Vaccine round-up: current and future vaccines against meningitis including propects for prevention of MenB

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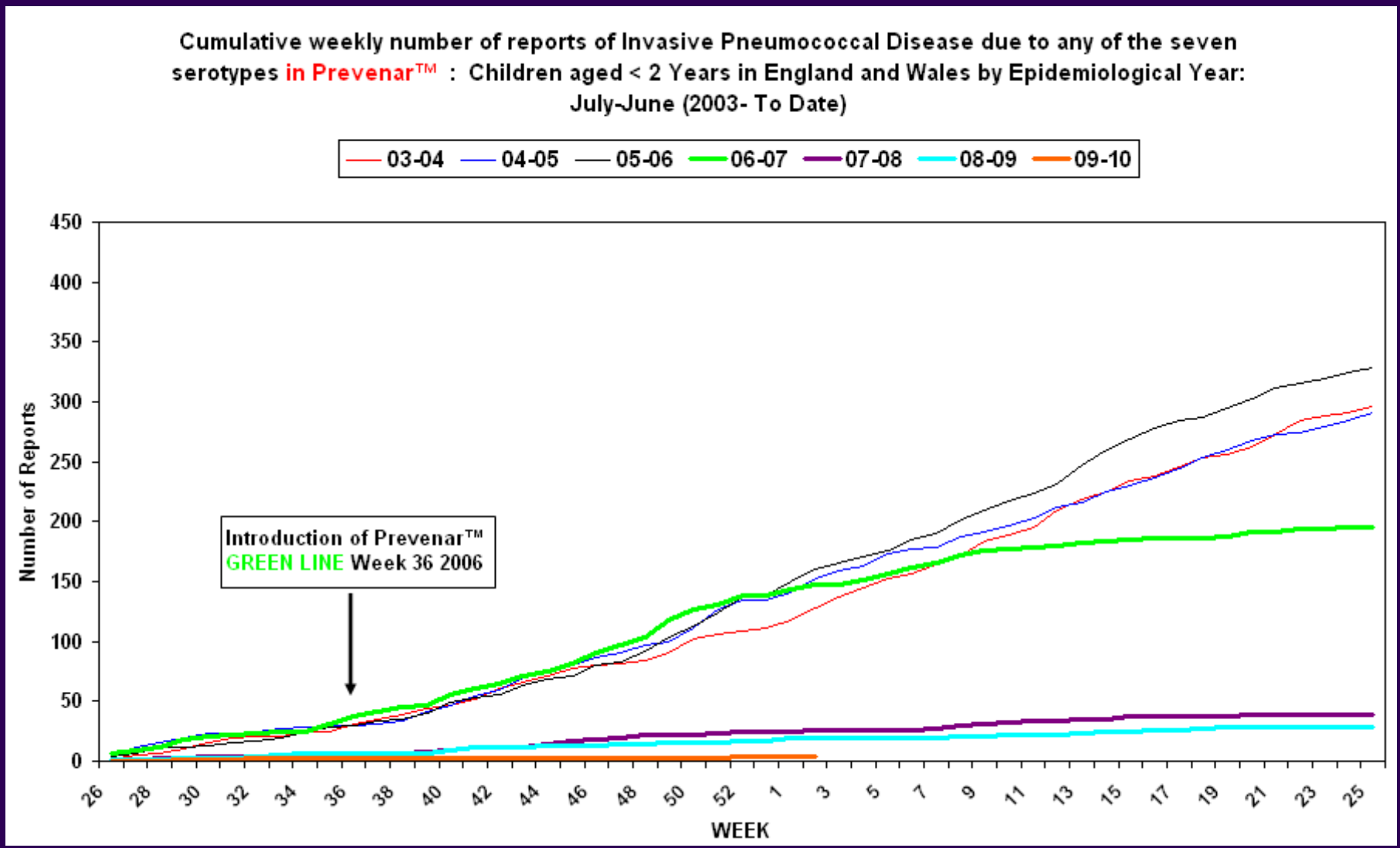
6th July 2010

Sept 2006 UK schedule

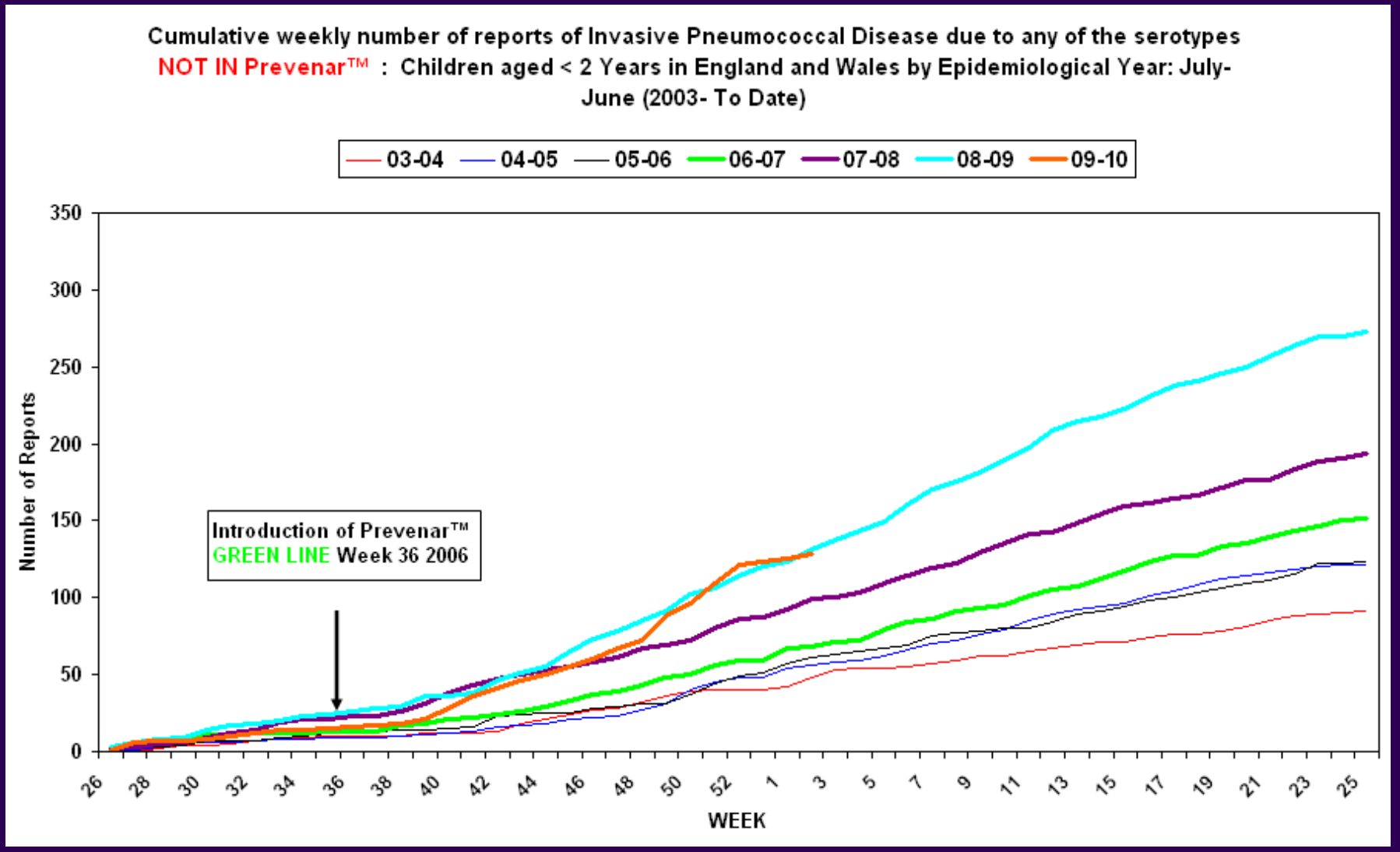
2 months	**DTaP/IPV/Hib + PCV7**
3 months	**DTaP/IPV/Hib + MCC vaccine**
4 months	**DTaP/IPV/Hib + MCC + PCV7** (MCC can be given at 5 months)
12 months	**Hib/MCC**
13 months	**MMR + PCV7**

The impact on Invasive Pneumococcal Disease , Children < 2 yrs: Serotypes contained in PCV7

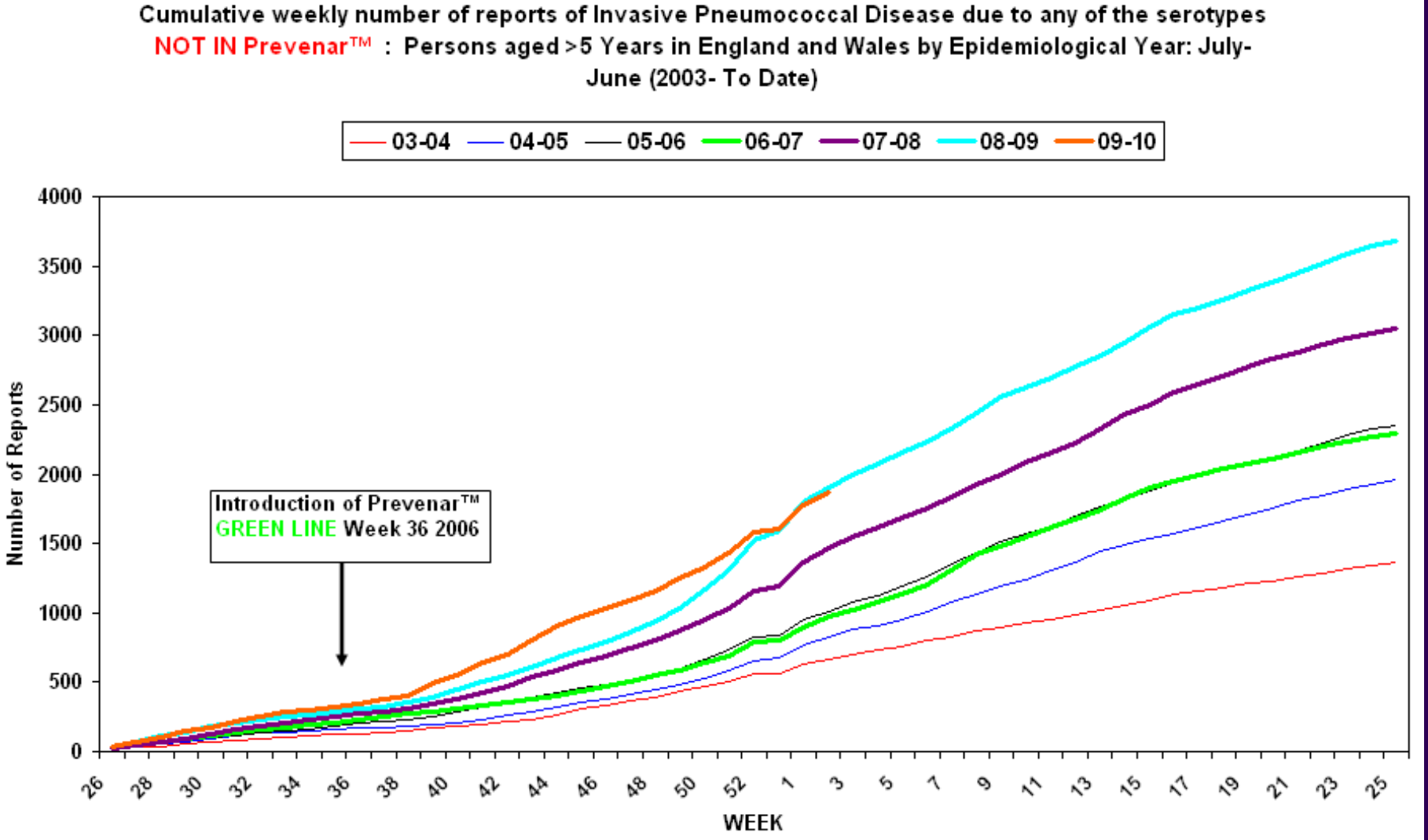
Health Protection Agency



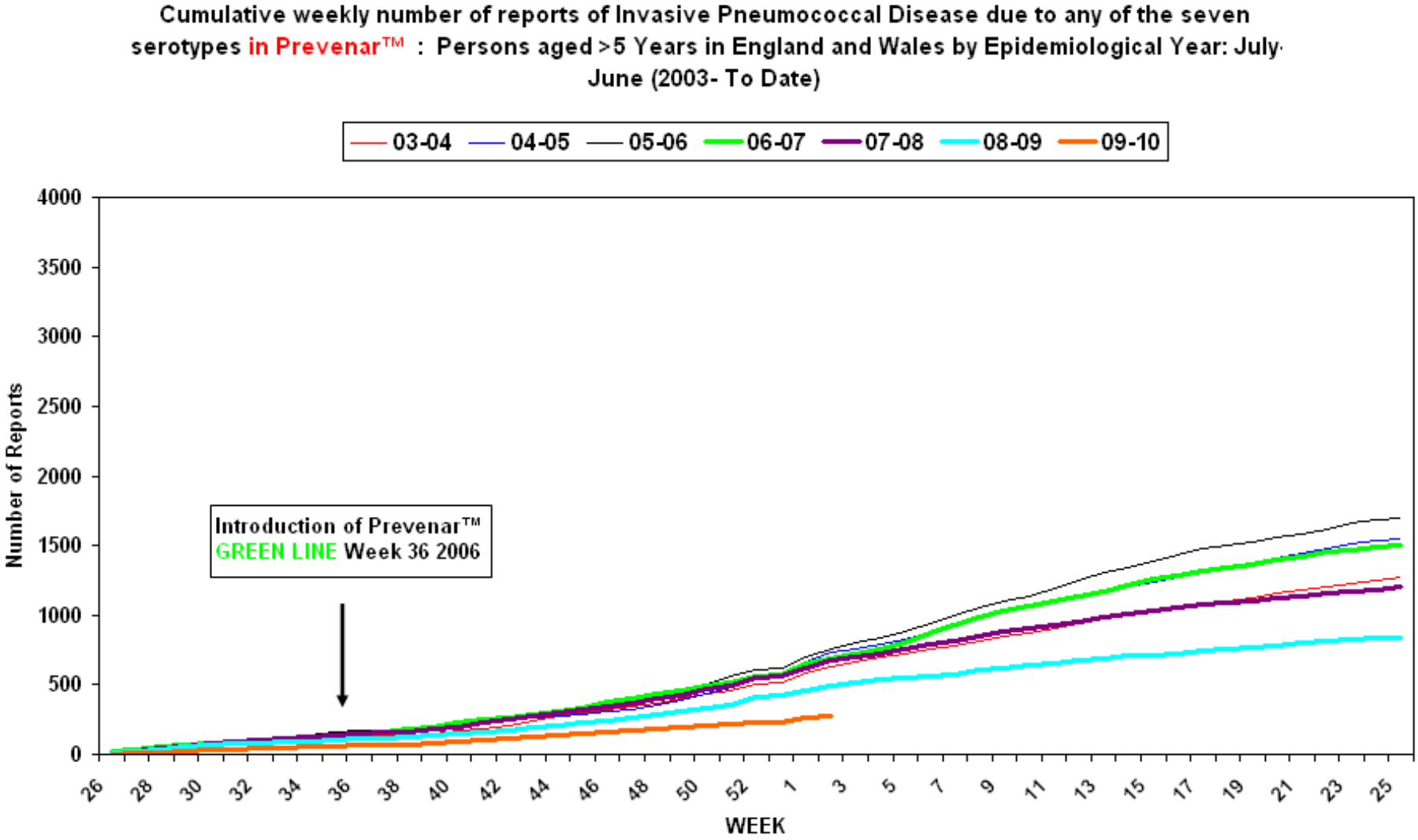
The impact on Invasive Pneumococcal Disease, Children < 2 yrs: Serotypes NOT contained in PCV7



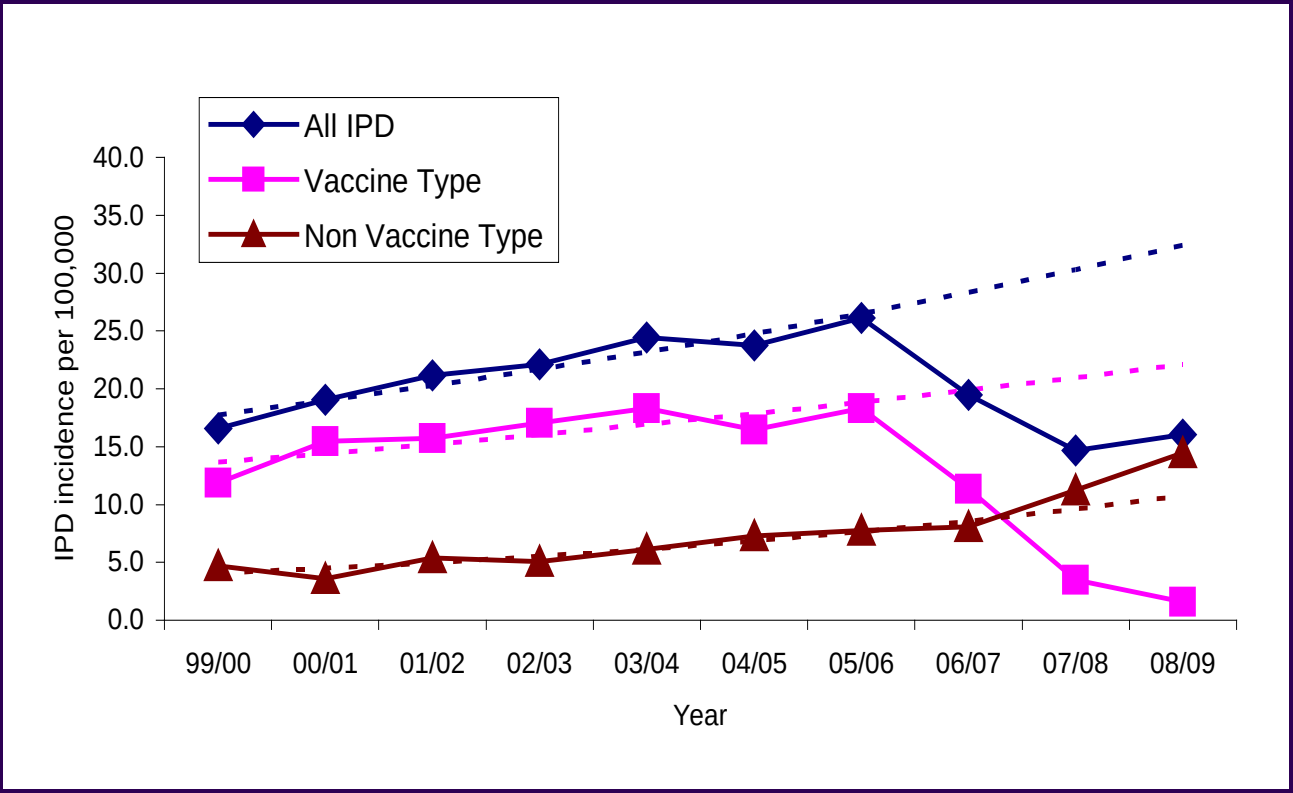
The impact on Invasive Pneumococcal Disease, Children ≥5 yrs: Serotypes NOT contained in PCV7



The impact on Invasive Pneumococcal Disease, Children ≥5 yrs: Serotypes contained in PCV7



IPD incidence in England and Wales by serotype: children < 5 yrs old 2/4/13 month schedule



Change 2008/9 vs 2005/6; All IPD -40% (-48, - 30)
VT -92% (-94, -89); NVT +88% (+23, +187)

Change 2008/9 vs predicted incidence in 2008/9 All IPD -51% (-60, -41)
VT -93% (-95, -90); NVT +35% (-22, +134)

Higher valency pneumococcal conjugates

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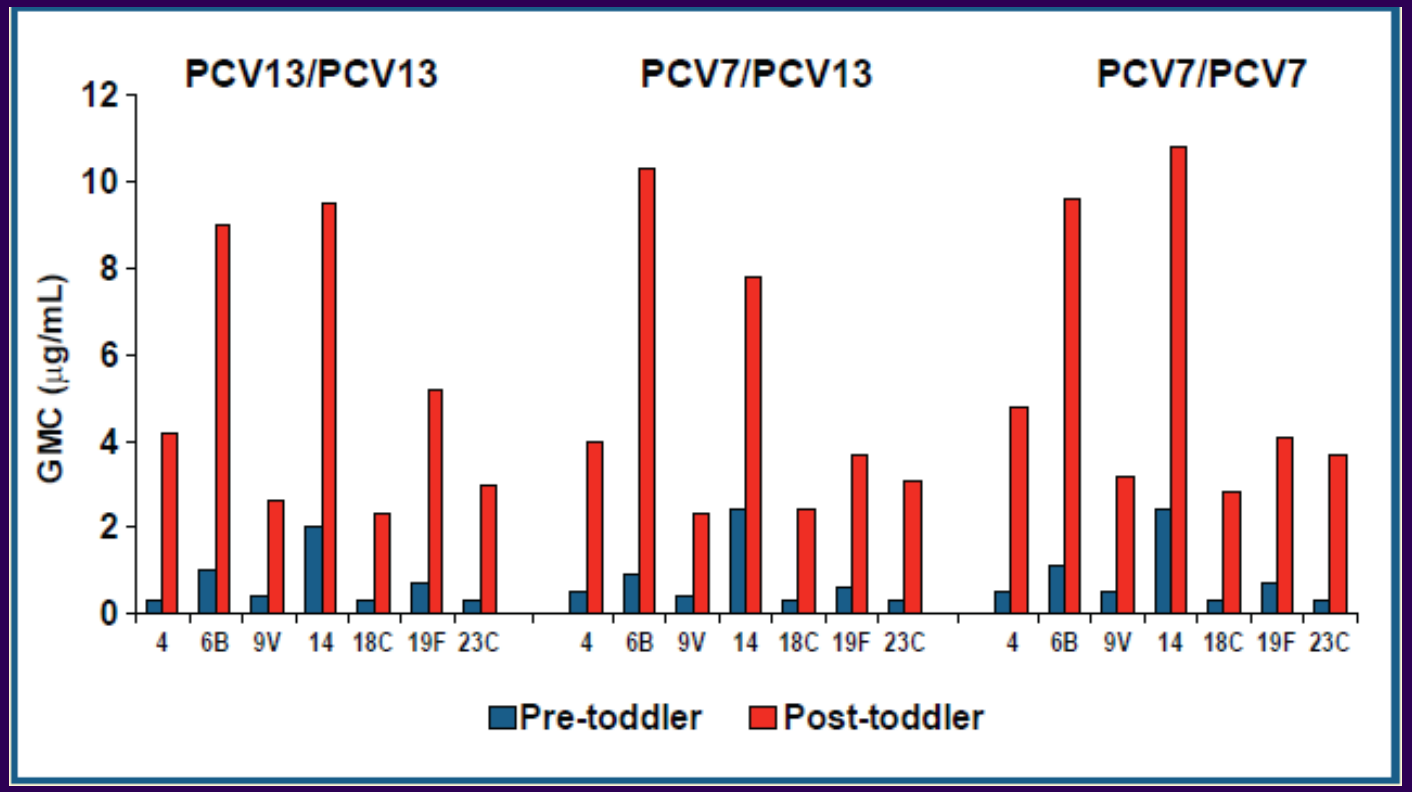
Prevenar13

1	3
4	5
6A	6B
7F	9V
14	18C
19A	19F
23F	

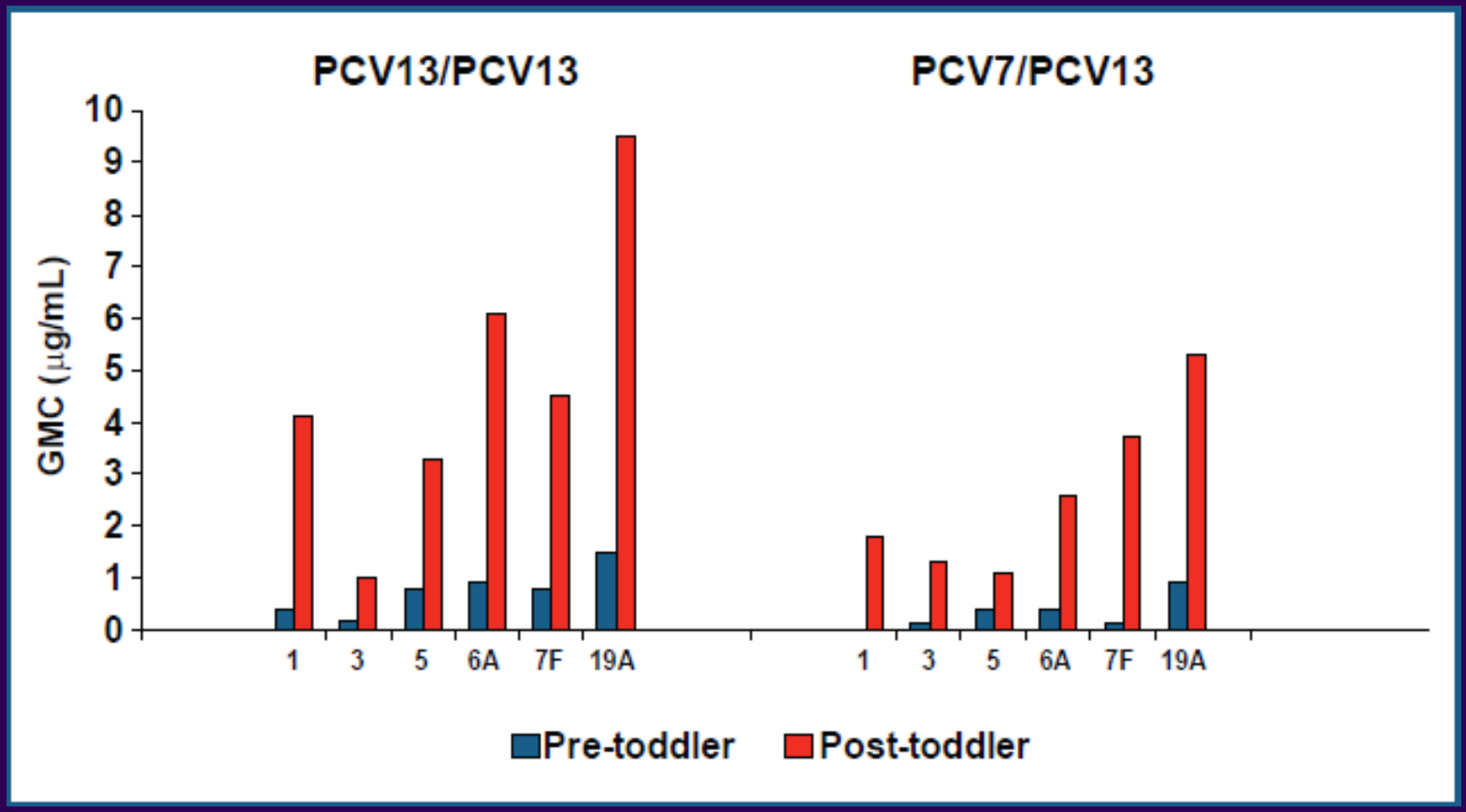
Synflorix

1	
4	5
	6B
7F	9V
14	18C
	19F
23F	NTHi

Comparison of pneumococcal IgG GMCs for the 7 common serotypes before and after the toddler dose



Comparison of pneumococcal IgG GMCs for the 6 additional serotypes before and after the toddler dose



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Pneumococcal

PNEUMOCOCCAL MENINGITIS NOTIFIABLE

Pneumococcal
January 2010

- in 2010, pneumococcal conjugate vaccine containing polysaccharide from thirteen common capsular types (including the seven capsular types in the earlier vaccine) replaced the seven valent conjugate vaccine.

The impact on Invasive Pneumococcal Disease, Children Under 2 yrs: Six serotypes in PCV13 but NOT in PCV7

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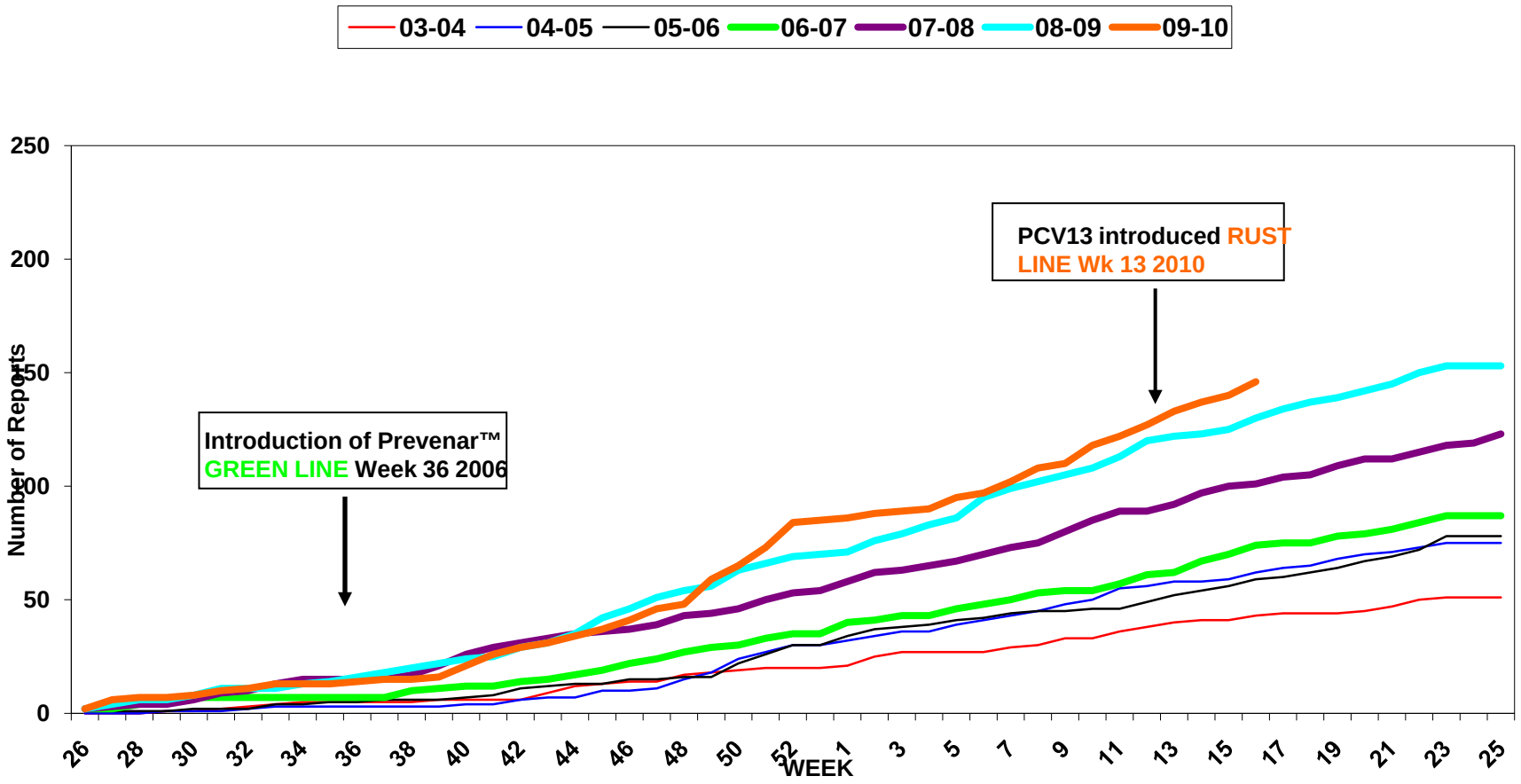
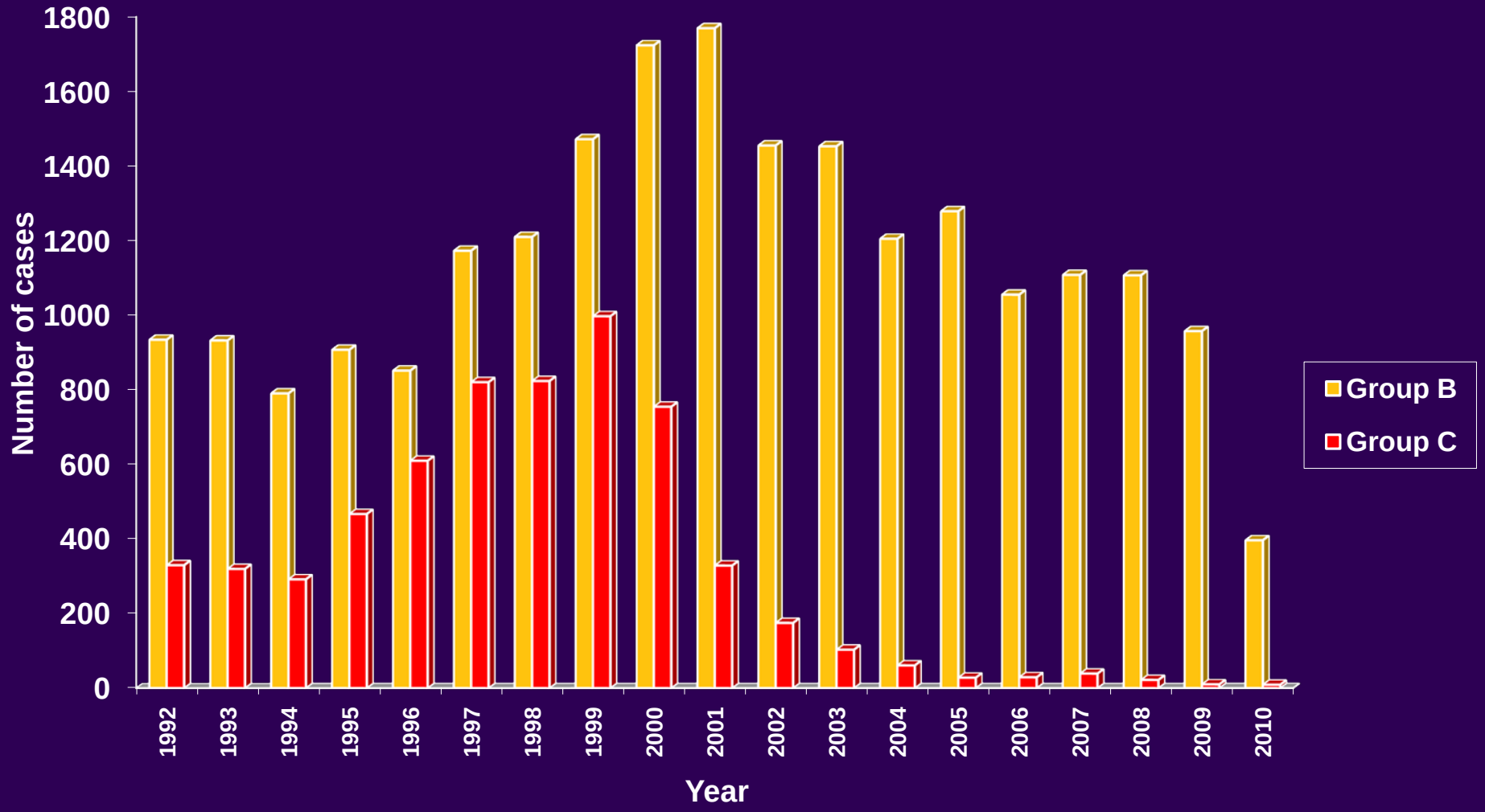
Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the six serotypes in Prevenar13™ but not in PCV7 : Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)

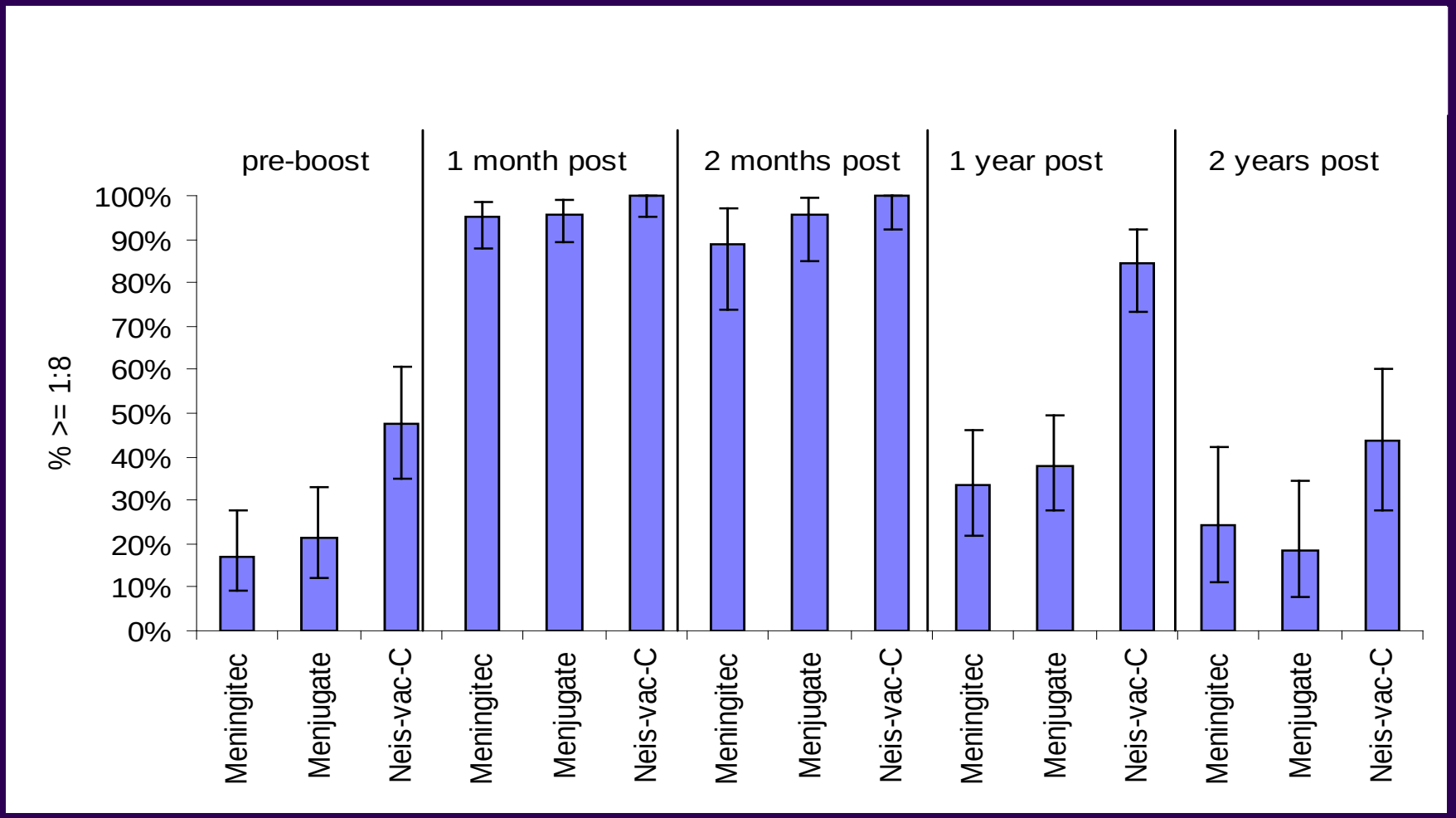


Annual cases of laboratory confirmed meningococcal disease England & Wales 1992 to 2010 (up to 24th June 2010)

Health Protection Agency



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



Borrow R, Andrews N, Findlow H et al. Clin Vaccine Immunol. 2010;17:154-9.

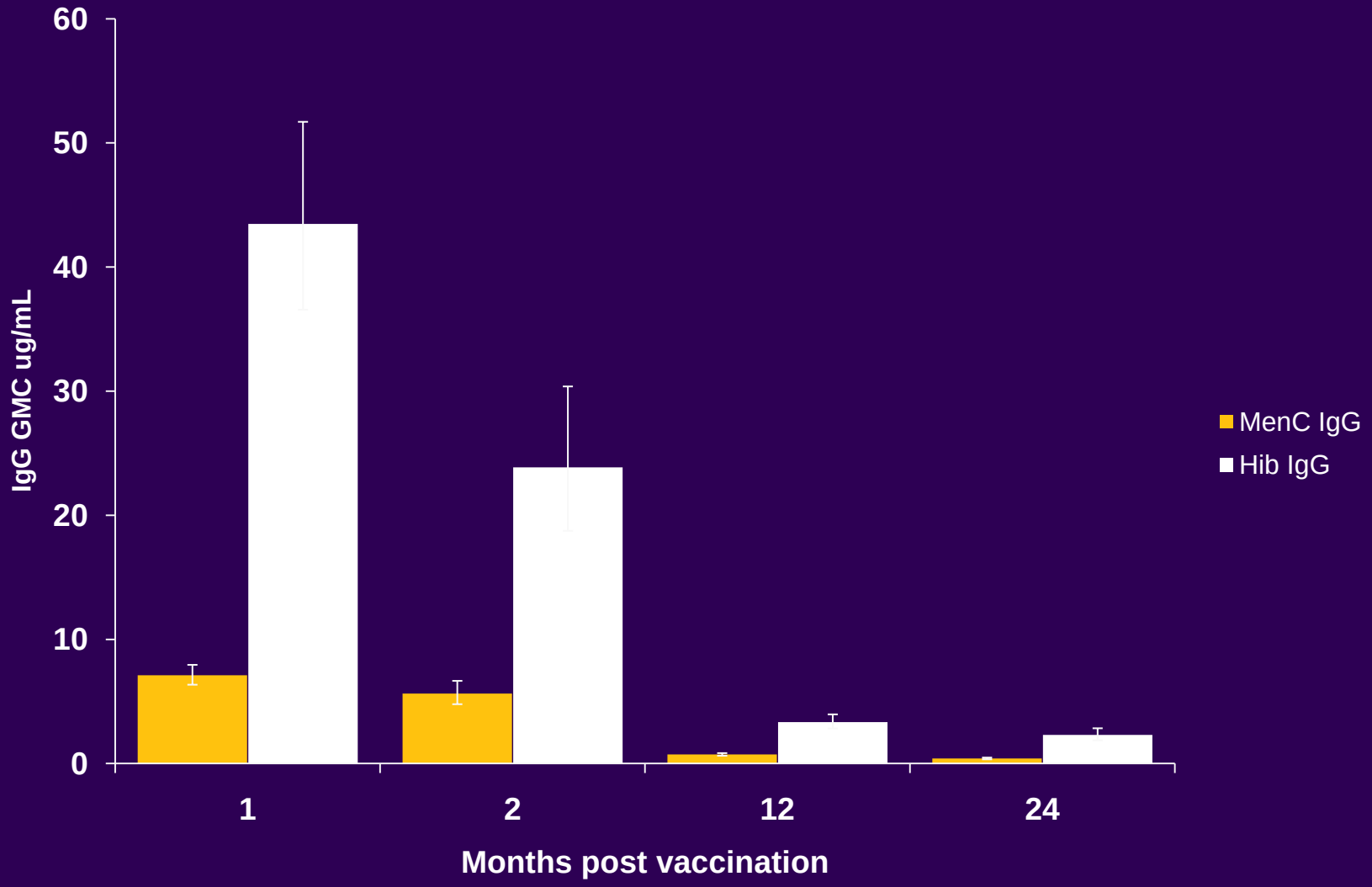
Antibody decay post-booster

Meningococcal SBA decay pattern post booster is very similar (-1.59) to that post primary (-1.55).

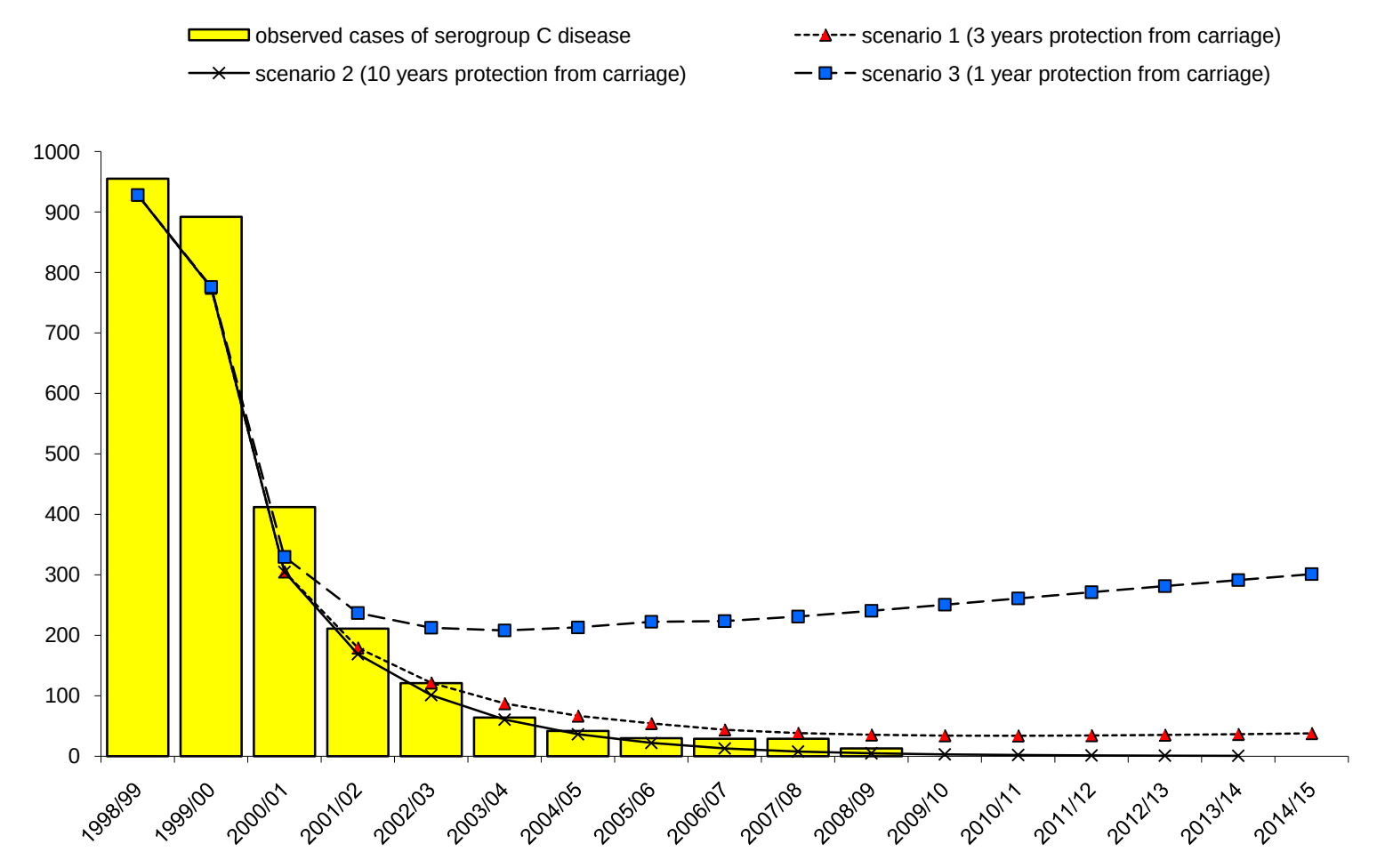
Thus as time doubles, SBA titres go down by two thirds.

Hib IgG decay pattern is -1.00 & MenC IgG -0.95, thus as time doubles, Hib & MenC IgG goes down by one half.

Comparison of meningococcal group C and Hib IgG GMCs at 1, 2, 12, and 24 months post boosting with Menitorix

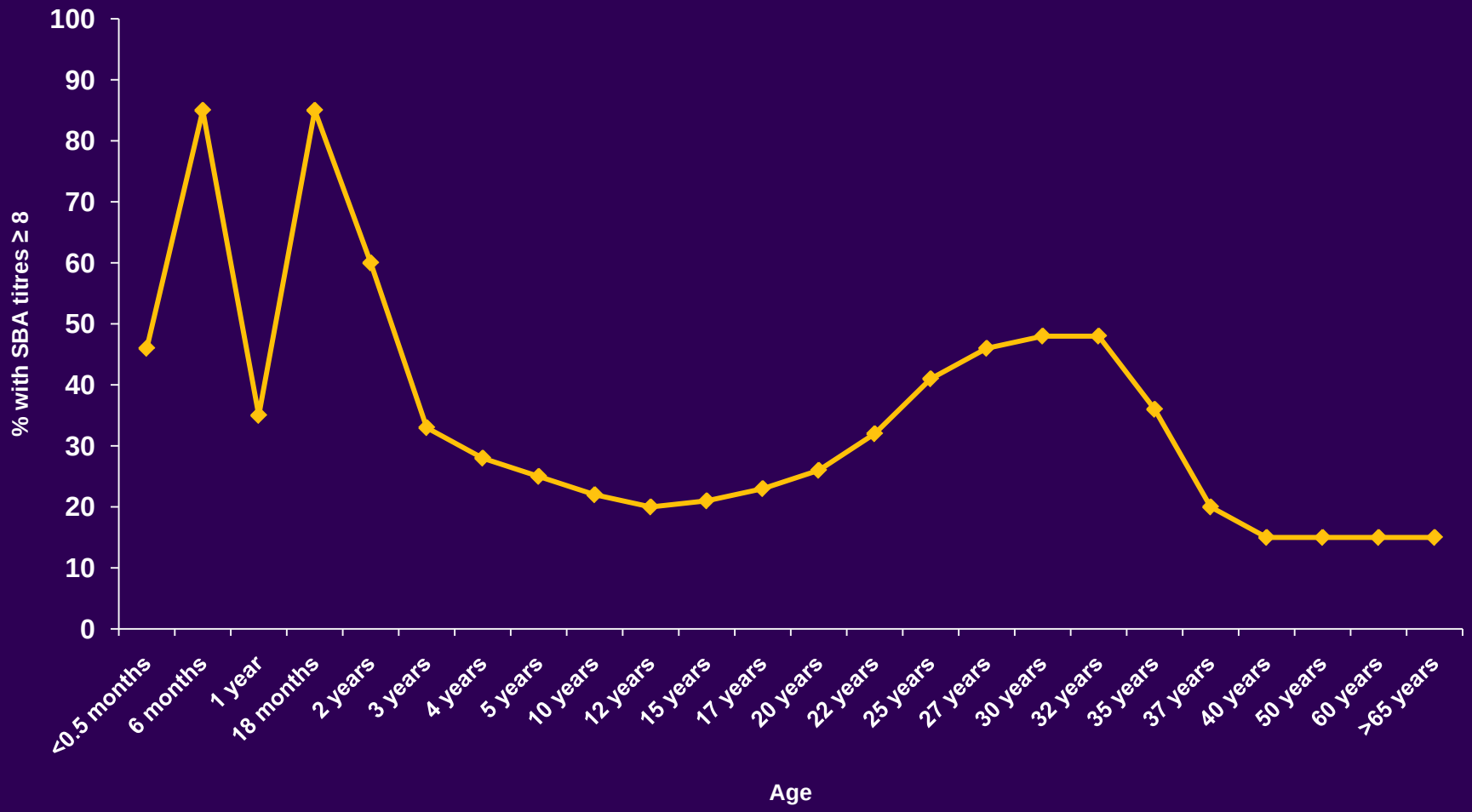


Model predictions and observed cases of laboratory confirmed serogroup C disease in England & Wales



Campbell H et al. Clin Vaccine Immunol 2010;17:840-7.

Predicted proportions of sera with serogroup C SBA titres ≥8 by age in England and Wales (2010).



Predicted data based upon Trotter CL *et al., Clin. Vaccine Immunol.* 2008 and Borrow *et al., Clin. Vaccine Immunol* . 2010.

Recommendations for an additional booster?

- Meningococcal serogroup C conjugate vaccination recommended at 12 to 15 months and 11 to 15 years of age in Switzerland.

- Canada recommends an adolescent booster dose for serogroup C (using either monovalent serogroup C conjugate or quadrivalent ACYW conjugate vaccine).

- Use of a quadrivalent conjugate vaccine 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.

Boosting, which vaccine?

Monovalent meningococcal group C conjugate vaccine:

NeisVac-C
Menjugate
Meningitec

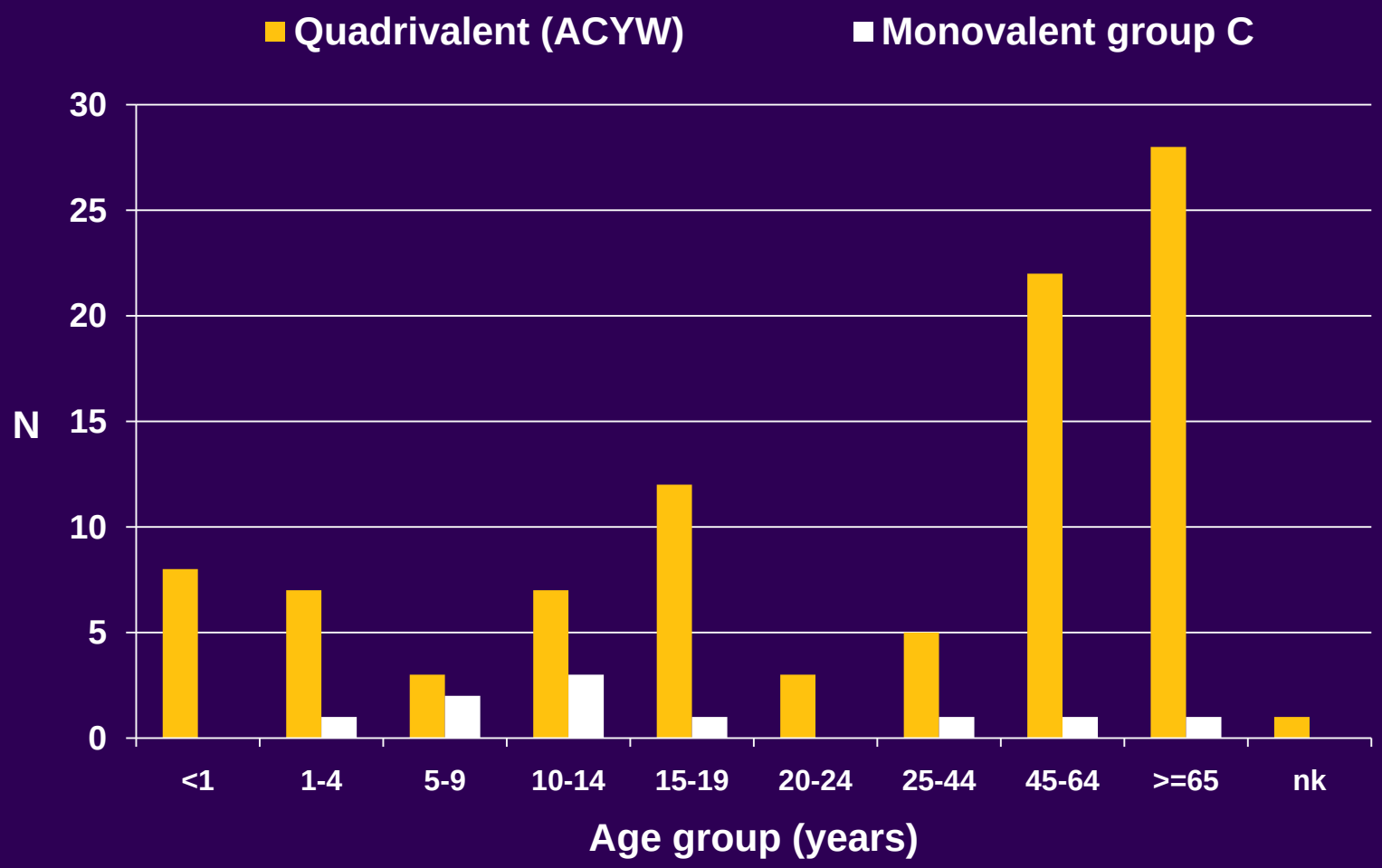
Meningococcal group C/Hib conjugate combination vaccine:

Menitorix

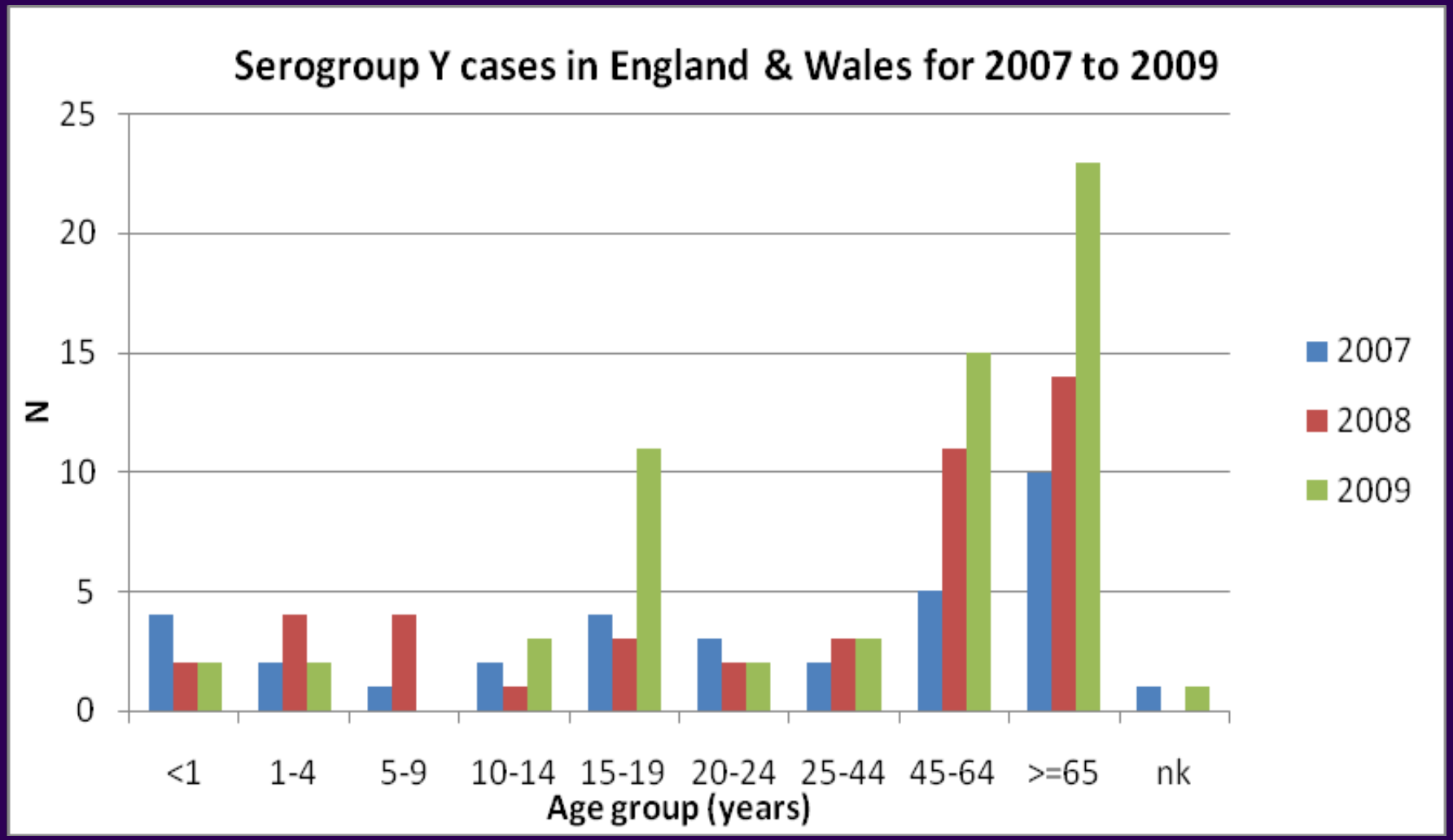
Meningococcal quadrivalent group A, C, Y and W135 conjugate:

Menveo
(Menactra)
(Nimenrix)

Number of vaccine-prevenable meningococcal cases in England & Wales, 2009



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



Licensed quadrivalent conjugate vaccines

Menactra, Sanofi Pasteur:

- Quadrivalent ACYW conjugate with diphtheria toxoid as carrier protein.
- 4 µg of each polysaccharide-protein conjugate.
- Pre-filled syringe.
- No adjuvant.
- Licensed in US, Canada for 11 to 55 year olds, 2 to 10 year olds for at risk groups.

Menveo, Novartis:

- Quadrivalent conjugate with CRM_{197} as carrier protein
- 5 µg of each of C, Y and w135 and 10 µg of group A polysaccharide.
- Group A portion lyophilised
- No adjuvant.
- Licensed in EU for > 11 years and US & Canada for 11 to 55 years.
- UK Green book, advises Menveo for travellers: infants < 1 year 2 doses, >1 year 1 dose.
- UK Recommendation for asplenics/complement deficient patients forthcoming.

Investigational quadrivalent conjugate vaccines

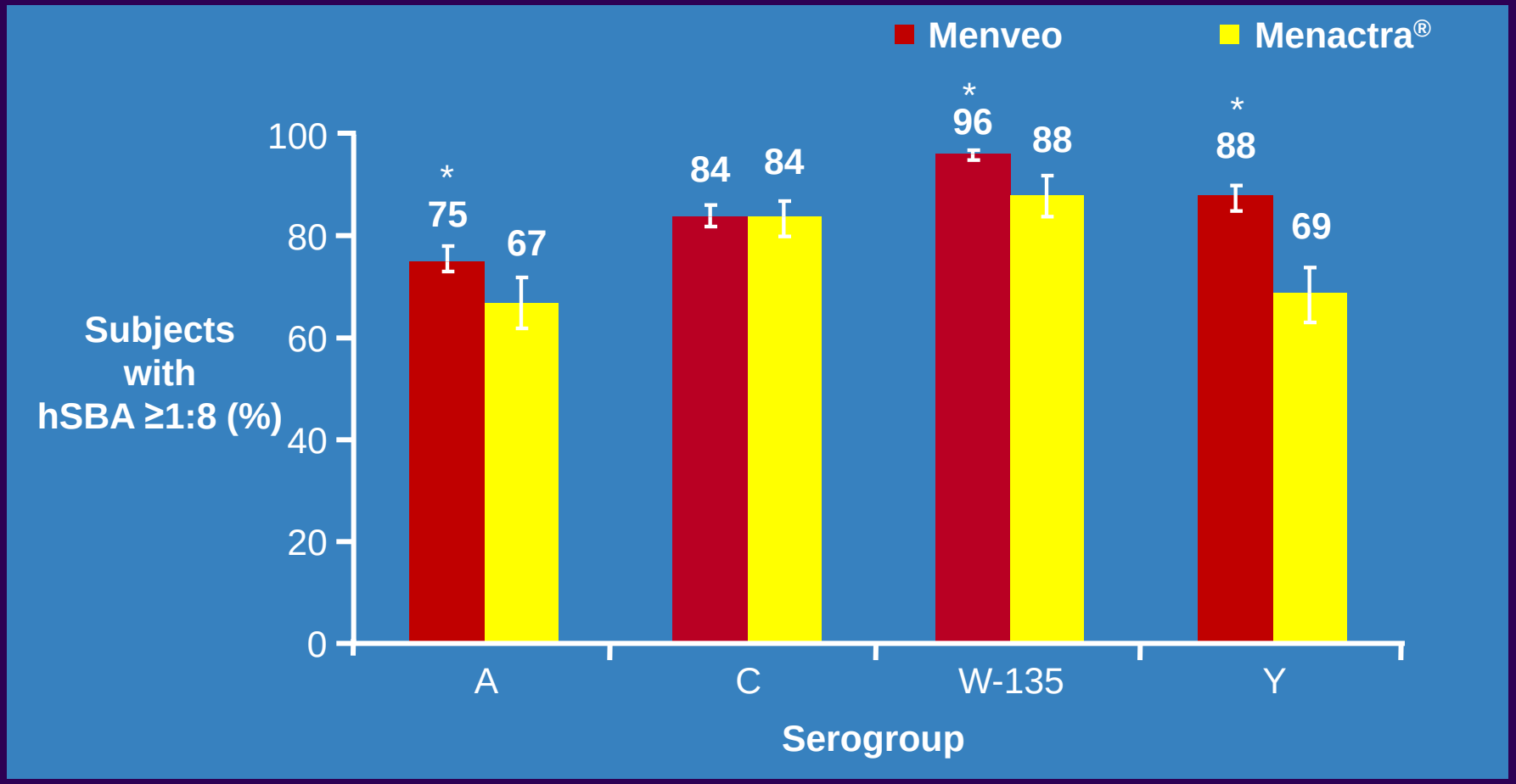
Nimenrix, GSK:

- **Quadrivalent conjugate with TT as carrier protein**
- **Phase III.**

TetraMen-T, Sanofi Pasteur:

- **Quadrivalent ACYW conjugate with TT as carrier protein**
- **Phase 11**

Phase III immunogenicity in adolescents hSBA titers ≥1:8 1 month post-vaccination, Menveo vs. Menactra



*Menveo statistically superior to Menactra®

Laboratory Confirmed Cases of Meningococcal Disease, England & Wales Five Weekly Moving Averages: 1999 to 2010

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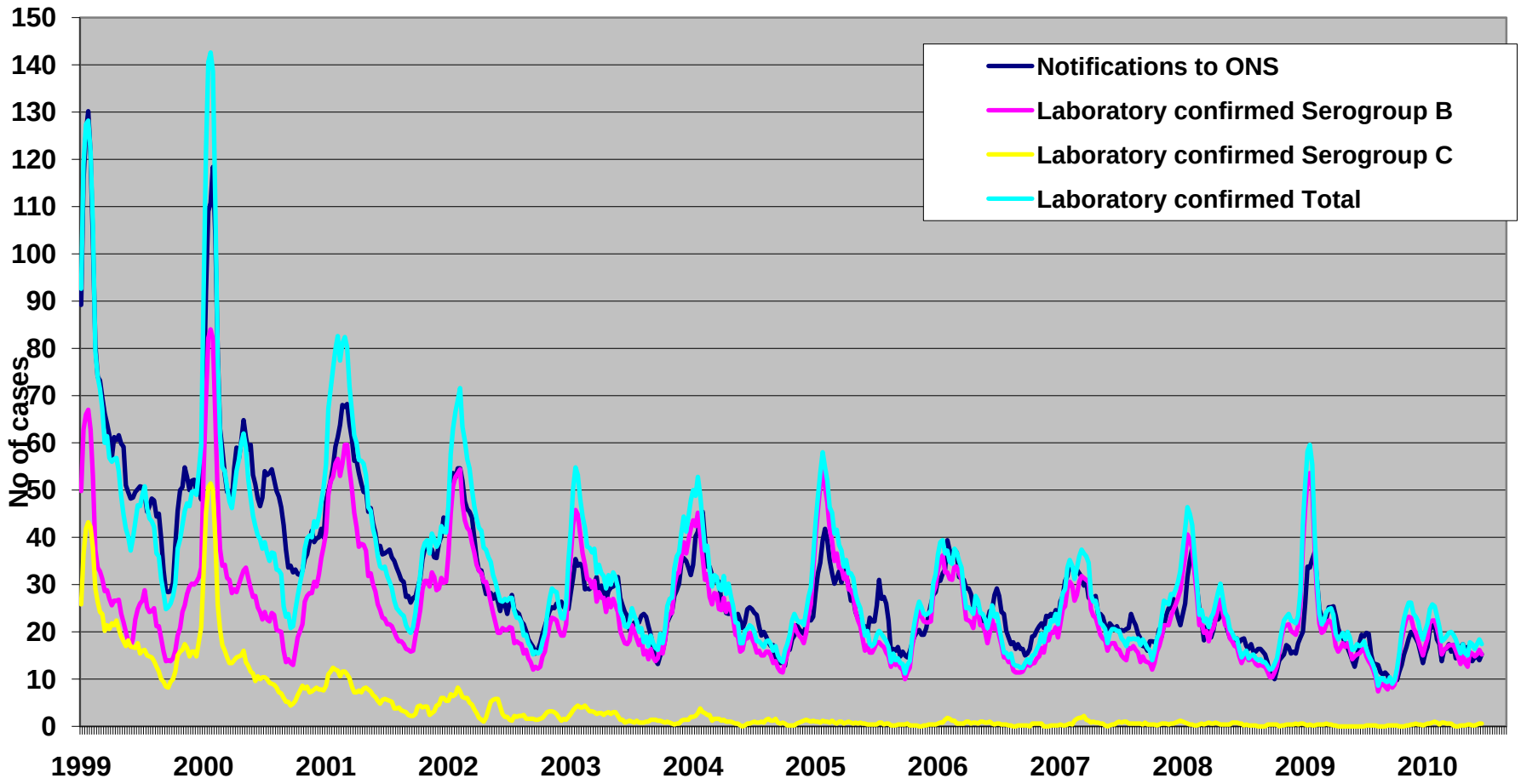

Meningococcal serogroup B vaccines

MenB capsule poorly immunogenic

Immunodominant antigens e.g.Porin A

Diverse

Poorly cross-protective

Solution:

Increase valency?

Alternative antigens?

MenB genome

Factor H (fH) binding protein (fHBP)

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Virulence factor

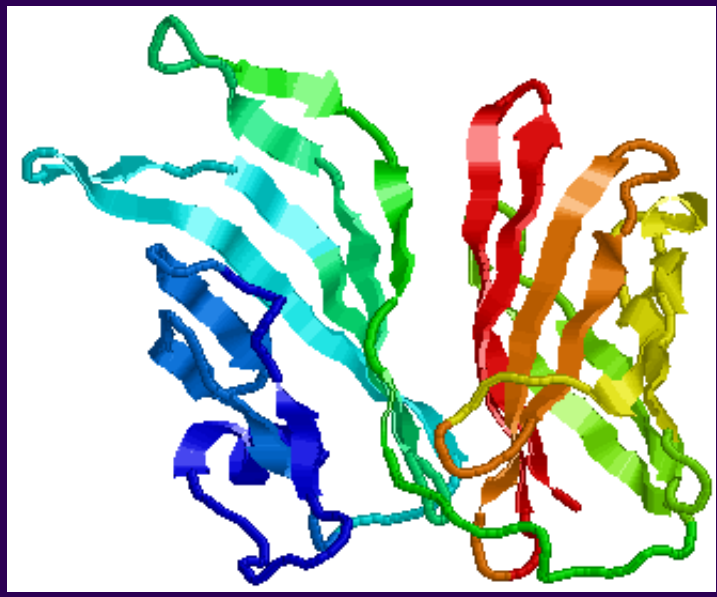
- binds fH→ down regulates alternative complement pathway

3 variant groups:

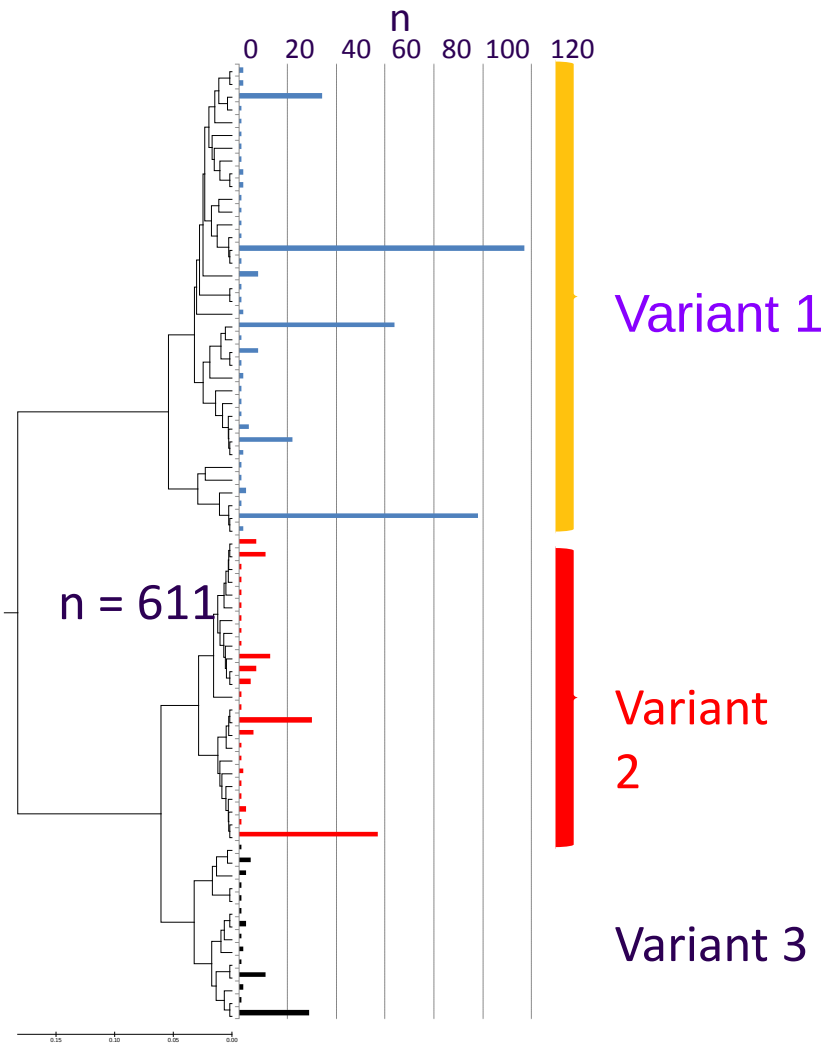
- Variant 1 (family B),
- Variants 2 and 3 (family A).

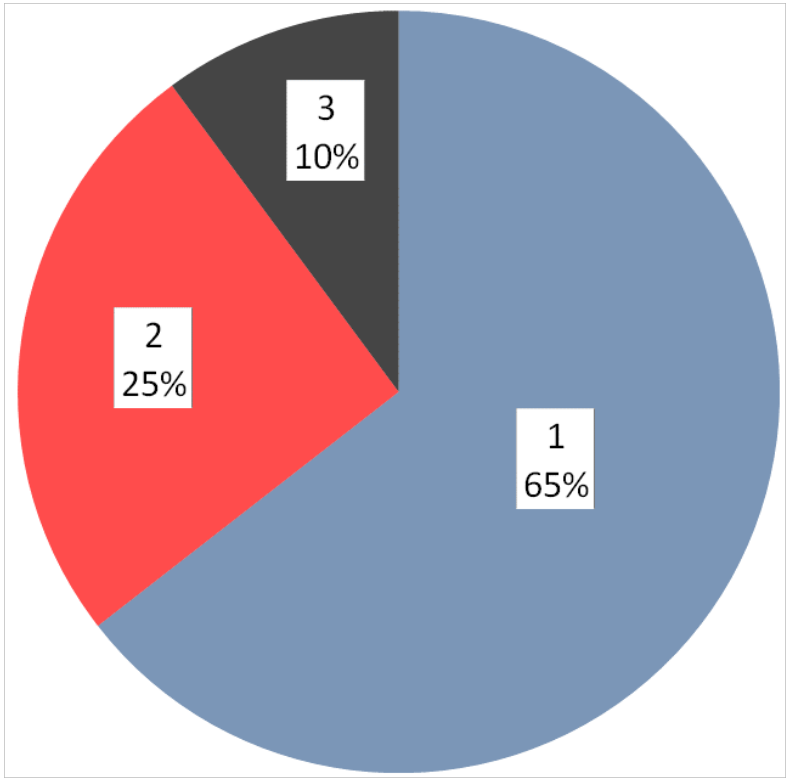
Intra-family cross-reactivity good

inter-family cross reactivity poor.



fHbp sub-variants in meningococcal isolates (all groups) from July 2007 to June 2008 (n = 611) (preliminary data)



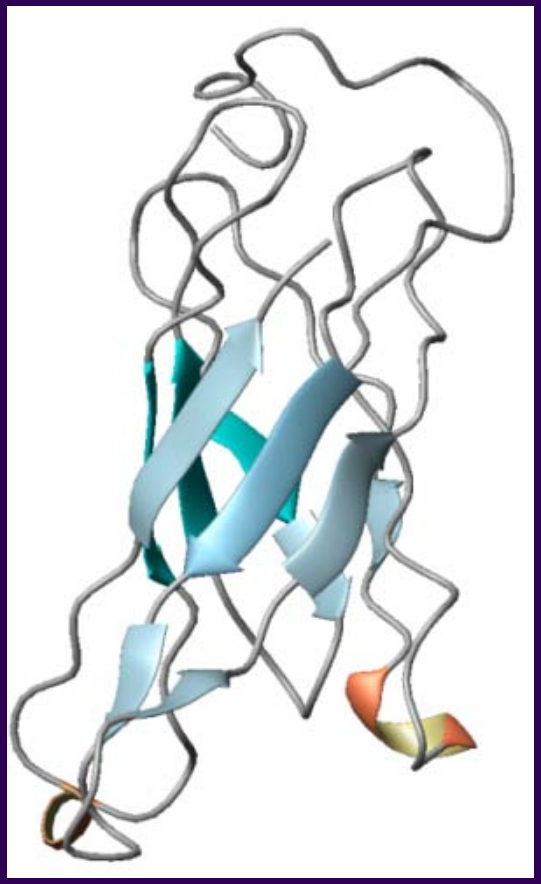


Neisserial heparin binding antigen (NHBA)

Putative virulence factor

- binds heparin → increased serum resistance?

Sub-variants highly cross-reactive



Neisserial adhesin A (NadA)

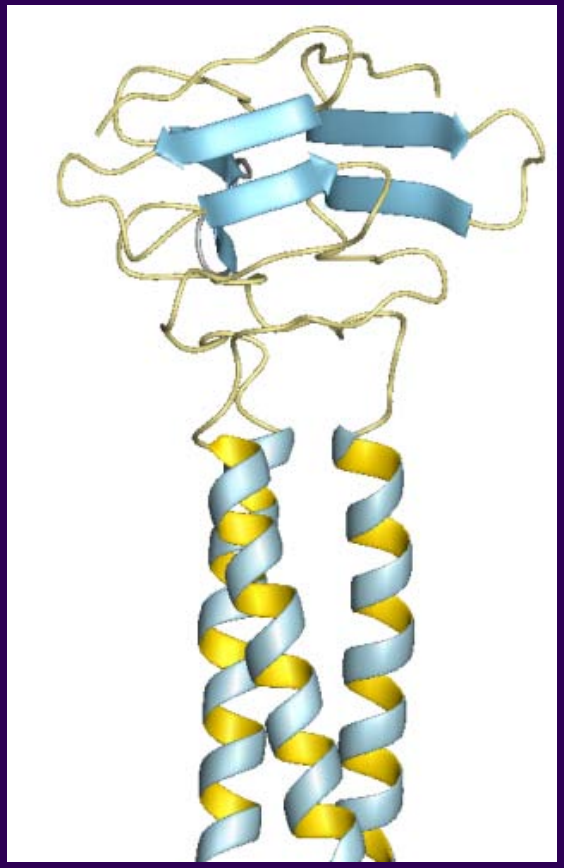
Pathogenicity factor, involved in host cell adhesion and invasion

Five variant groups – variants 1 to 5

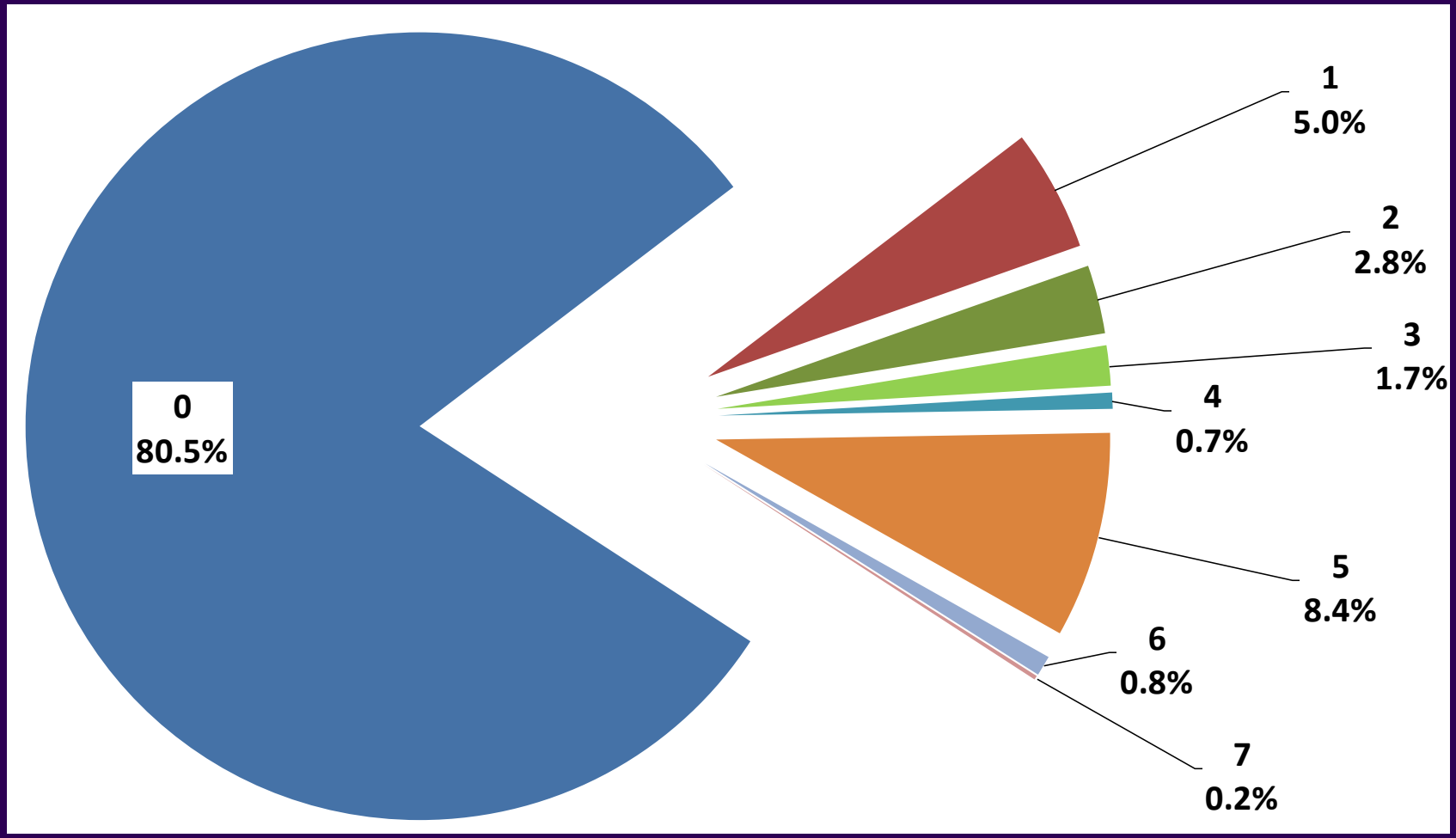
Variants 1, 2 and 3 cross-protective

Variants 4 and 5 don’t cross-react with variants 1, 2 and 3.

Presence ranges from 0% (e.g. cc41/44, cc269) to 100% (e.g. cc32)

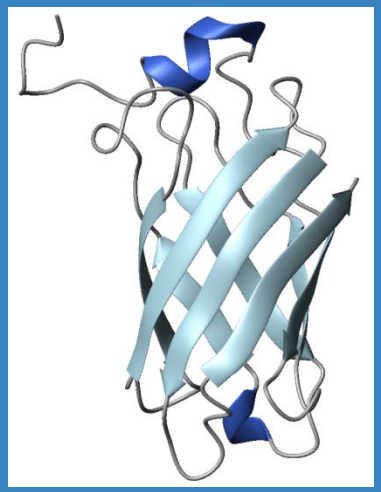


NadA variants among meningococcal isolates (all groups) from July 2007 to June 2008 (n = 604) (Preliminary data)

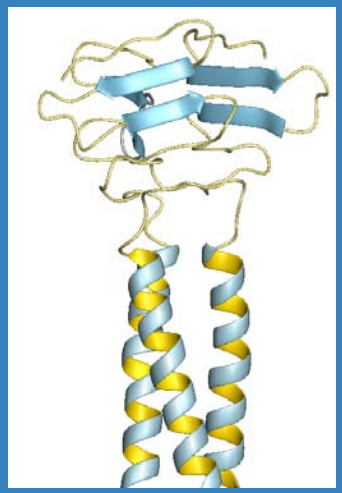


- approx 7% of variant 1 sub-variants contained deletions (half of which resulted in frameshift)
- approx 47% of variant 2 sub-variants contain IS1301 and a further 24% contain various deletions (of which 6% resulted in a frameshift)
- approx 20% of variant 3 subvariants were frameshifted due to a large deletion

Novartis MenB vaccine contains 4 main antigens

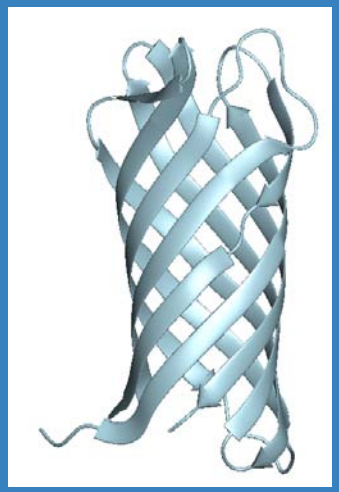


fHBP 1.1



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	-

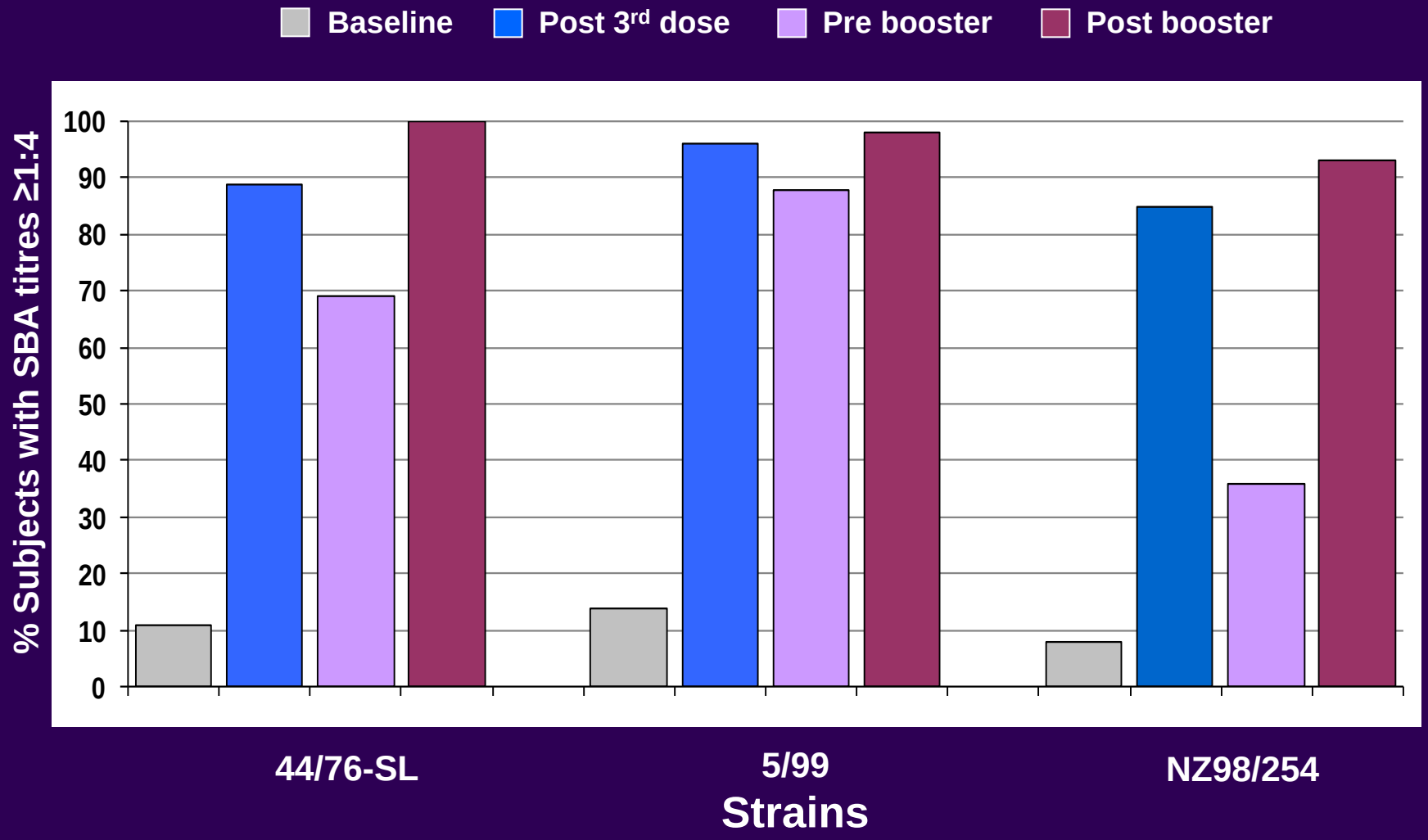
UK infant trial

rMenB vaccine with or without OMV

at 2, 4, 6 and 12 months of age.

Miller E, Pollard AJ, Borrow R, Findlow J, Dawson T, Morant A, John T, Snape M, Southern J, Morris R, Cartwright K, Oster P. 26th Meeting of the European Society for paediatric Infectious diseases – ESPID, Graz, Austria, 14th May 2008

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



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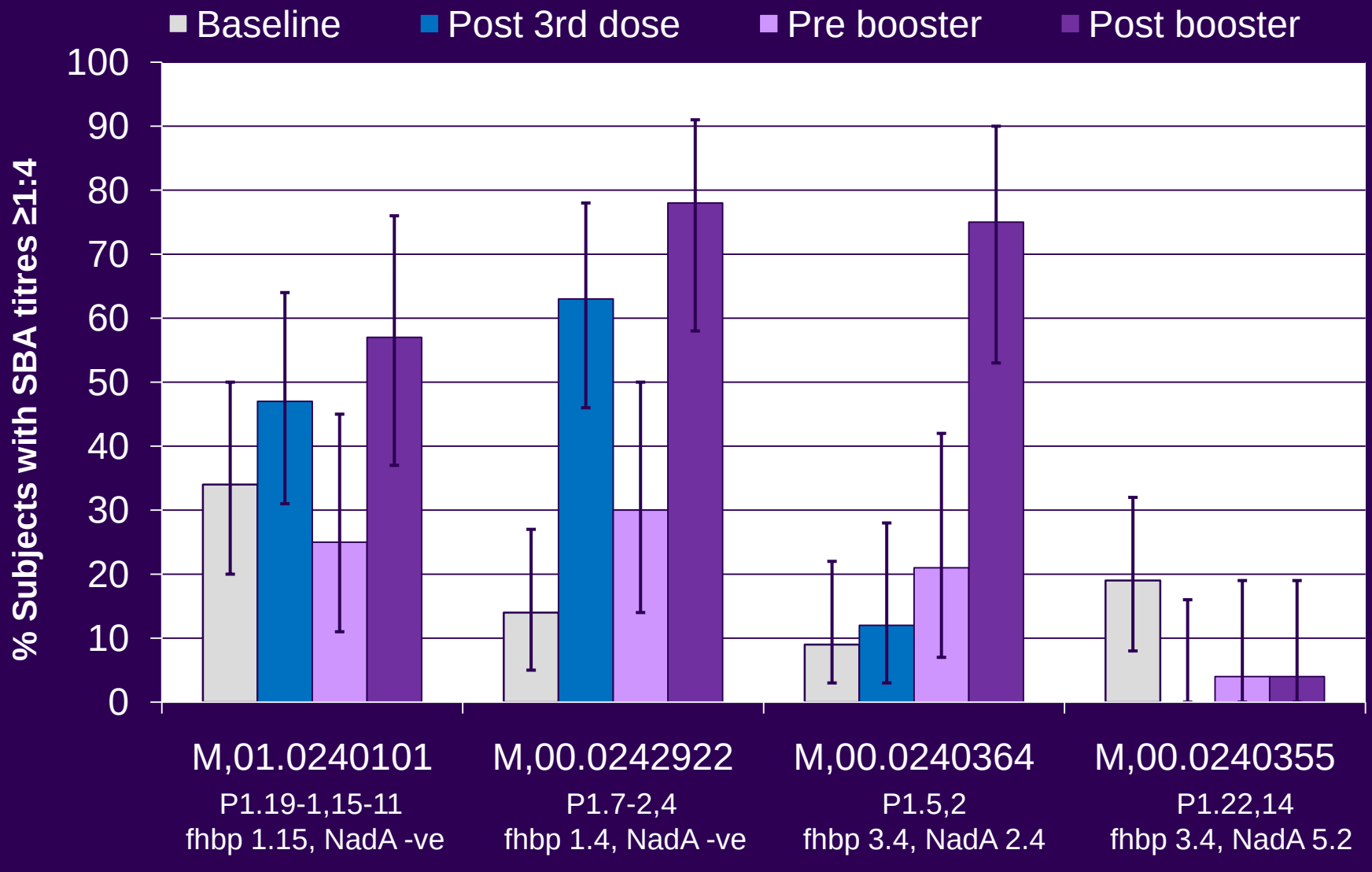


Safety & immunogenicity in dose-ranging and formulation –finding meningococcal B (MenB) vaccine study in 2-month-old infants

Novartis

Estimated enrollment:	1600
Study start date:	July 2009
Estimated study completion date:	September 2011
ClinicalTrials.gov Identifier:	NCT00937521

Arms:

1 Vaccine candidate formulation I
2 Vaccine candidate formulation II
3 Vaccine candidate formulation III
4 Vaccine candidate formulation IV
5 Vaccine candidate formulation V
6 Vaccine candidate formulation VI
7 Control
8 Vaccine candidate formulation I with antipyretic

Pfizer (Wyeth) rLP2086 vaccine

- LP2086 recombinantly expressed in *E. coli* and purified to homogeneity.
- LP2086 = factor H binding protein
- 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).

Pfizer (Wyeth) MenB

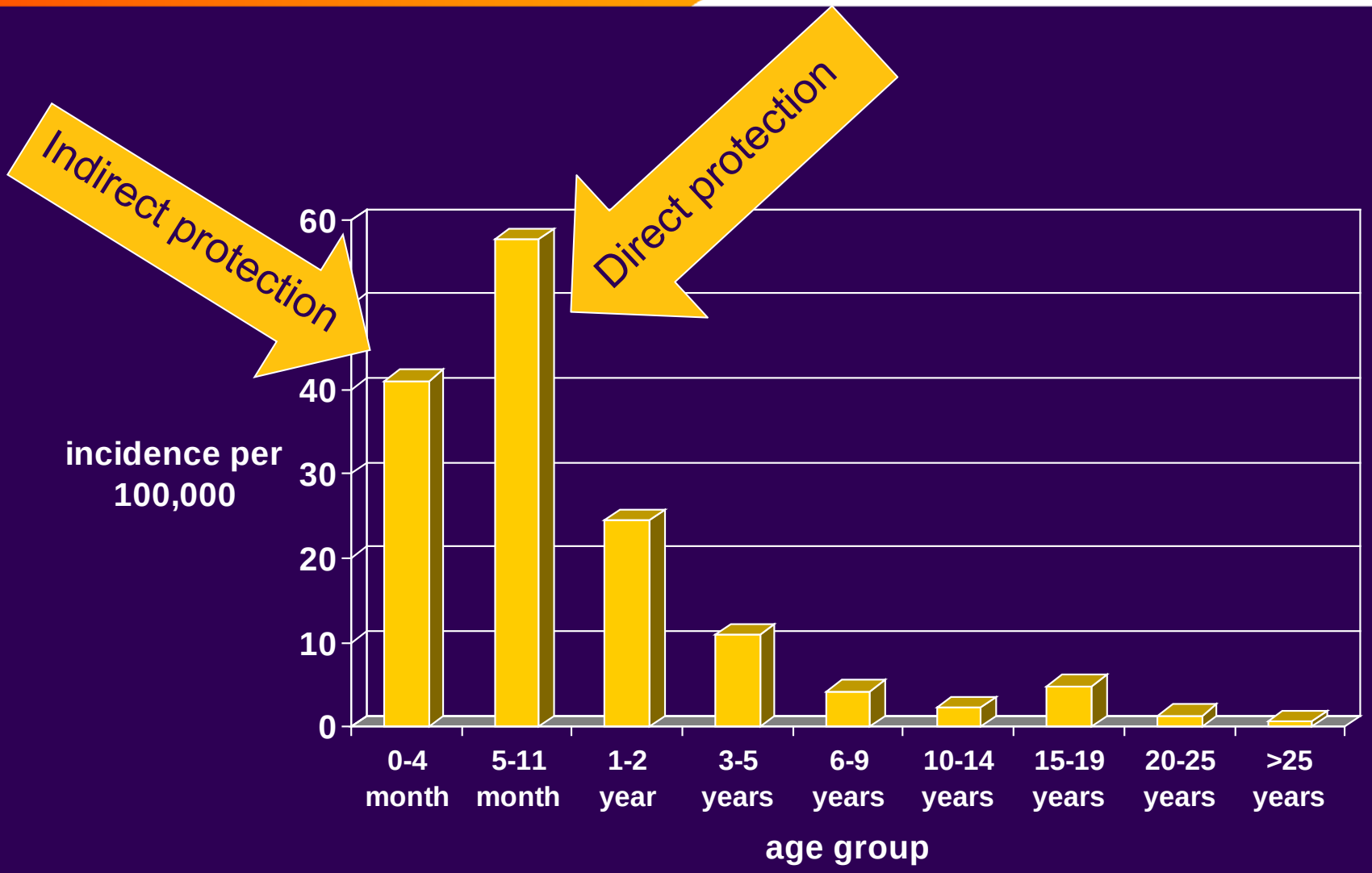
- Encouraging phase 1 trial results
- Vaccine relatively well tolerated.
- Dose-dependent reactogenicity & SBA responses.
- % of responders approaching 100% for some strains, varied by definition of responder, and by strain tested.
- GMTs varied by strain tested, expression critical.
- Moving ahead with Phase 2 studies.
- Study Evaluating Safety, Tolerability, and Immunogenicity of Meningococcal B Vaccine in Healthy Infants, this study is not yet open for participant recruitment. Verified by Wyeth, September 2009.

16th International Pathogenic Neisseria Conference, Sept 2008, Rotterdam, the Netherlands

MenB vaccines the way forward…

- Have determined genotypic coverage.
- Need to determine phenotypic coverage.
- Need to determine optimal schedule.
- Concomitant vaccination/serology.
- Herd immunity?
- Cost effectiveness.

Incidence of MenB disease in England & Wales 2008



Meningitis Vaccine Project Goal

Eliminate epidemic meningitis as a public health problem in Sub-Saharan Africa through the development, testing, licensure, and widespread use of conjugate meningococcal vaccines.

Prequalification clears the way for phased introduction of MenAfriVac™

- MenAfriVac™, a vaccine developed through the Meningitis Vaccine Project (MVP) to protect against life-threatening meningococcal meningitis, today (23rd June 2010) received prequalification from the World Health Organization (WHO).

- The action clears the way for phased introduction of the vaccine in Africa later this year.

Conclusions

- Higher valency pneumococcal now in use.
- Meningococcal C disease still under control in UK.
- Novel meningococcal B vaccines nearing licensure.
- Meningococcal Y cases in UK increasing but quadrivalent vaccines licensed.
- Monovalent group A vaccines for sub-Saharan Africa !