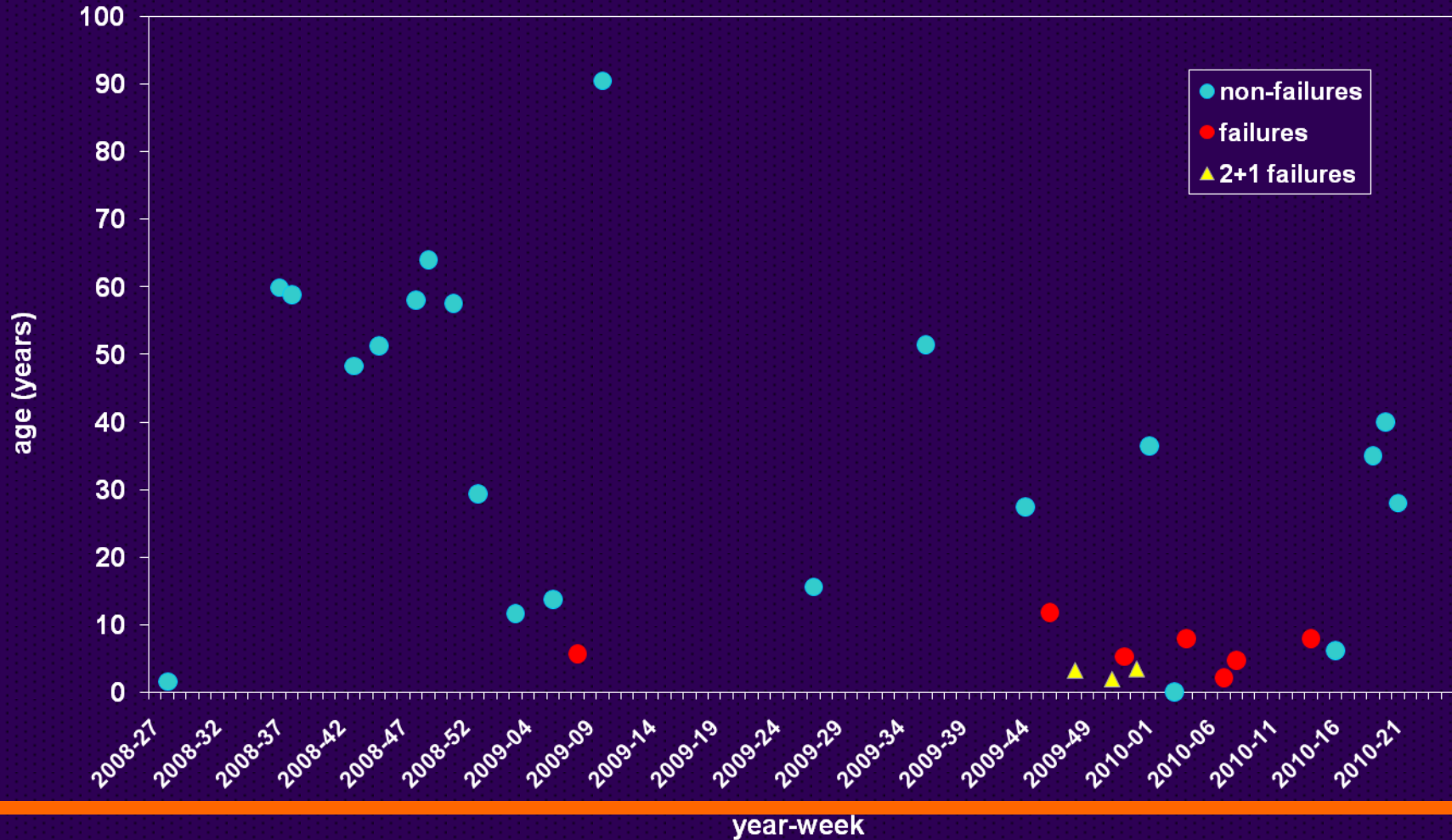
Cross sectional analysis by age at sampling



Annual cases of laboratory confirmed meningococcal disease England & Wales 1992 to 2010 (up to 5th October 2010)



Age and week of onset for 2008/9 and 2009/10 serogroup C cases

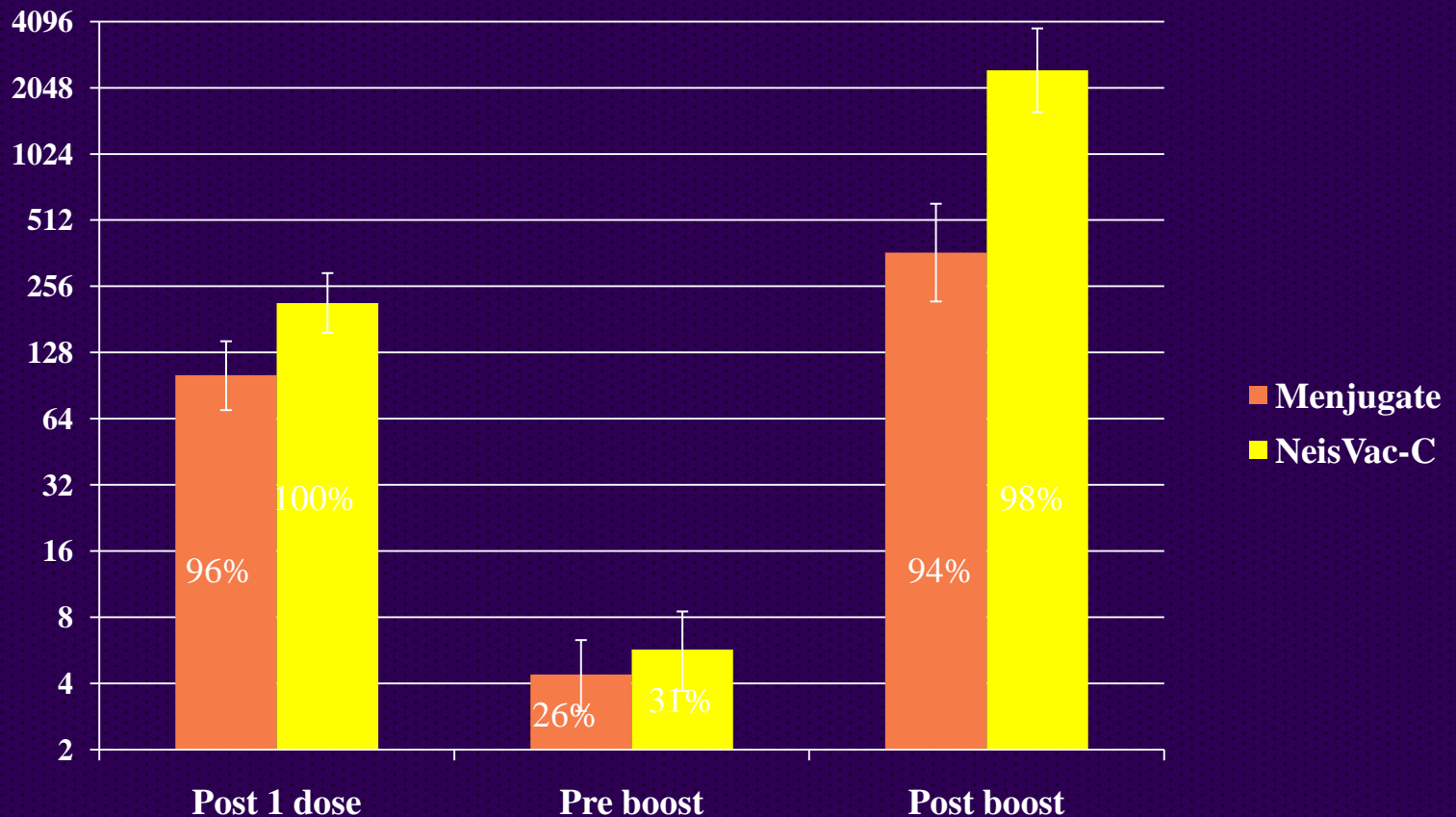


Study of a single dose of NeisVac-C and Menjugate in a single dose schedule.

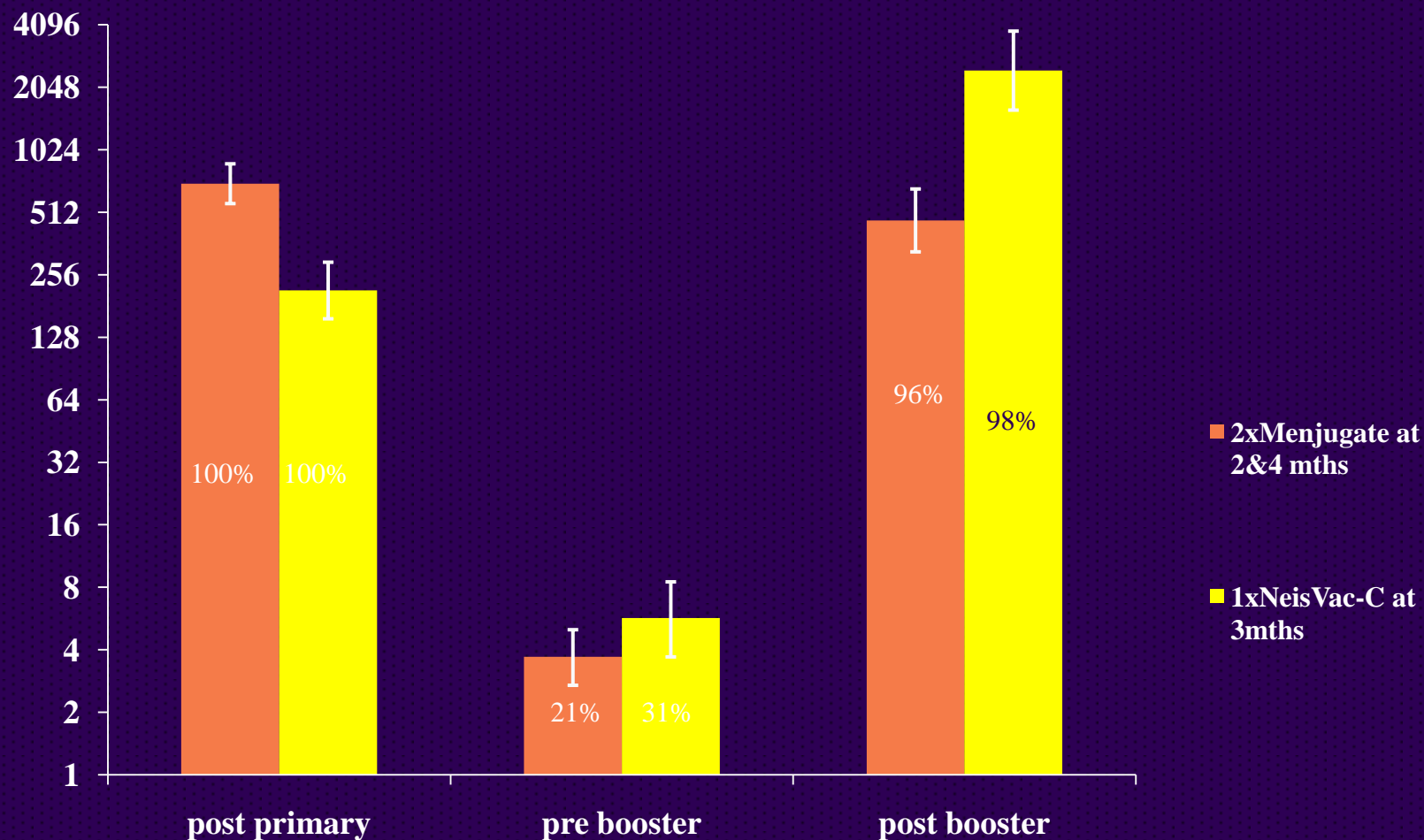


Group	2 months	3 months	4 months		5 months	12 months		13 months
	Vaccines	Vaccines	Vaccines	Bleed	Bleed	Vaccines	Bleed	Bleed
1	Pediacel Prevenar	Pediacel <u>Menjugate</u>	Pediacel Prevenar	✓	✓	Menitorix Prevenar MMR	✓	✓
2	Pediacel Prevenar	Pediacel <u>NeisVac-C</u>	Pediacel Prevenar	✓	✓	Menitorix Prevenar MMR	✓	✓

Meningococcal serogroup C SBA GMTs following a single dose of Menjugate or NeisVac-C at 3 months of age and pre and post Menitorix booster at 12 months of age



Meningococcal serogroup C SBA GMTs following either 2 primary doses of Menjugate or 1 primary dose of NeisVac-C

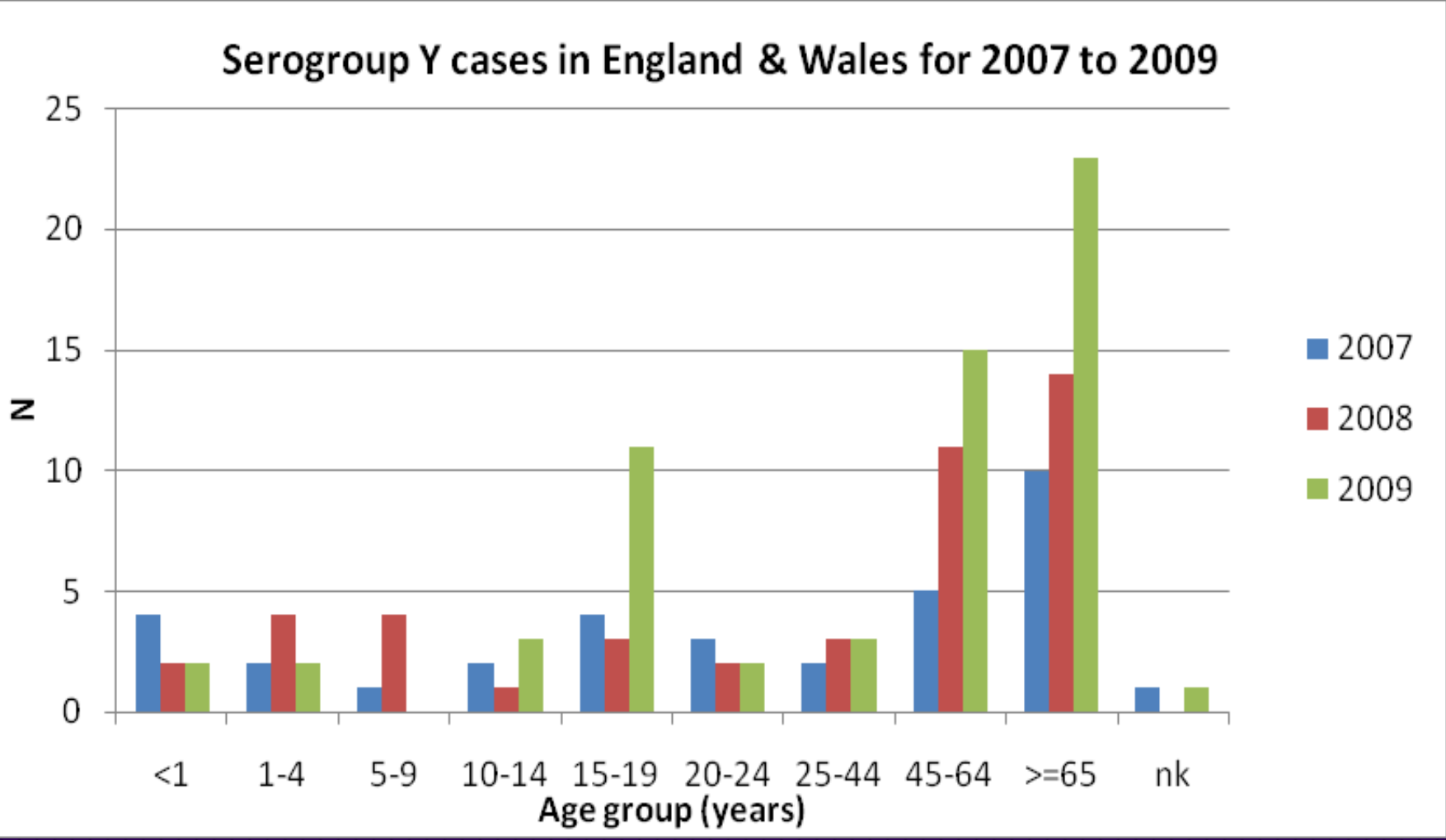


New schedules?

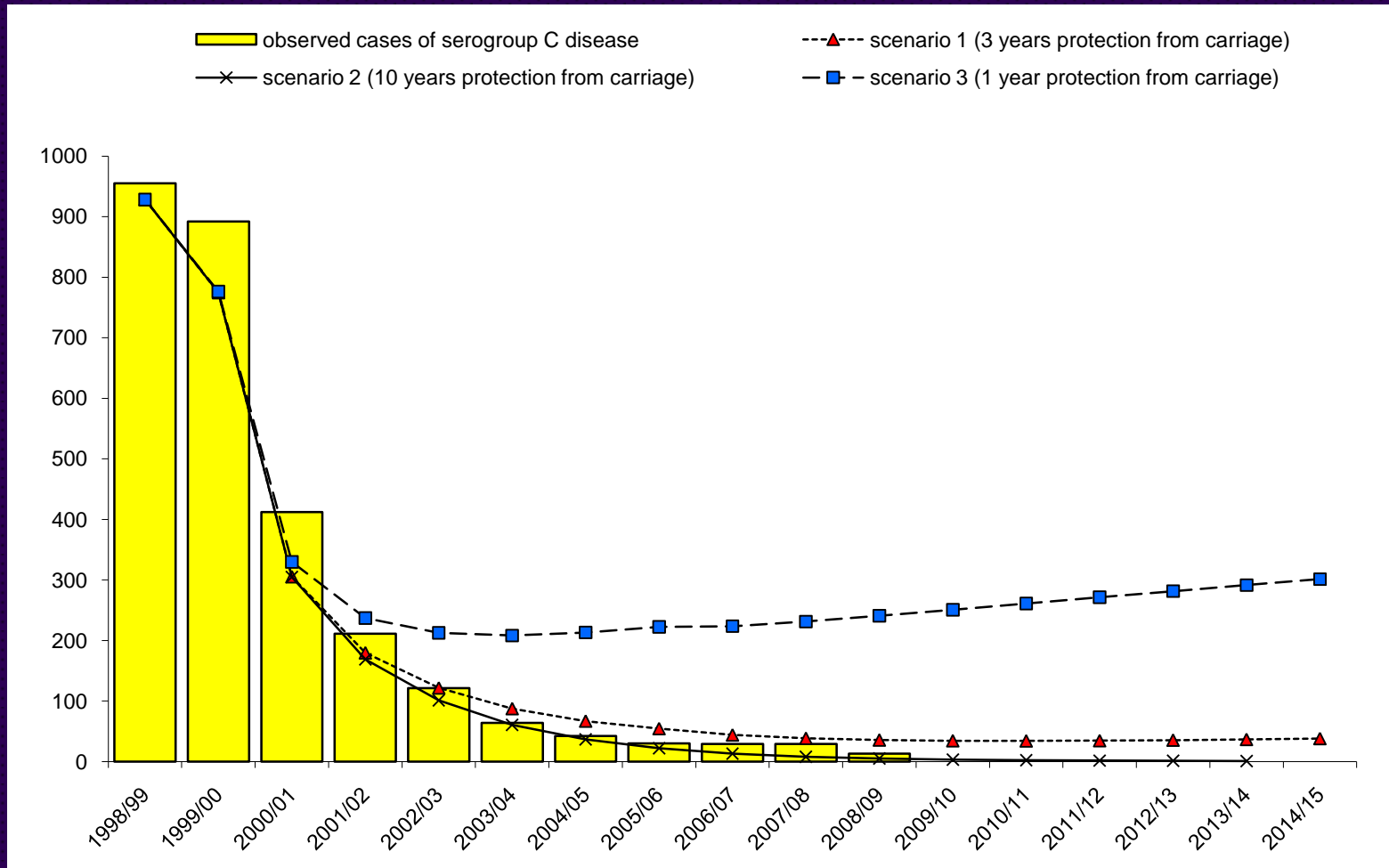


- A single dose of MCC-TT given at 3 months of age followed by a single dose of Menitorix at 12 months of age gives a superior booster response than 2 doses of MCC-CRM₁₉₇
- Move 4 month dose to preschool or adolescence?
- Use of a quadrivalent conjugate vaccine in adolescent years will act as a booster for serogroup C and a priming dose for A, Y and W135.
- Additional benefit of the A, Y and W135 components of a quadrivalent conjugate vaccine will vary upon epidemiology.

Increase in serogroup Y disease in England & Wales, 2007 to 2009



Model predictions and observed cases of laboratory confirmed MenC disease in England & Wales



Summary so far....



- **A single primary dose of NeisVac-C is sufficient to prime in infancy.**
- **Antibody levels wane rapidly both post primary and booster at 12 months of age.**
- **Antibody levels at a population level following the catch-up campaign are waning.**
- **Future booster doses in adolescent years will be required.**
- **Given current UK epidemiology, a quadrivalent conjugate booster would be optimal.**

Meningococcal conjugate vaccines



Name	Serogroups	Carrier protein	Manufacturer	Licensed
Meningitec	C	CRM ₁₉₇	Pfizer	Yes, ≥ 2 months
Menjugate	C	CRM ₁₉₇	Novartis	Yes, ≥ 2 months
NeisVac-C	C	TT	Baxter	Yes, ≥ 2 months
Menitorix	C/Hib	TT	GSK	Yes, ≥ 2 months
Menactra	A,C,Y,W135	Diphtheria	Sanofi Pasteur	Yes, US & Canada, 2 to 55 years at risk, 11 years and over
Menveo	A,C,Y,W135	CRM ₁₉₇	Novartis	Yes, Europe, US, Canada, from 11 years.
Nimenrix	A,C,Y,W135	TT	GSK	In development
MenAfrivax	A	TT	SII	WHO prequalified

1,038,457 people in Burkina Faso, Mali, and Niger immunised in 17 days with MenAfriVac™



The first round of vaccination with MenAfriVac™ started in Mali on September 13 and ended on September 29 2010 in Burkina Faso and Niger. Vaccine coverage reached 98.63% in Burkina Faso, 98% in Mali, and 85% in Niger.

Lessons learned from the district-level immunisation campaigns will be critical for implementing country-wide introduction of the vaccine in the three countries in December of this year.

Travel: Immunisation against infectious disease - 'The Green Book' 28th July 2010



Age	Conjugate ACWY (Menveo®)	Polysaccharide ACWY (ACWY Vax)
Infants under 1 year*	'off label' First dose of 0.5ml. Second dose of 0.5ml one month after the first dose.	Not recommended
Children aged 1 year to 4 years	'off label' Single dose of 0.5ml.	Not recommended
Children aged 5 to 10 years	'off label' but preferred Single dose of 0.5ml.	Single dose of 0.5ml
Individuals aged ≥ 11 years	Single dose of 0.5ml. (preferred)	Single dose of 0.5ml

* Replace the MCC vaccine with Menveo if the infant requires Menveo at the same time as the routine MCC vaccinations. If the infant has already had two MCC vaccinations then two Menveo vaccinations should also be given.

Children and adults with asplenia or splenic dysfunction : Immunisation against infectious disease – ‘The Green Book’



One dose of Hib/MenC vaccine (Menitorix).

Followed by two months later:

One dose of MenACWY conjugate vaccine (Menveo).

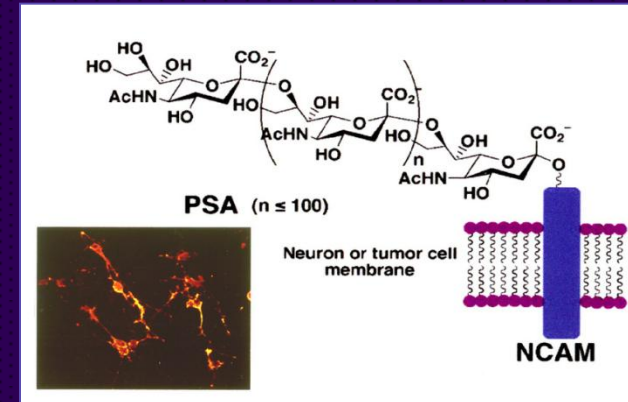
Group B vaccines

Polysaccharide: α 2-8 linked polysialic acid

E. coli K1

Pasteurella haemolytica A2

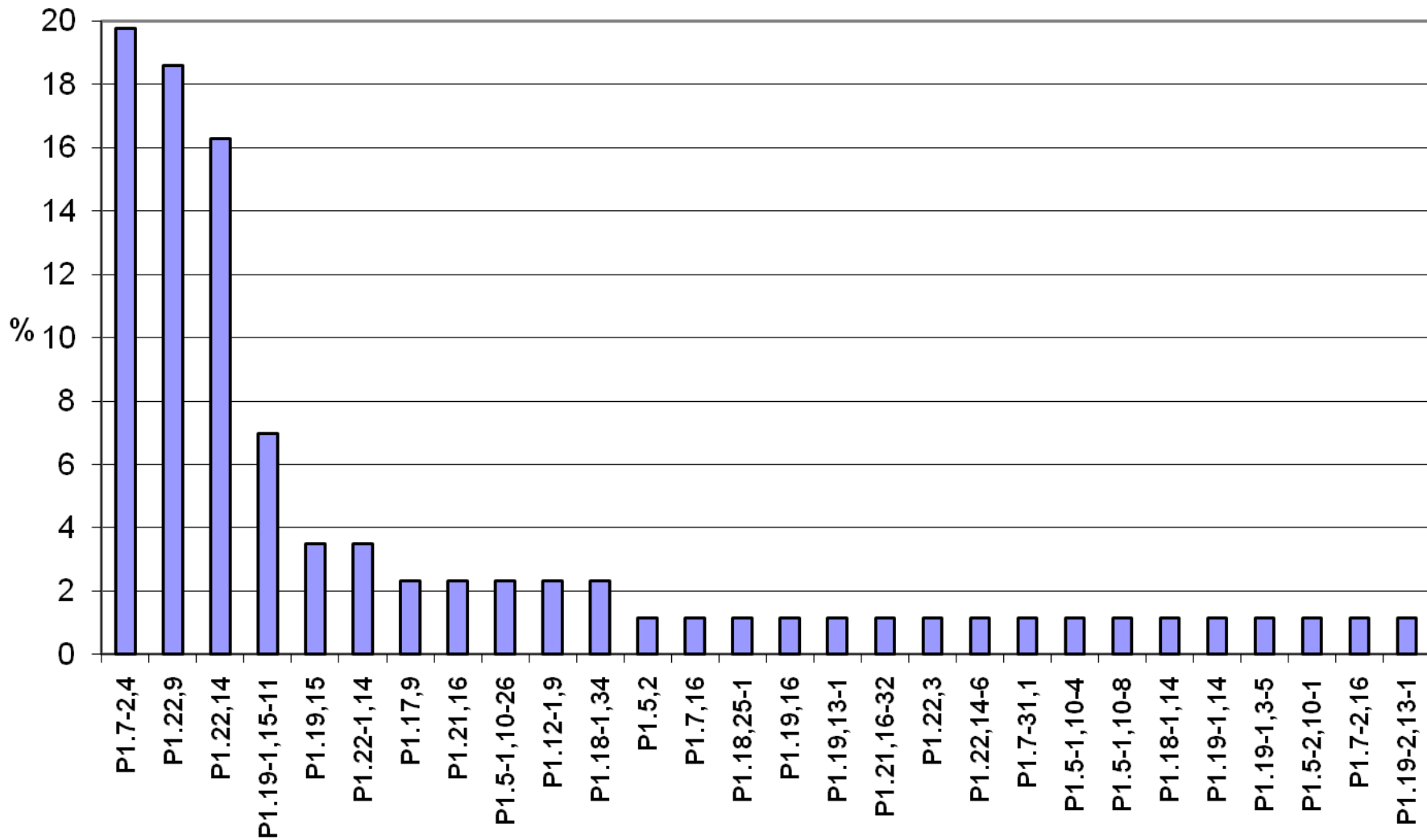
Moraxella nonliquefaciens



Molecular mimicry (sialic acid residues), poorly immunogenic

N-propionylated polysaccharide conjugate induced IgM specific to B polysaccharide and IgM & IgG to NPr B polysaccharide but no functional activity.

PorA subtypes of serogroup B meningococcal case isolates submitted to the Health Protection Agency MRU in January 2008 (n = 87)







Correlates of protection

- Immunogenicity studies, rather than efficacy studies, are sufficient for licensure of 'group B' meningococcal vaccines.
- Elevated serum bactericidal antibody (SBA) titres against a broad range of representative strains.
- If no SBA activity, efficacy studies will be required.

Meningococcal outer membrane vesicle OMV trials

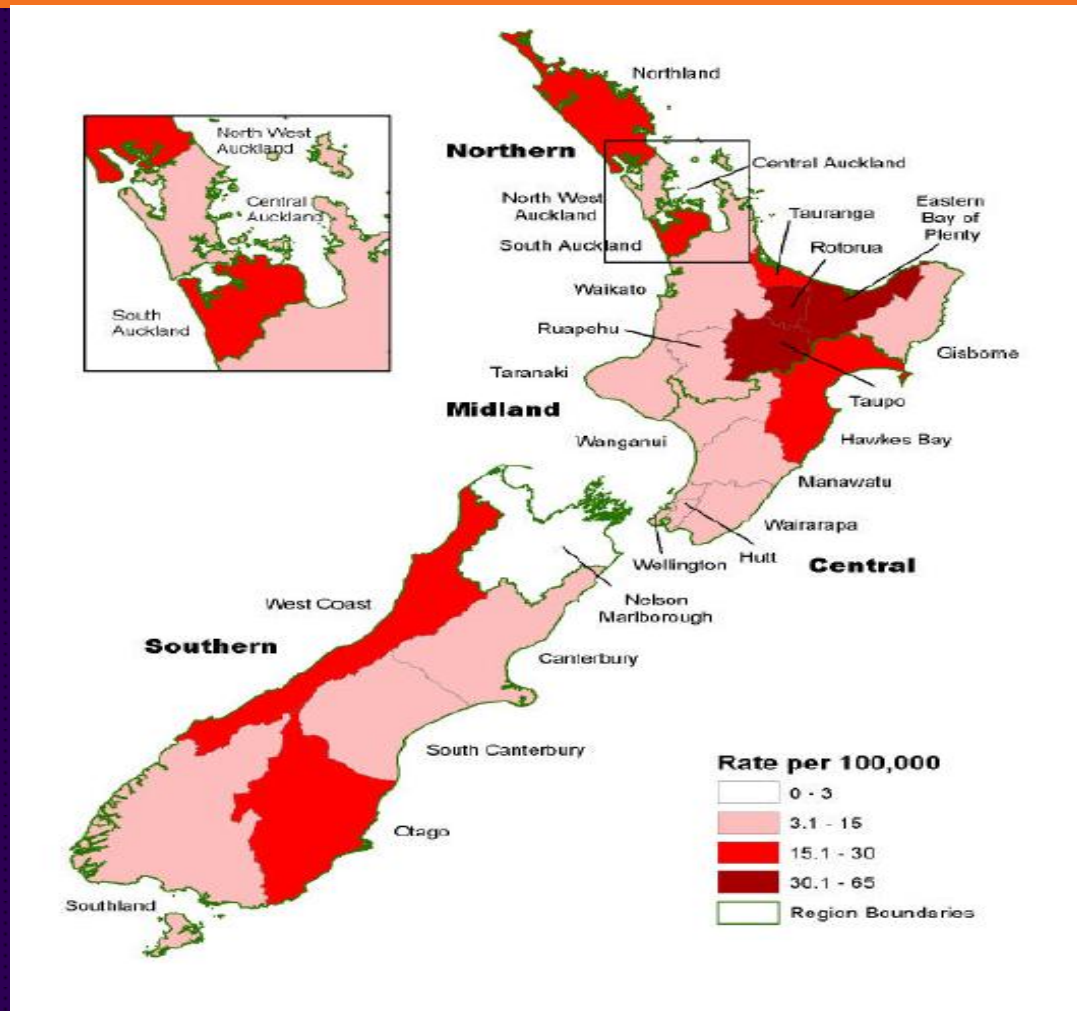


	Year	Age group	Vaccine	Estimated efficacy
 Cuba	1987-89	10 - 14 years	4:P1.15+C	83%
 Brazil	1989-91	3 months - 6 years	4:P1.15+C	47-74%
 Norway	1989-91	11 - 16 years	15:P1.16	57%
 Chile	1987-89	1 - 21 years	15:P1.3+C	51%

Meningococcal OMV Vaccines for New Zealand

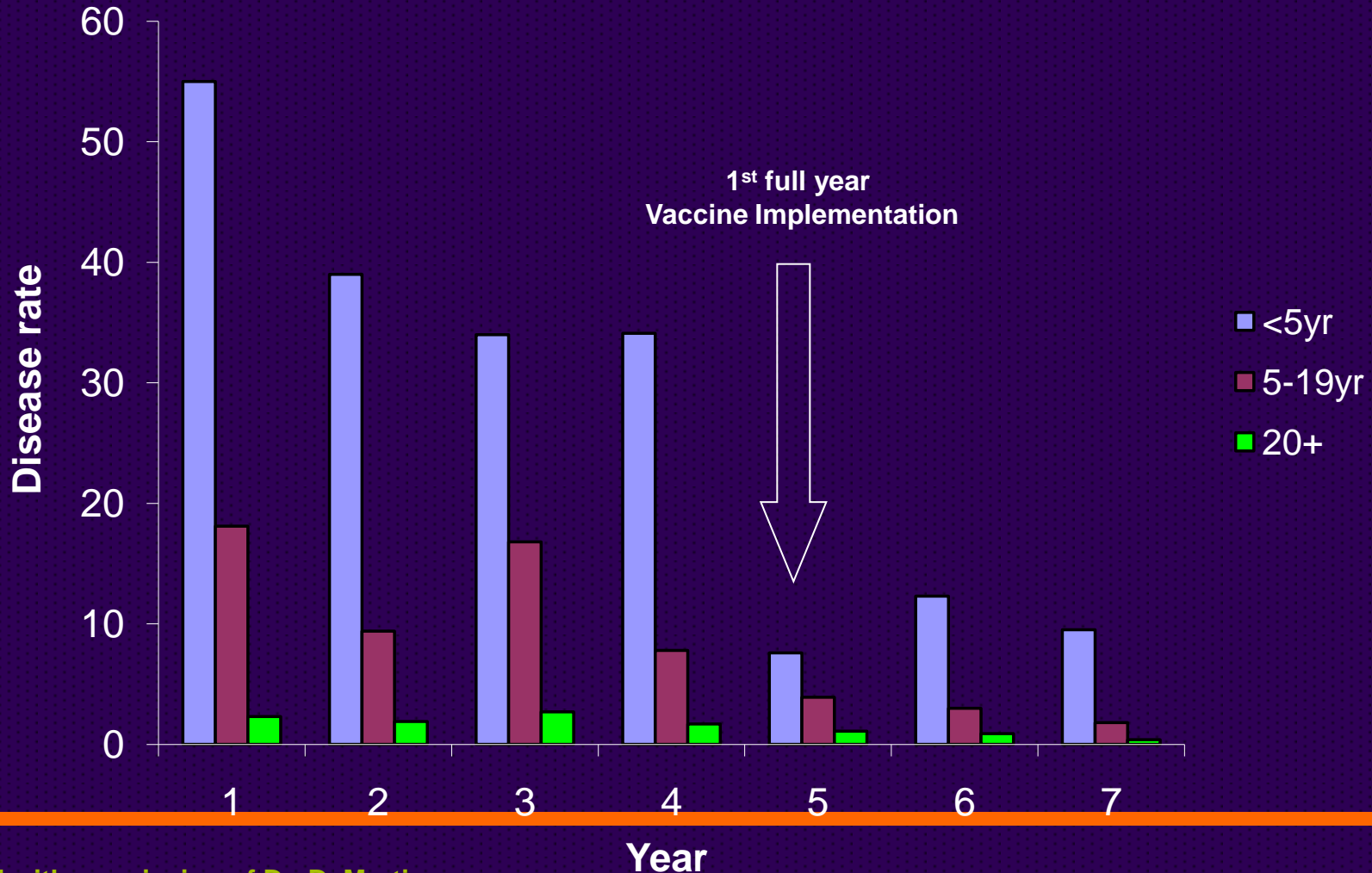


2002

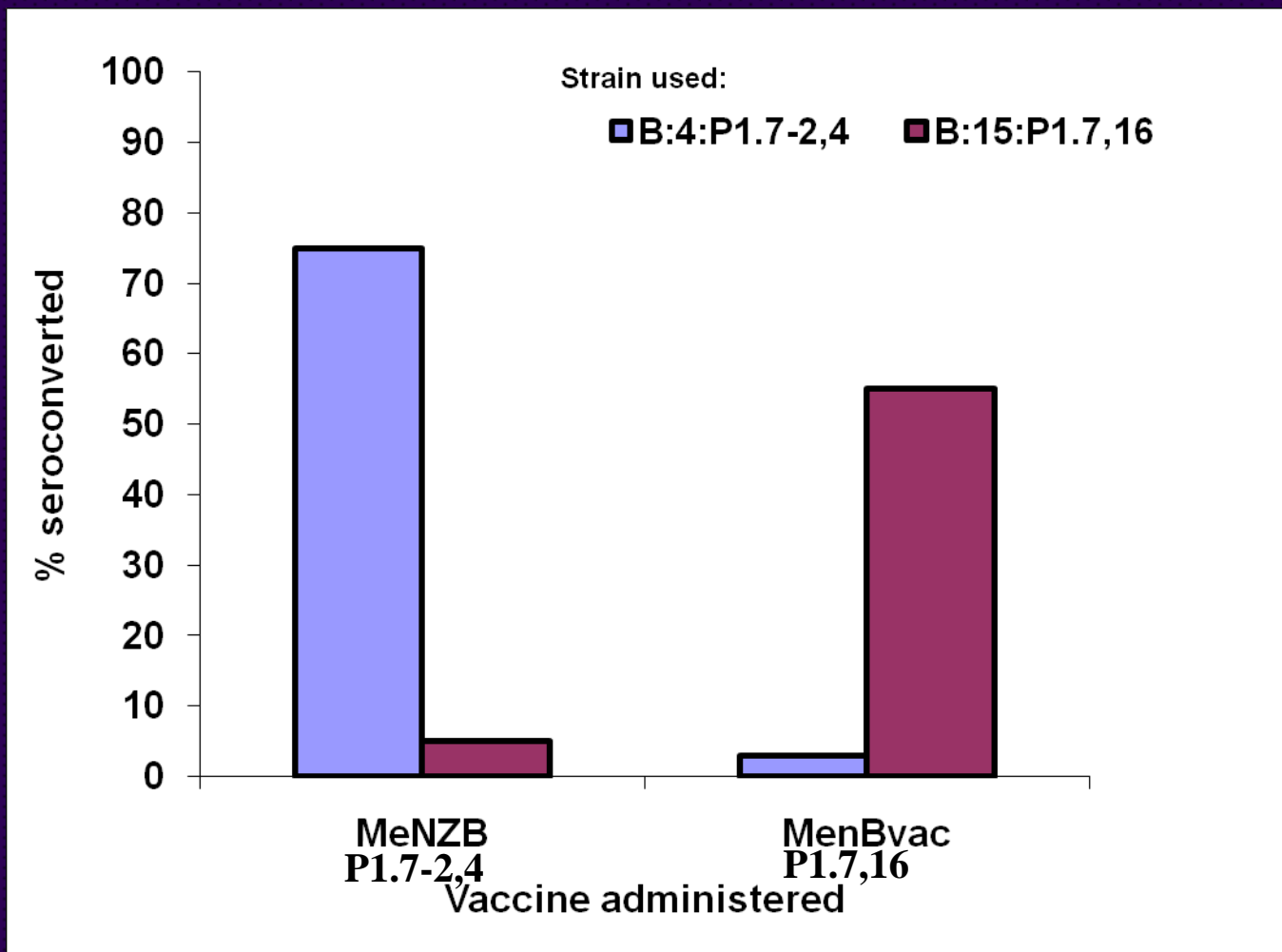


Due to B:4:P1.7-2,4

Epidemic strain meningococcal disease rates Northern region by year and age-group

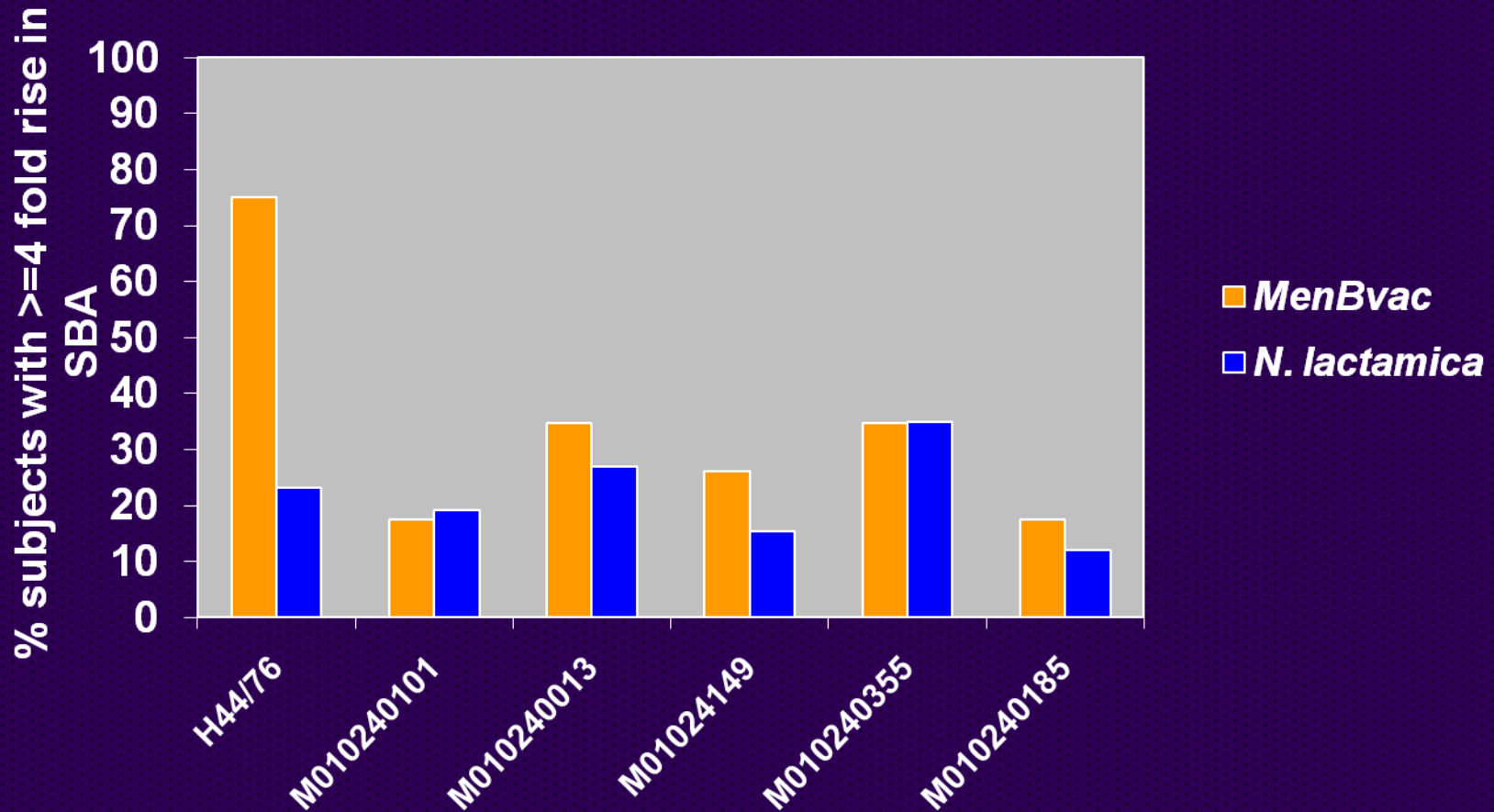


Proportion of children aged 16 to 24 months who have seroconverted in the serum bactericidal antibody assay to their vaccine strain or a heterologous strain following either 3 doses of MeNZB or MenBvac

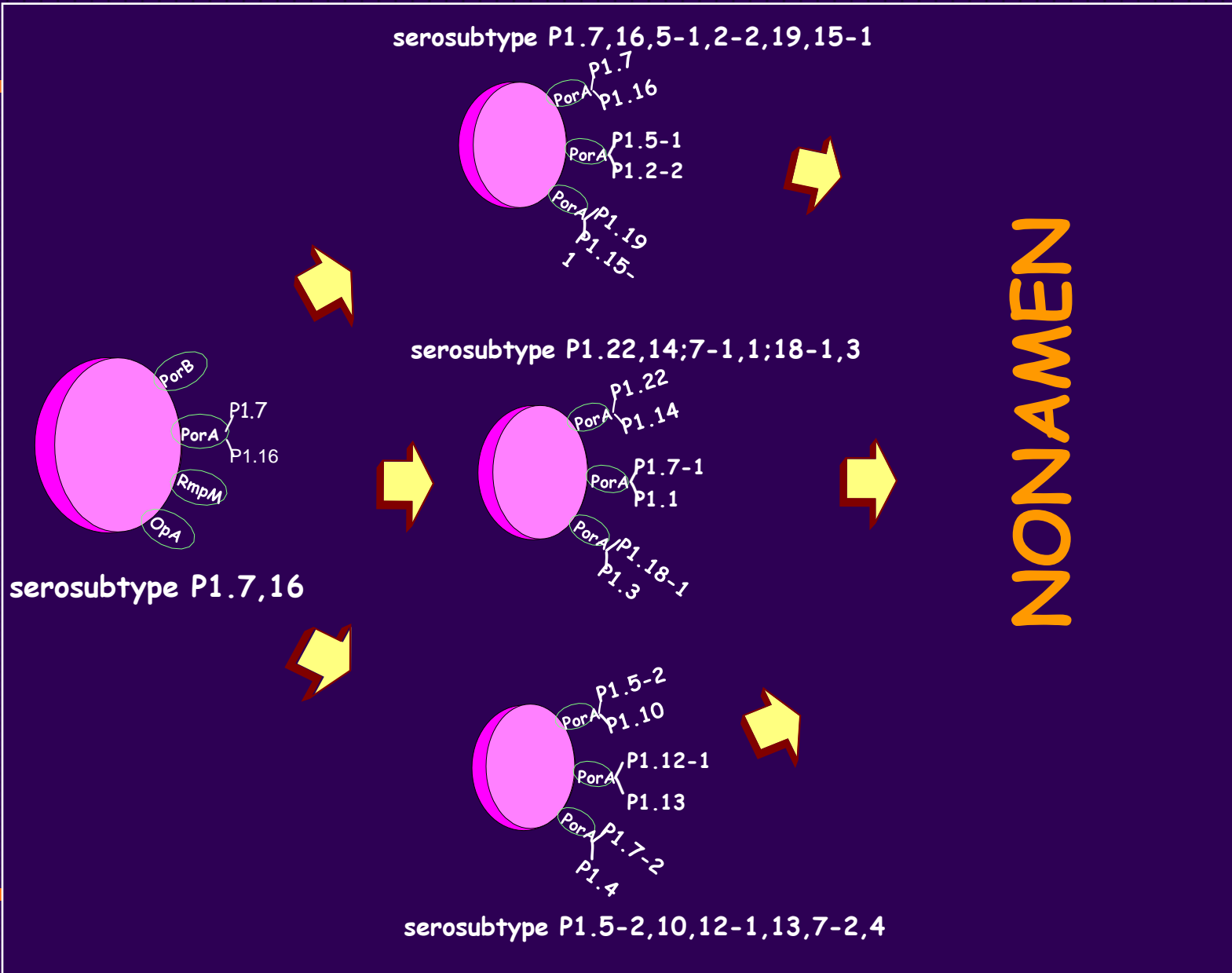


Neisseria lactamica

% Subjects with a ≥ 4 fold rise in SBA titre (post 3 doses)
Comparison of MenBvac with *N. lactamica* OMV



RIVM PorA approach



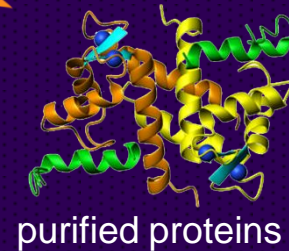
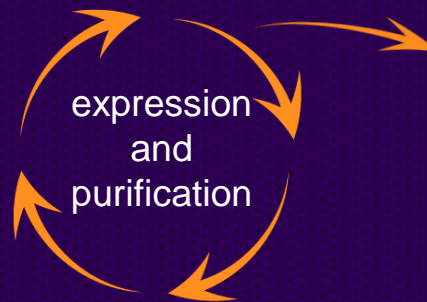
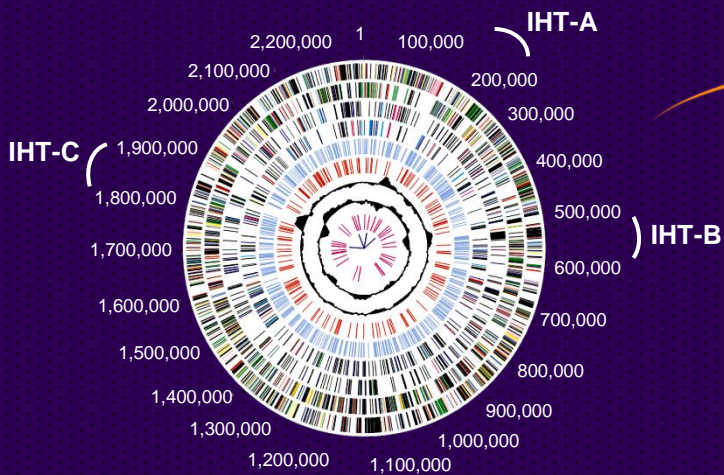
NONAMEN

Novel Antigens Identified by Reverse Vaccinology



Based on the genome sequence of MC58, **570** 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



purified proteins



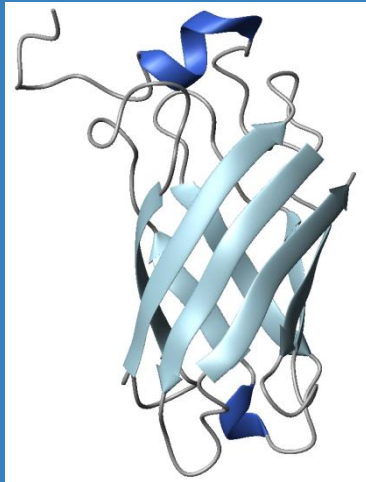
immunizations

Sera used to confirm surface exposure of novel proteins

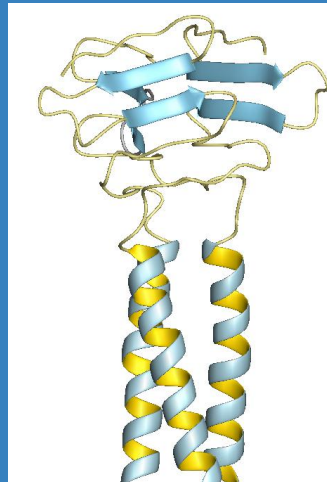


28 novel protein antigens with bactericidal activity were identified

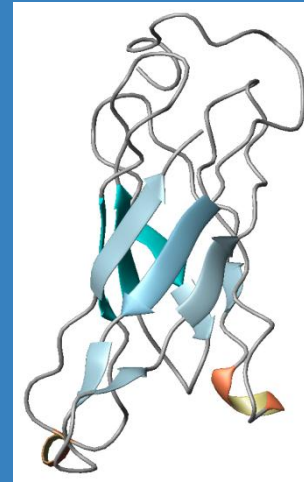
Novartis MenB vaccine contains 4 main antigens



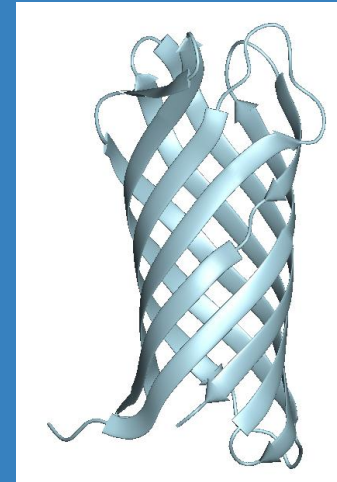
fHBP 1.1



NadA



GNA2132



PorA
(presented as
part of an OMV)

Target strains used in the SBA assay

Antigen	Designation	PorA	fHBP	NadA
PorA	NZ 98/254	P1.7-2,4	1.10	-
NadA	5/99	P1.5,2	2.8	+
fHBP	44/76-SL	P1.7,16	1.1	-

UK infant trial

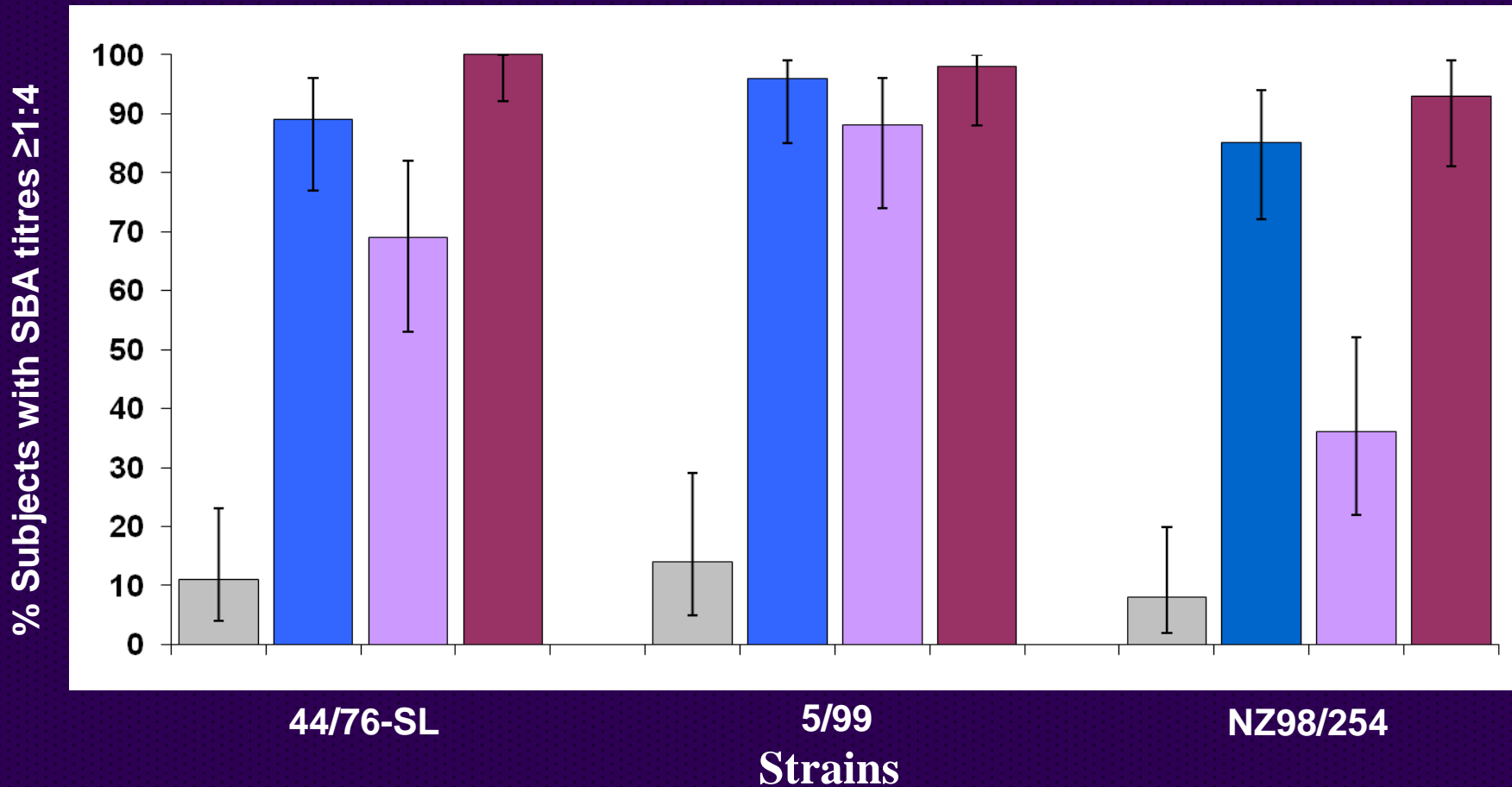


**rMenB vaccine with or without OMV
at 2, 4, 6 and 12 months of age.**

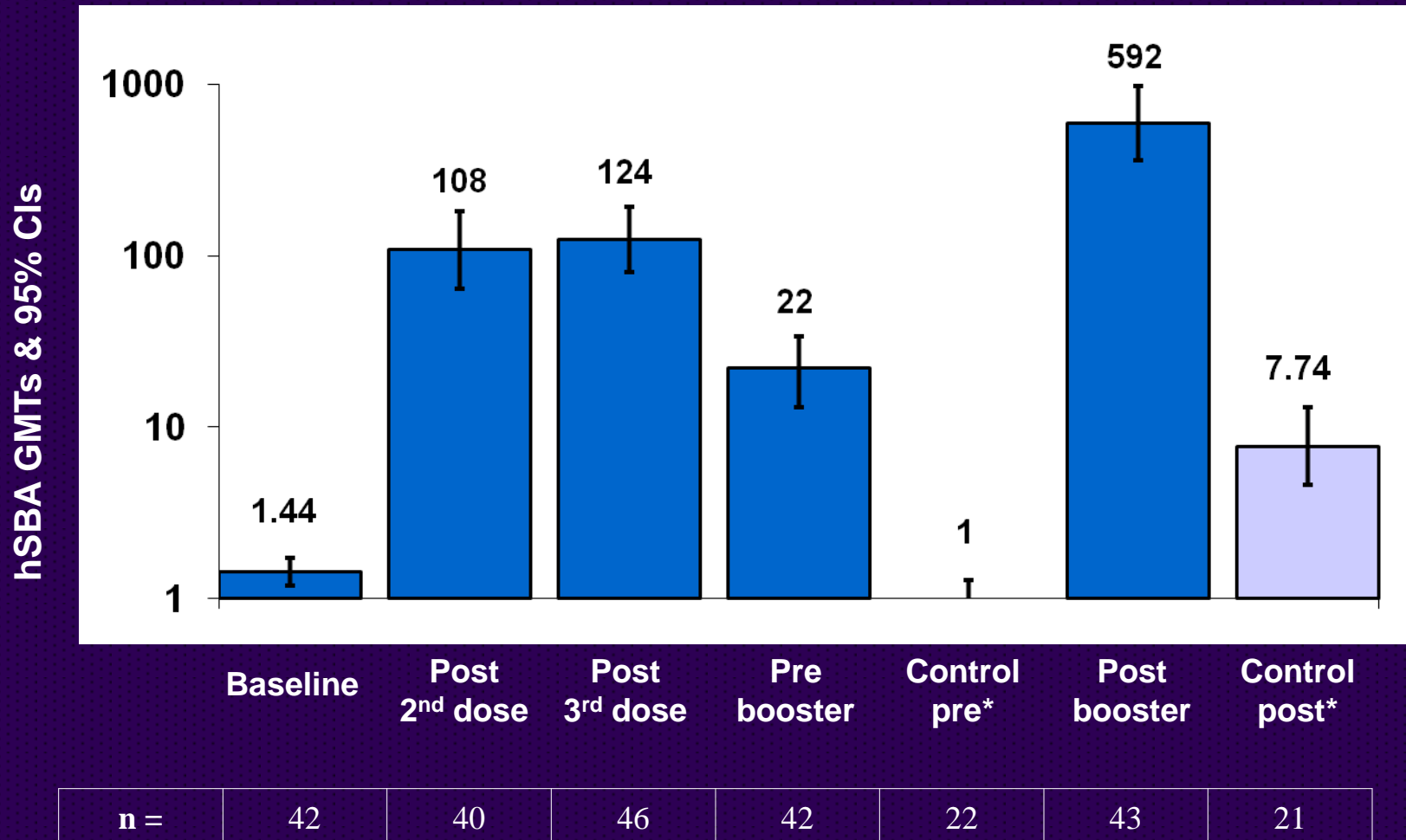
Proportion of subjects with hSBA titres $\geq 1:4$ before & after rMenB+OMV vaccine



■ Baseline ■ Post 3rd dose ■ Pre booster ■ Post booster



Geometric mean hSBA titres after rMenB+OMV vaccine for: 5/99 (NadA)



*Control group = A single dose of rMenB + OMV at 12 months.

Pfizer rLP2086 vaccine



LP2086 recombinantly expressed in *E. coli* and purified to homogeneity.

Vaccine formulation developed for clinical studies contains two rLP2086 proteins- one from Subfamily A and one from Subfamily B.

Induce bactericidal antibodies cross-reactive against all fHbp variants, depending on expression level.

Phase I and Phase II (18 to 25 year olds, 8 to 14 year olds and 18 to 36 month olds).

- Encouraging phase 1 trial results
 - Vaccine relatively well tolerated
 - Dose-dependent reactogenicity & SBA responses
 - % of responders approaching 100% for some strains, varied by definition of responder, and by strain tested
 - GMTs varied by strain tested, expression critical
- Moving ahead with Phase 2 studies

Multivalent group B meningococcal vaccine based on outer membrane vesicles

Walter Reed Army Institute of Research, Maryland, USA

- Native OMVs
- Each strain modified to express a different PorA, a different core LOS and an increased expression of one conserved antigen (fHbp1, fHbp2, NadA, Opc).
- Phase I completed, safe and induced SBA

GSK

- Recombinant OMV technology
- Upregulate key protective antigens
- Down regulate variable immunodominant antigens
- Modify LOS

Coverage?



What is the potential coverage of these new vaccines eg PorA?

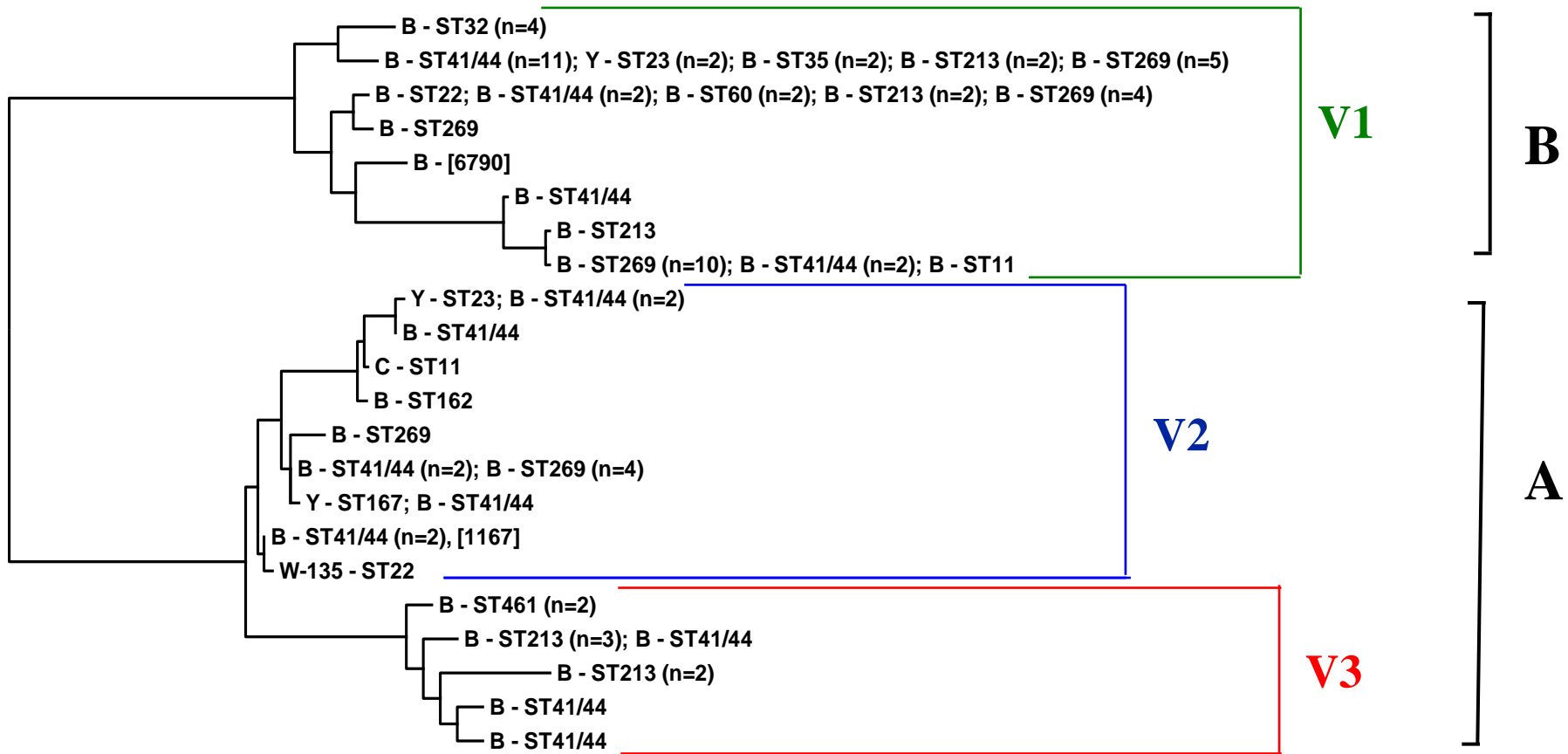
- 29 different variants of P1.4 (P1.4, P1.4-1 etc)*
- From PorA sequenced case isolates submitted to HPA MRU (1985 to 2008), 492 belonged to P1.4 family.
- P1.4 n = 478 (97.2%) All mab[#] +ve
- P1.4-1 n = 13 (2.6%) All mab -ve
- P1.4-5 n = 1 (0.2%) Mab -ve

From Jan 2008 the % of isolates with P1.4 = 20%

Antigens variants - fHbp



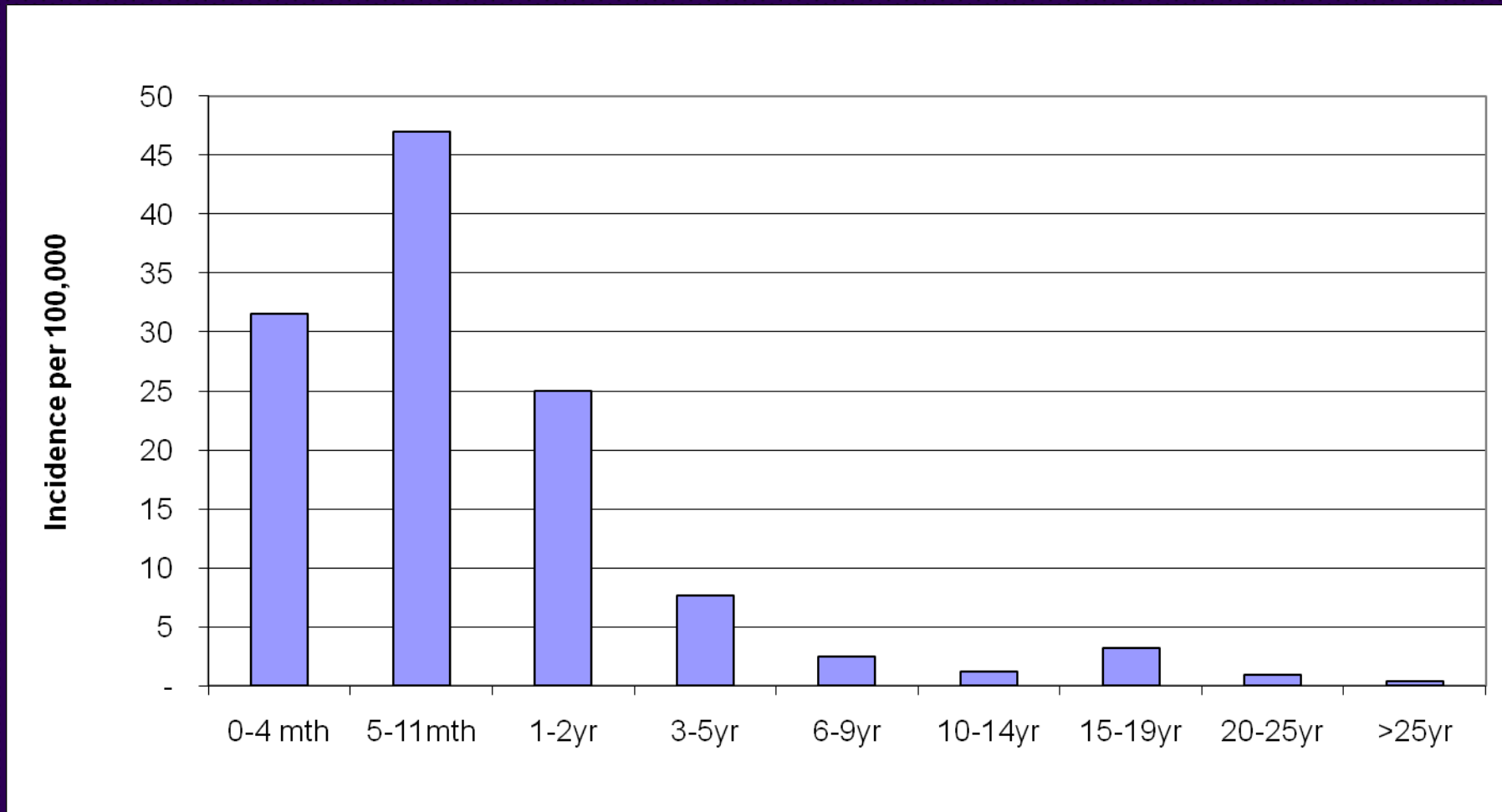
fHbp variants for England & Wales case isolates in Jan 2008



10

- Present in all case strains, genetic diversity, **expression variable**

Incidence of serogroup B disease for 2006 for England, Wales and Northern Ireland



No. of B cases for 2008: 115 227 316 199 103 76 174 60 239

Serogroup B conclusions



- **Group B vaccine trials are underway after a hiatus of a decade.**
- **Need to determine immunogenicity to predict effectiveness.**
- **Need to determine potential coverage.**
- **Which age groups should be vaccinated?**
- **Are carriage studies required?**