Meningitis vaccines: then, now, the future

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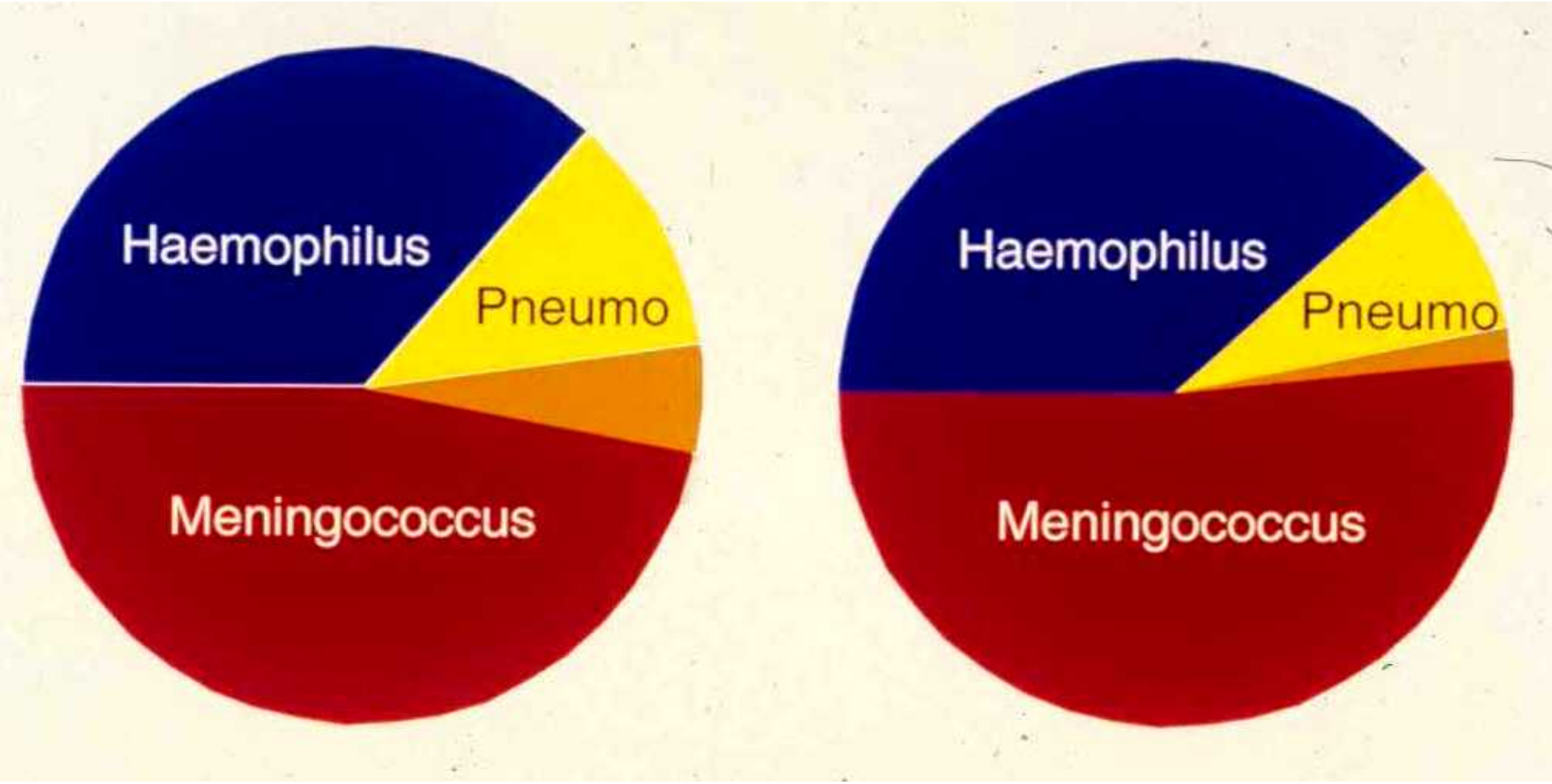
Major invasive bacterial pathogens

- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Streptococcus pneumoniae*

- *Escherichia coli*
- *Streptococcus agalactiae*

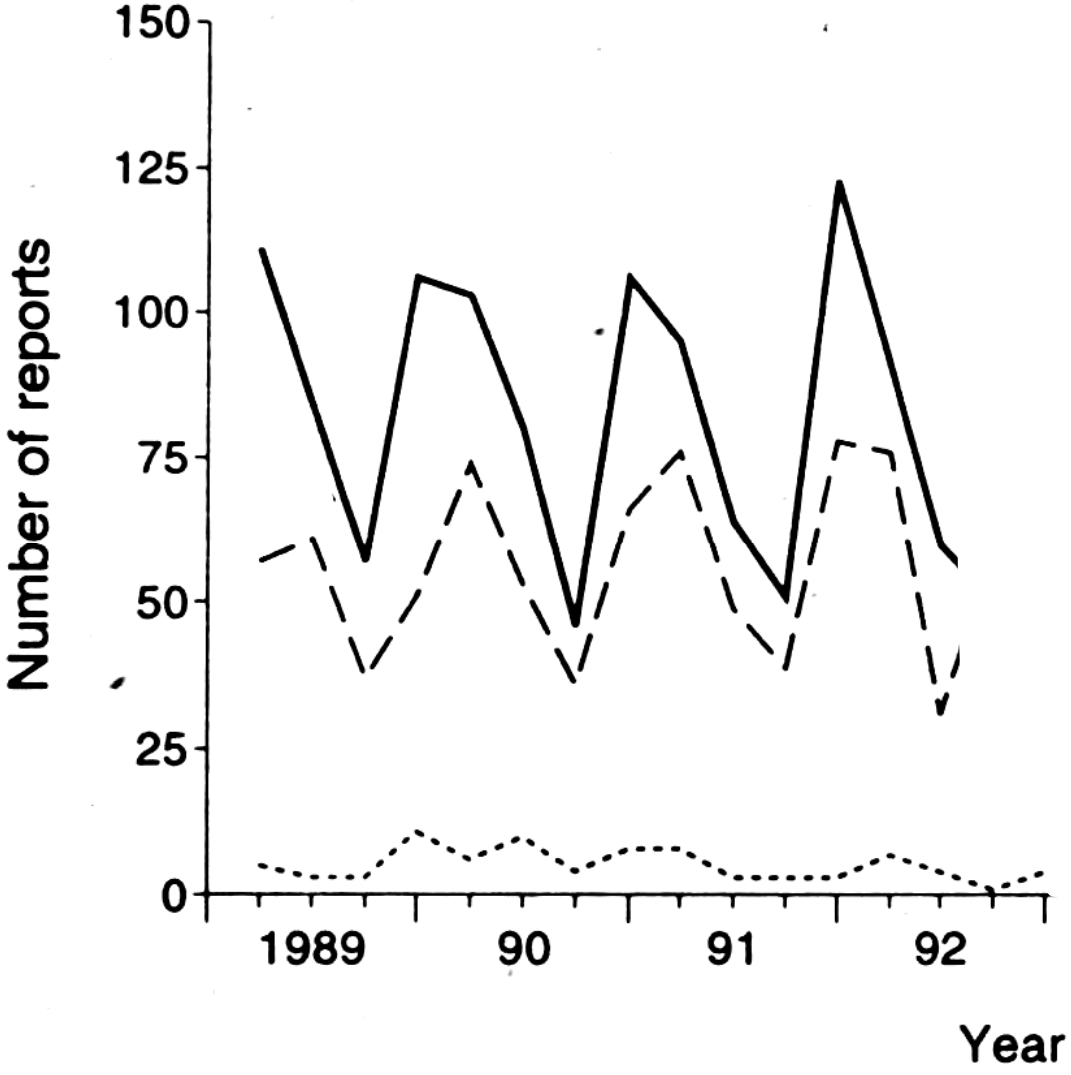
Bacterial meningitis in children aged 1 month - 15 years



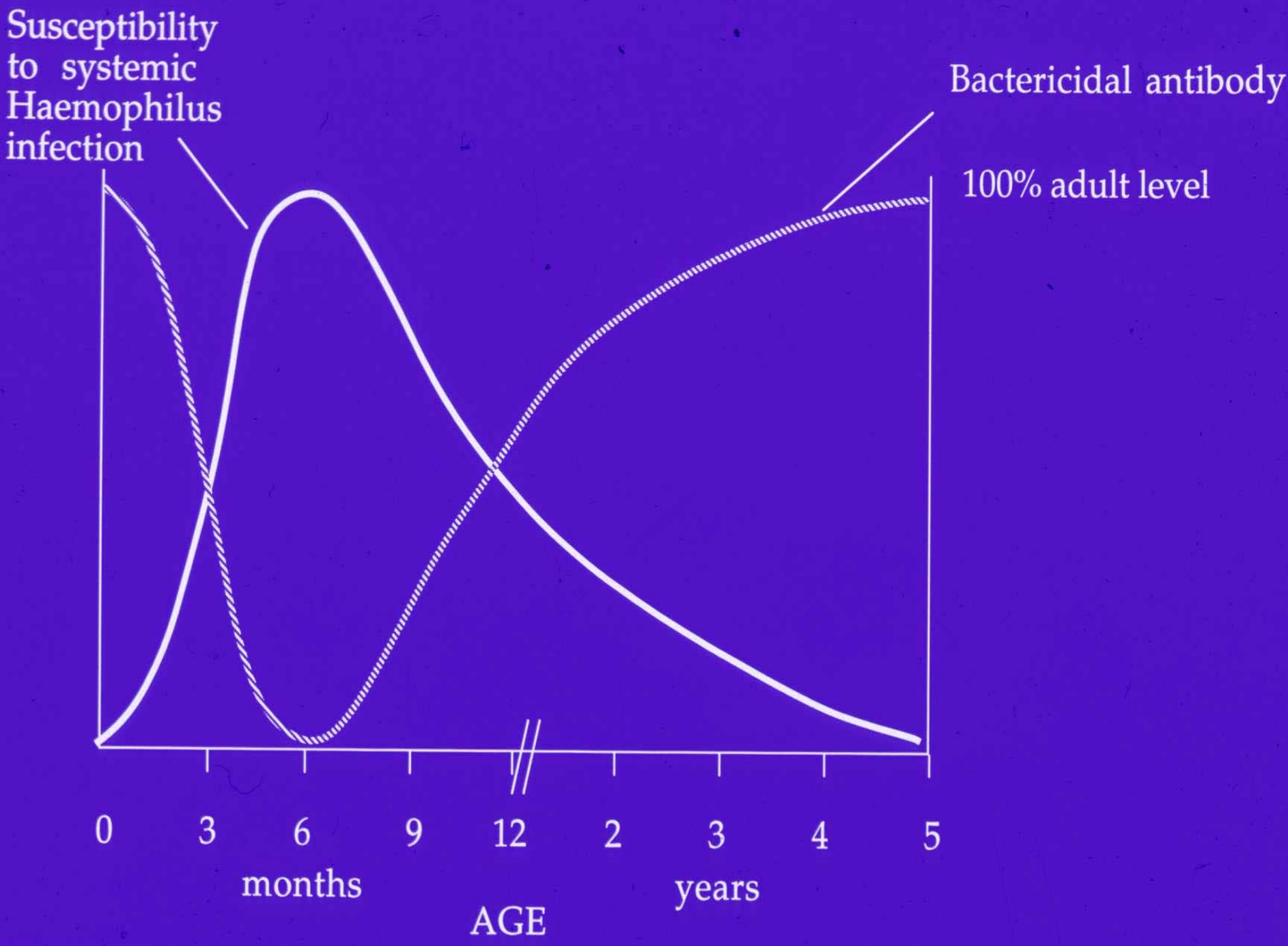
United Kingdom, 1987
Commun. Dis. Report, 1988

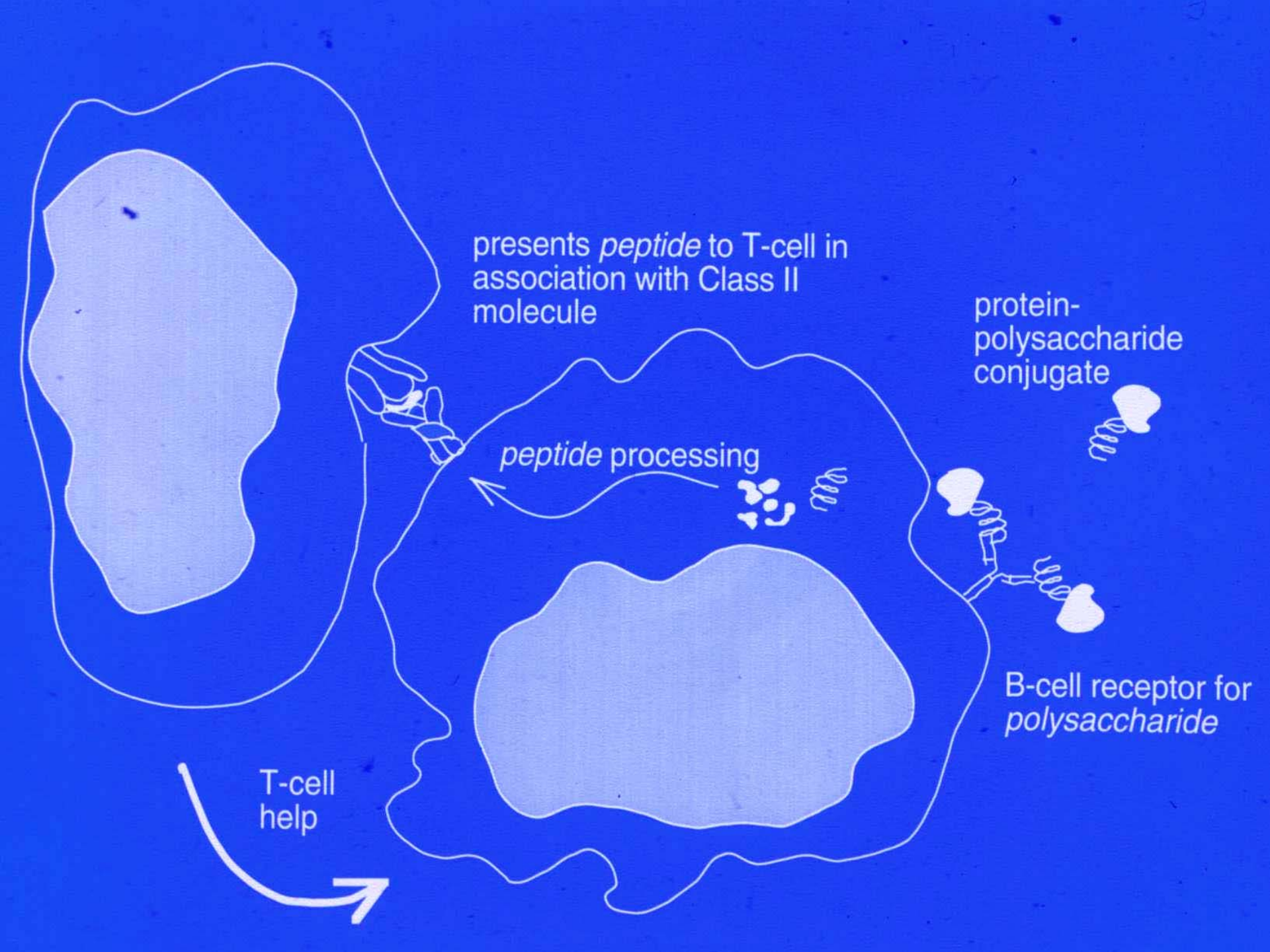
Heifei, China, 1990-2
Yang *et al*., 1996

Cases of *H. influenzae* type b meningitis (quarterly reports)



"sawtooth" pattern with winter peaks of invasive infection


Susceptibility to systemic Haemophilus infection
Bactericidal antibody
100% adult level
0
3
6
9
12
2
3
4
5
months
years
AGE


presents *peptide* to T-cell in association with Class II molecule
protein-polysaccharide conjugate
peptide processing
B-cell receptor for *polysaccharide*
T-cell help

Haemophilus meningitis in the UK
introduction of Hib-conjugate vaccine

- 1989 1259 cases reported

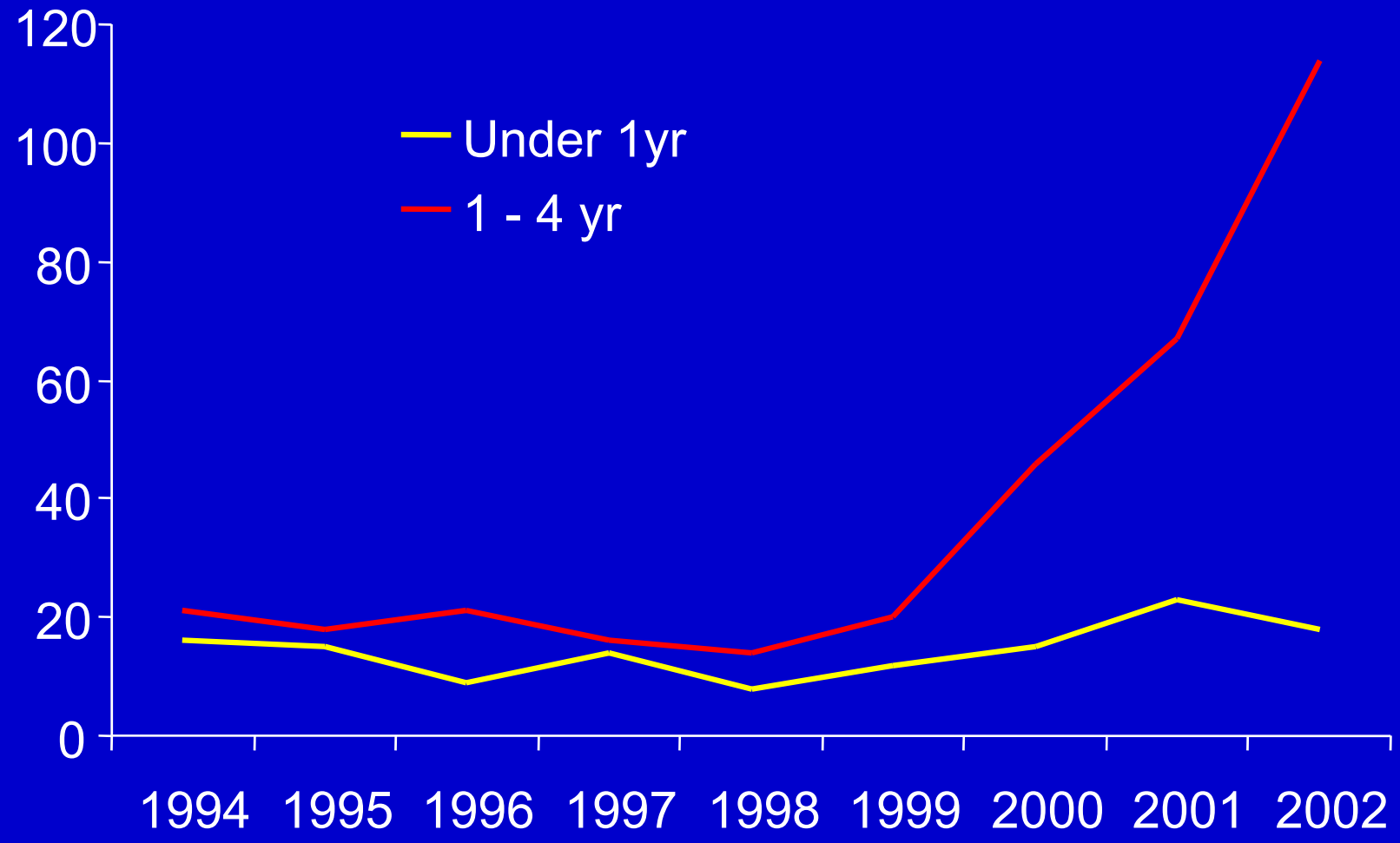
from October 1992

- Routine infant vaccination at 2/3/4 m
- Catch-up vaccination of all children < 4 y
- No booster

- 1996 46 cases reported

- 96% efficacy

Haemophilus returns …



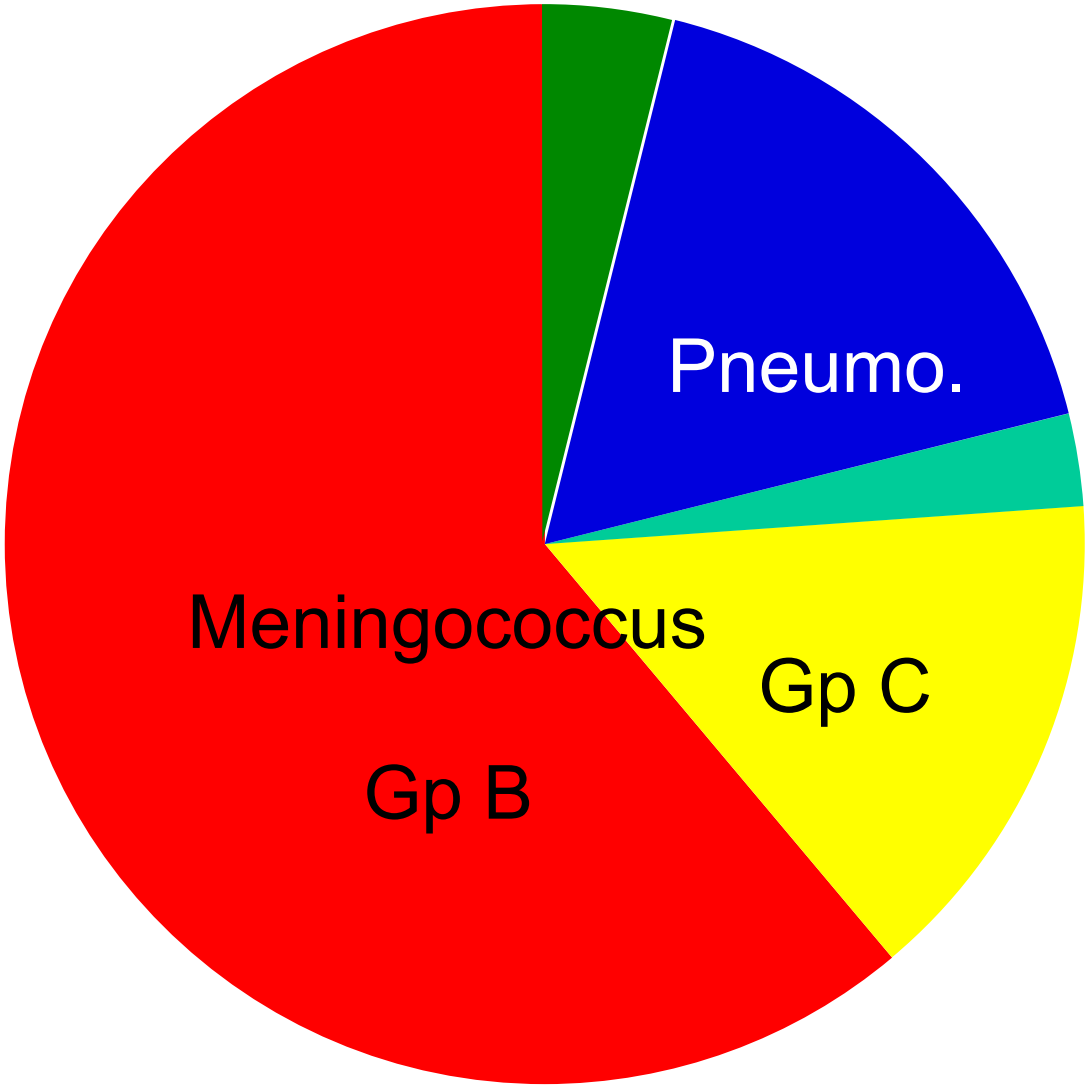
England & Wales, HPA C.f.I data

Fall in effectiveness of Hib vaccination ACTION

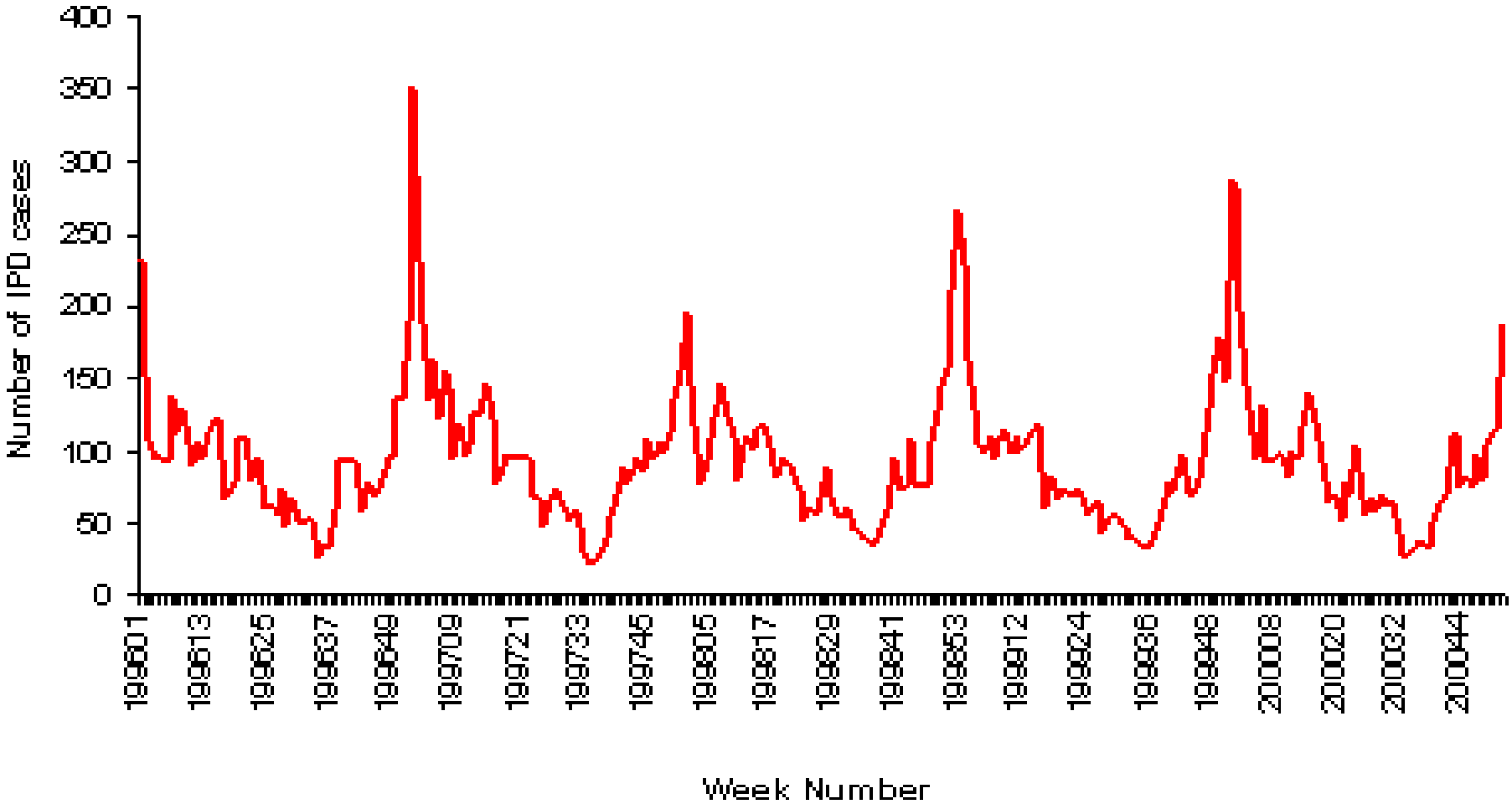
- 2003:
  "catch up" reinforcing dose of Hib vaccine to all children aged between 1 and 4 years old.

- From Sept 2006:
  routine reinforcing booster with Menitorix at 1 year of age.

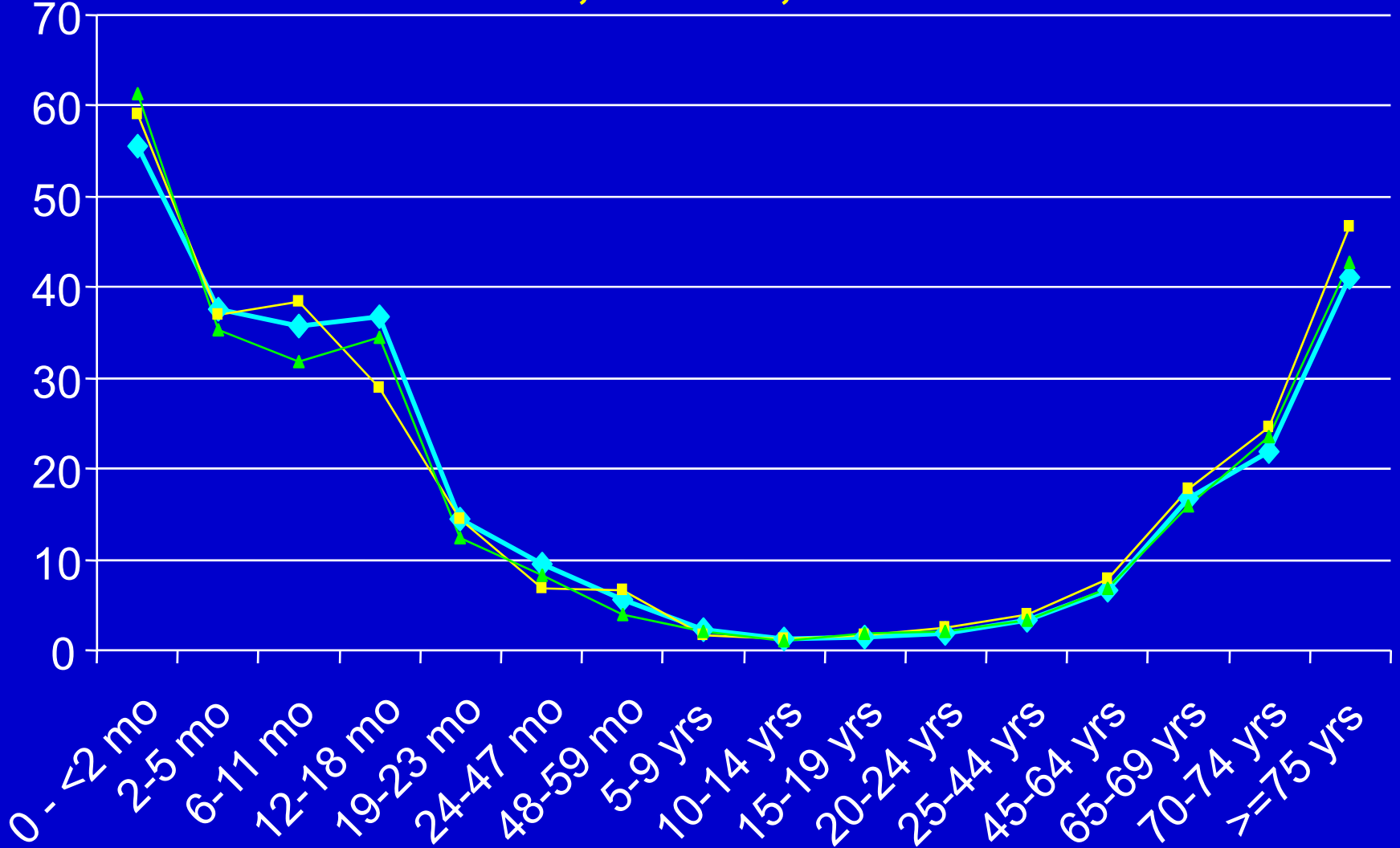
Post-neonatal bacterial meningitis in the UK 1995



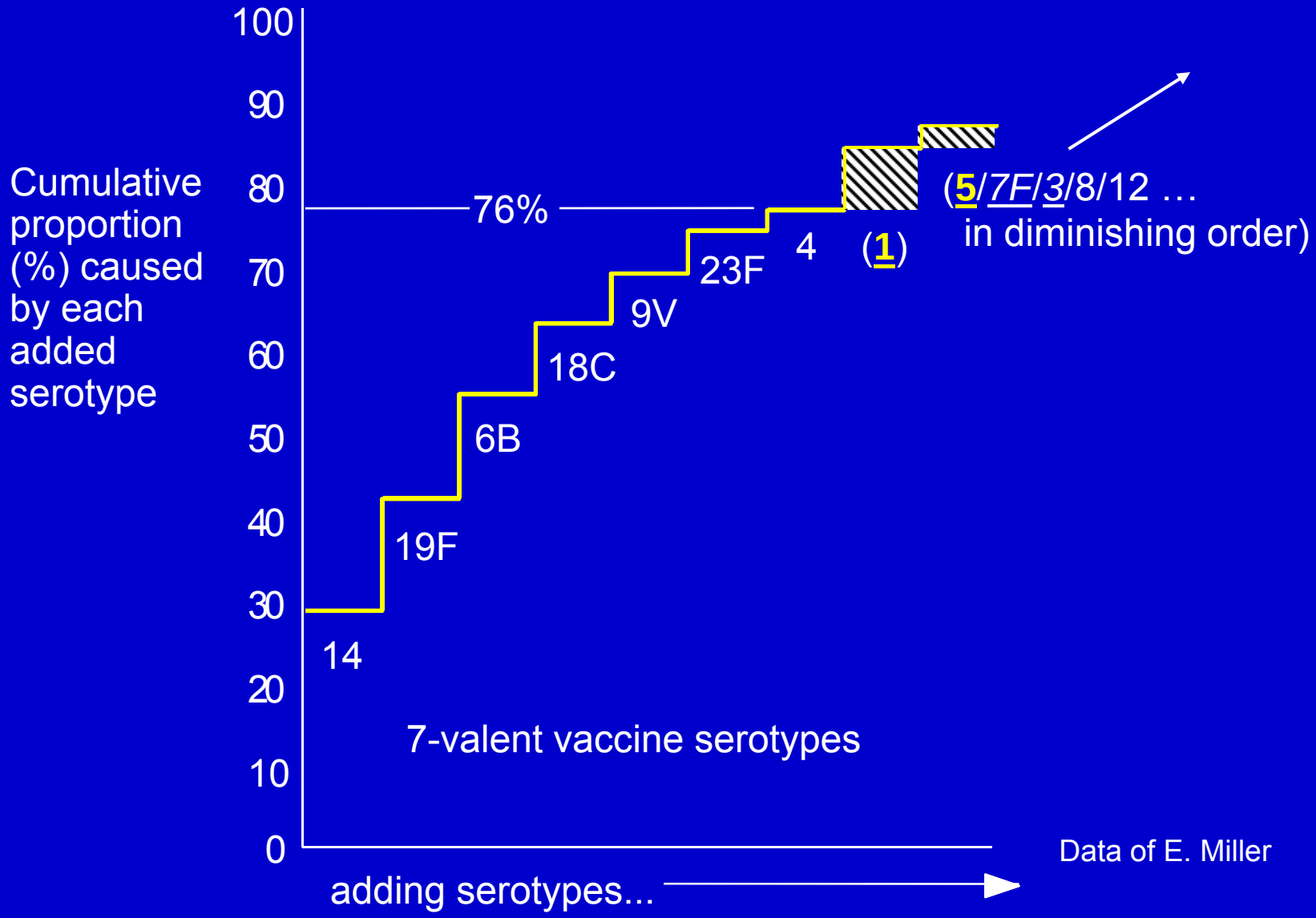
Weekly number of invasive pneumococcal disease (IPD) cases, England and Wales 1996-2000



Invasive pneumococcal infection, E&W, incidence per 100,000 by age group: 1996, 1997, 1998



Pneumococcal serotypes from cases of invasive disease children aged 0-14 y, E&W, 1996-8



Pneumococcal conjugate vaccines

- aimed initially at children, especially ≤ 2 yrs
- seeking to prevent invasive infection, pneumonia and otitis media

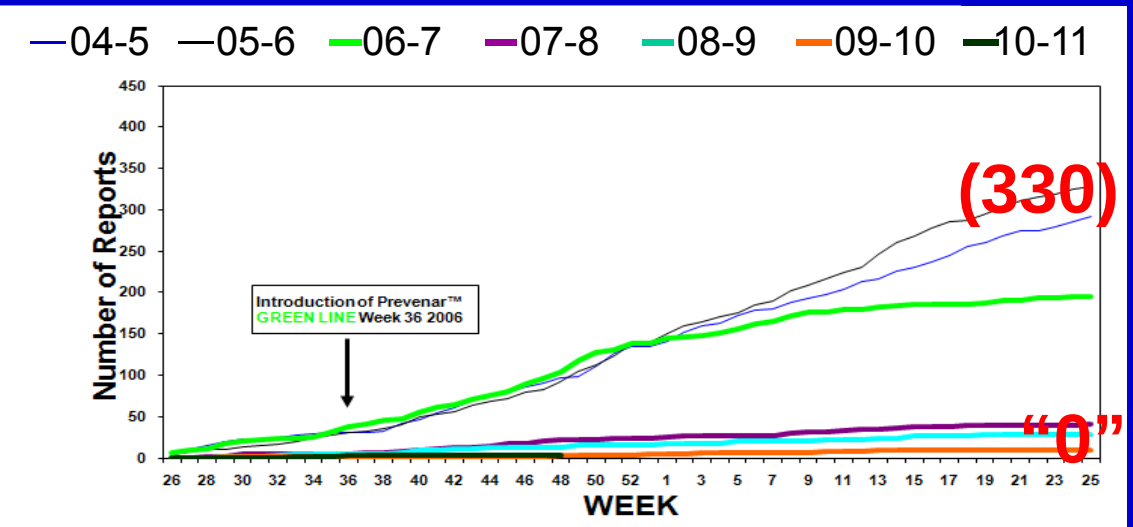
- Coverage depends on:
  - strains responsible for disease in the community
  - complexity of vaccine composition

Conjugate pneumococcal vaccine in UK – April 2006

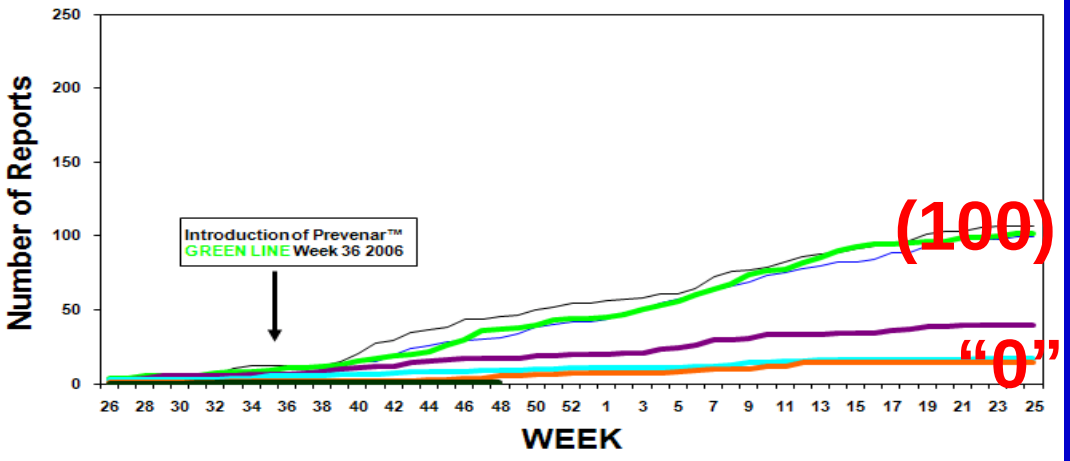
- Prevenar7 introduced into the UK primary schedule (USA since 1999).
- Serotypes 4, 6B, 9V, 14, 18C, 19F, 23F
- 2m, 4m + reinforcing dose at 13m.
- anticipated 76% coverage (96-98 data).

Invasive pneumococcal disease (E&W) due to any of the seven serotypes in Prevenar7

cumulative weekly reports



under 2 years old



2 – 4 years old

UK impact of Prevenar7, 2008-10

- Very substantial reduction in invasive infections caused by vaccine types . . .
- . . . BUT significant increase in 7F, 19A, 22F
- . . . AS WELL AS natural secular trends with other non-vaccine serotypes : 1, 8, 9N
- 19A increase *not* associated with antimicrobial resistance

Conjugate pneumococcal vaccine in UK – September 2010

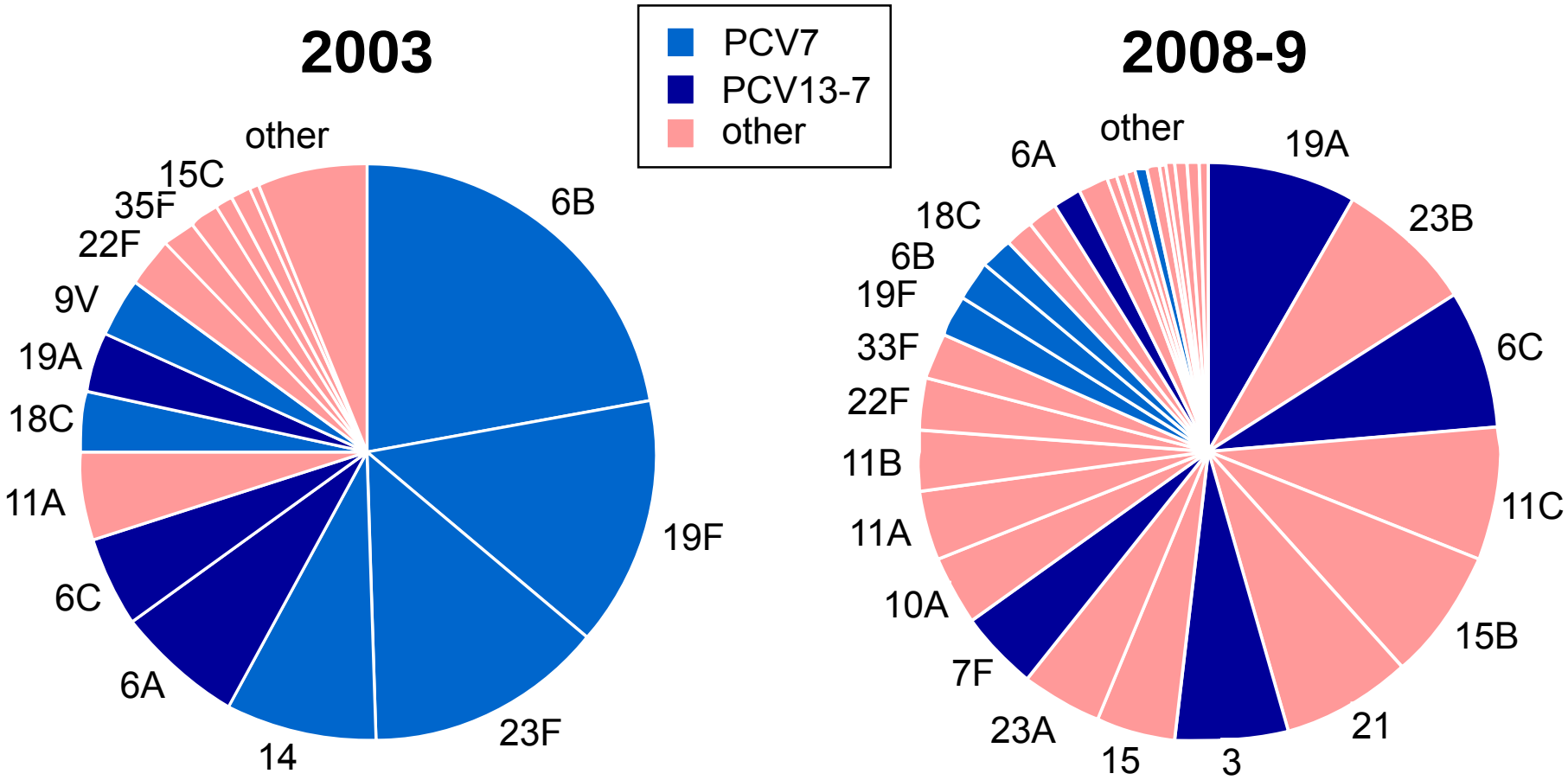
- Prevenar13

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

  - In England and Wales in 2009/10 the 6 additional serotypes accounted for:
  - 67% invasive pneumococcal disease in <5Y
  - 52% in 5-64Y
  - 45% in ≥ 65y

Serotype distribution in **carried pneumococci** pre- and post-PCV7 introduction: *HPA C.f.I. data*

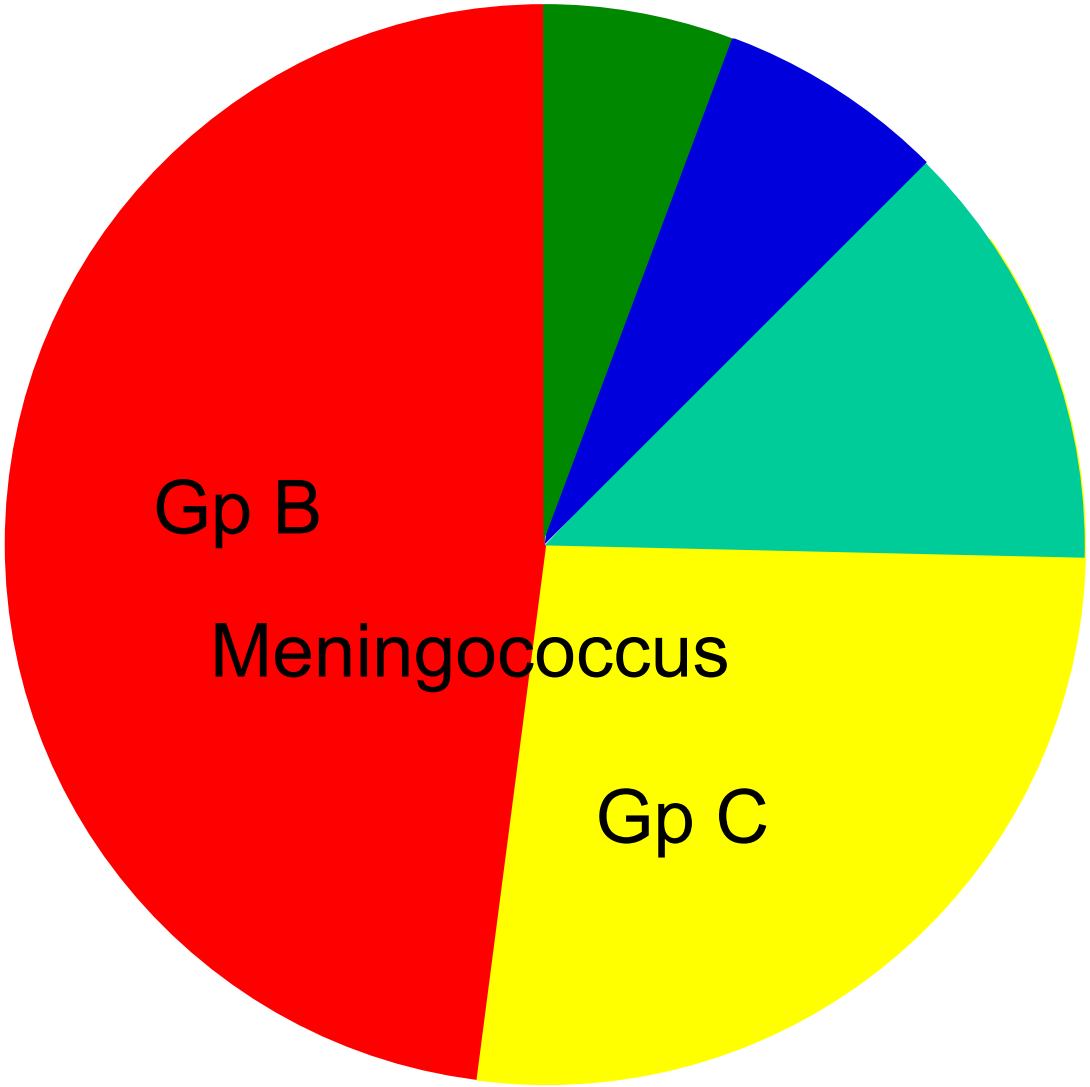
carriage rates ~50% in <5s



& currently causing invasive infection but not detected in carriage . . .

1, 8 , 12F, 20, 16F, 15C, 5, 15A

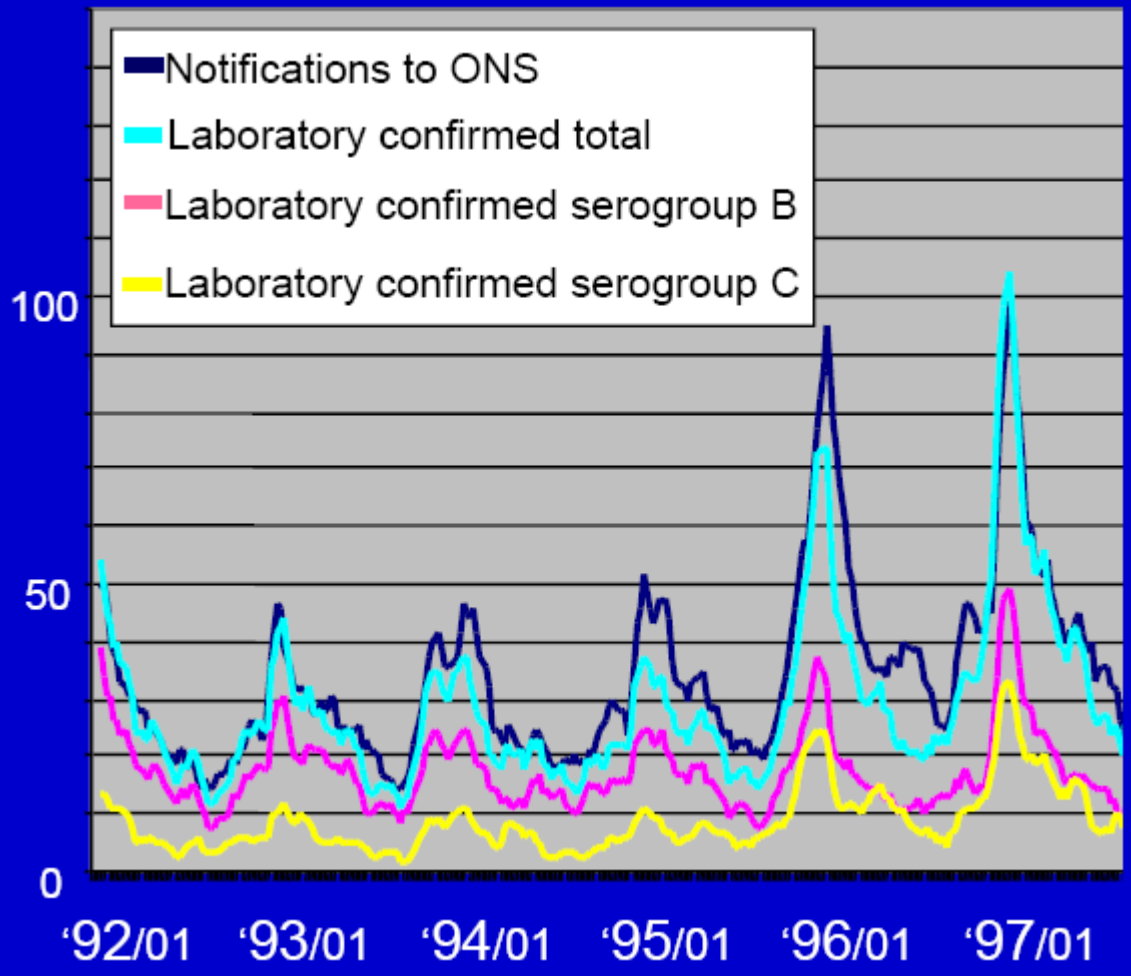
Bacterial meningitis in the UK, after PnC vaccine



Cases of Meningococcal Disease

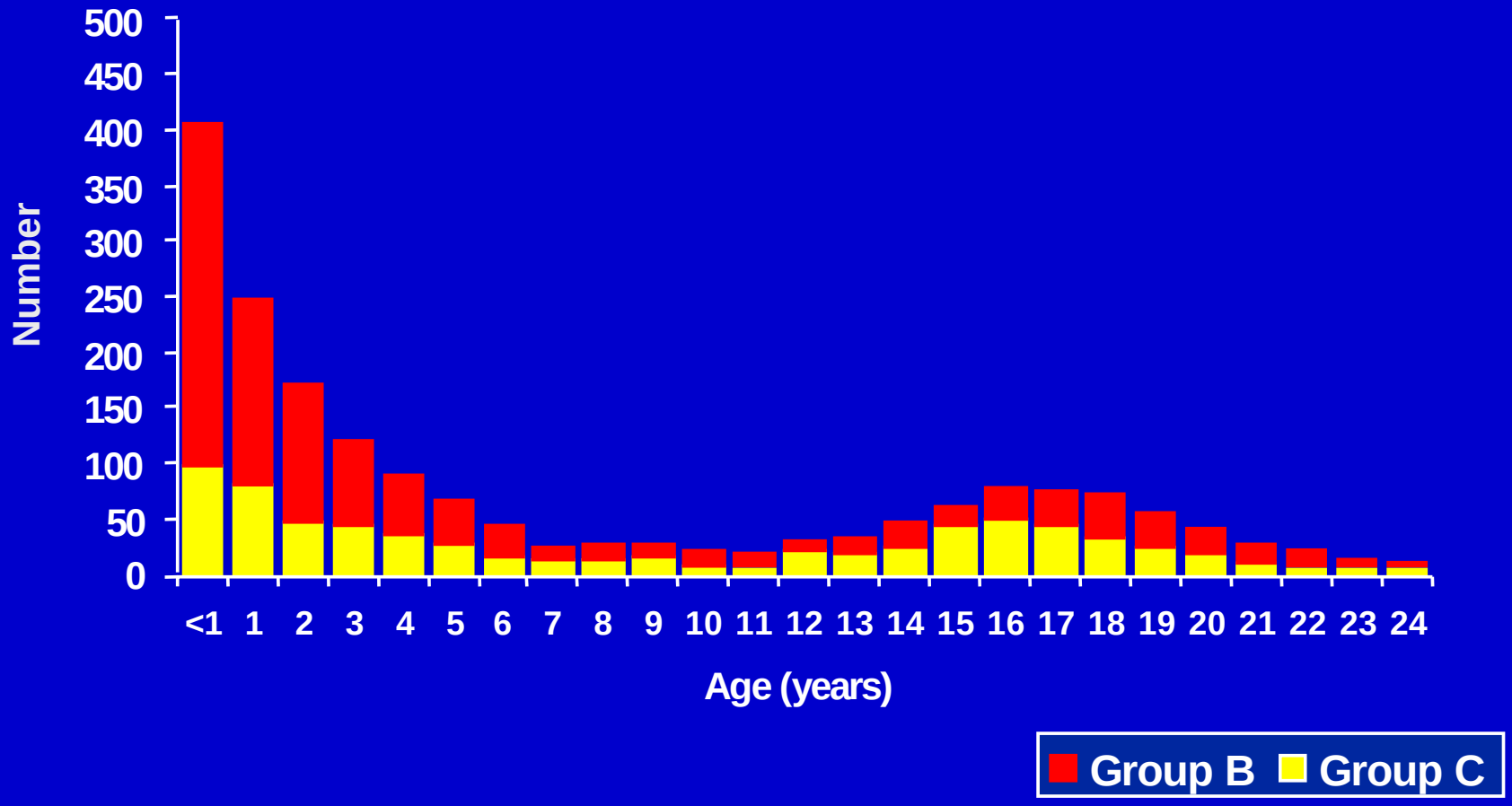
England & Wales - 5-weekly moving averages

1992 to 1997



Meningococcal disease by age

Isolates referred to PHLS, 1998/9

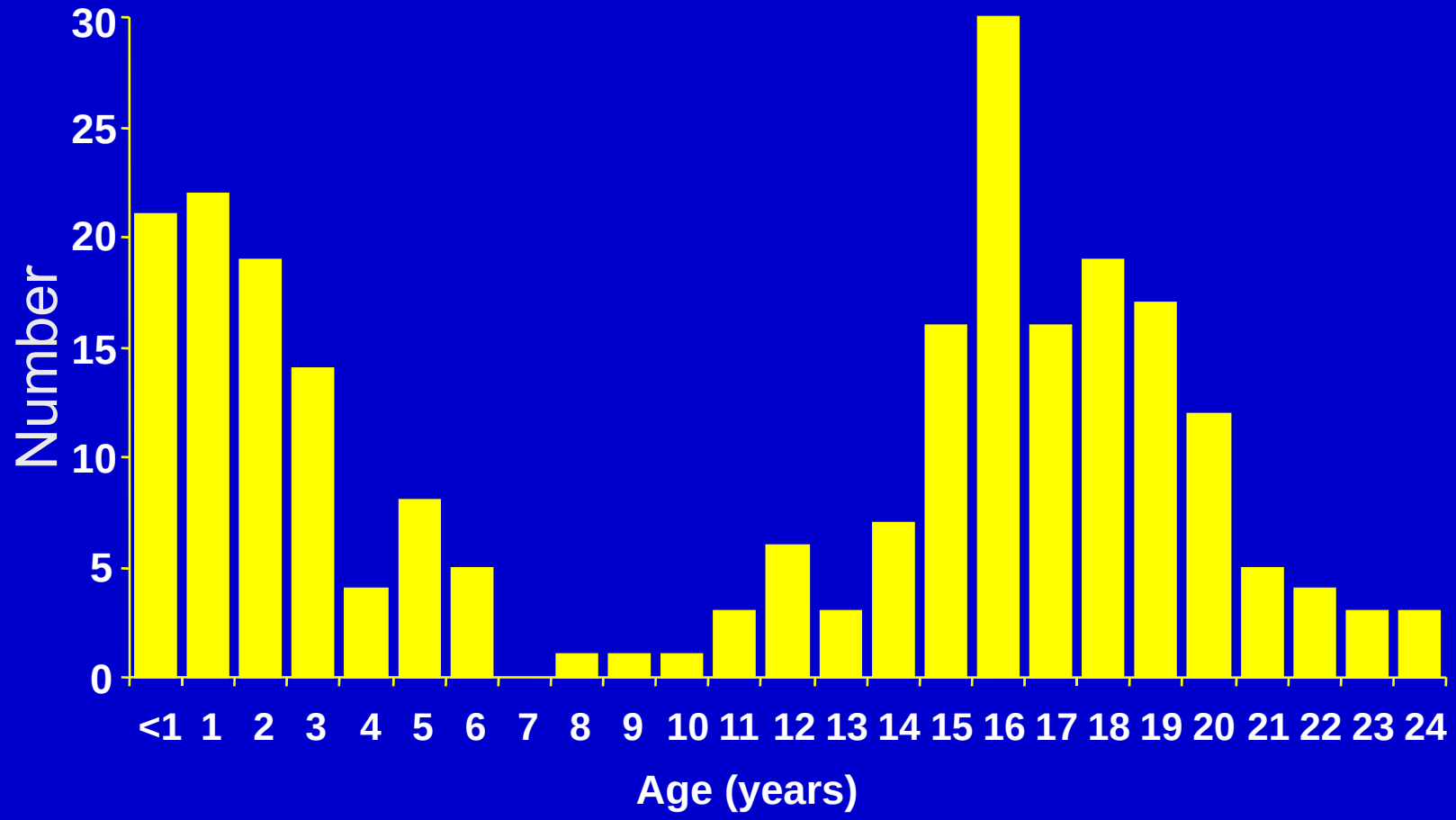


Serogroup C meningococcal infection by age

Isolates referred to PHLS, 1998/9

Serogroup C meningococcal deaths by age

Isolates referred to PHLS, 1994/5 - 1998/9



Implementation of Group C meningococcal vaccination in the UK, November 1999 -

Serogroup C polysaccharide-protein conjugate vaccines from three manufacturers (Wyeth, Chiron, Baxter).

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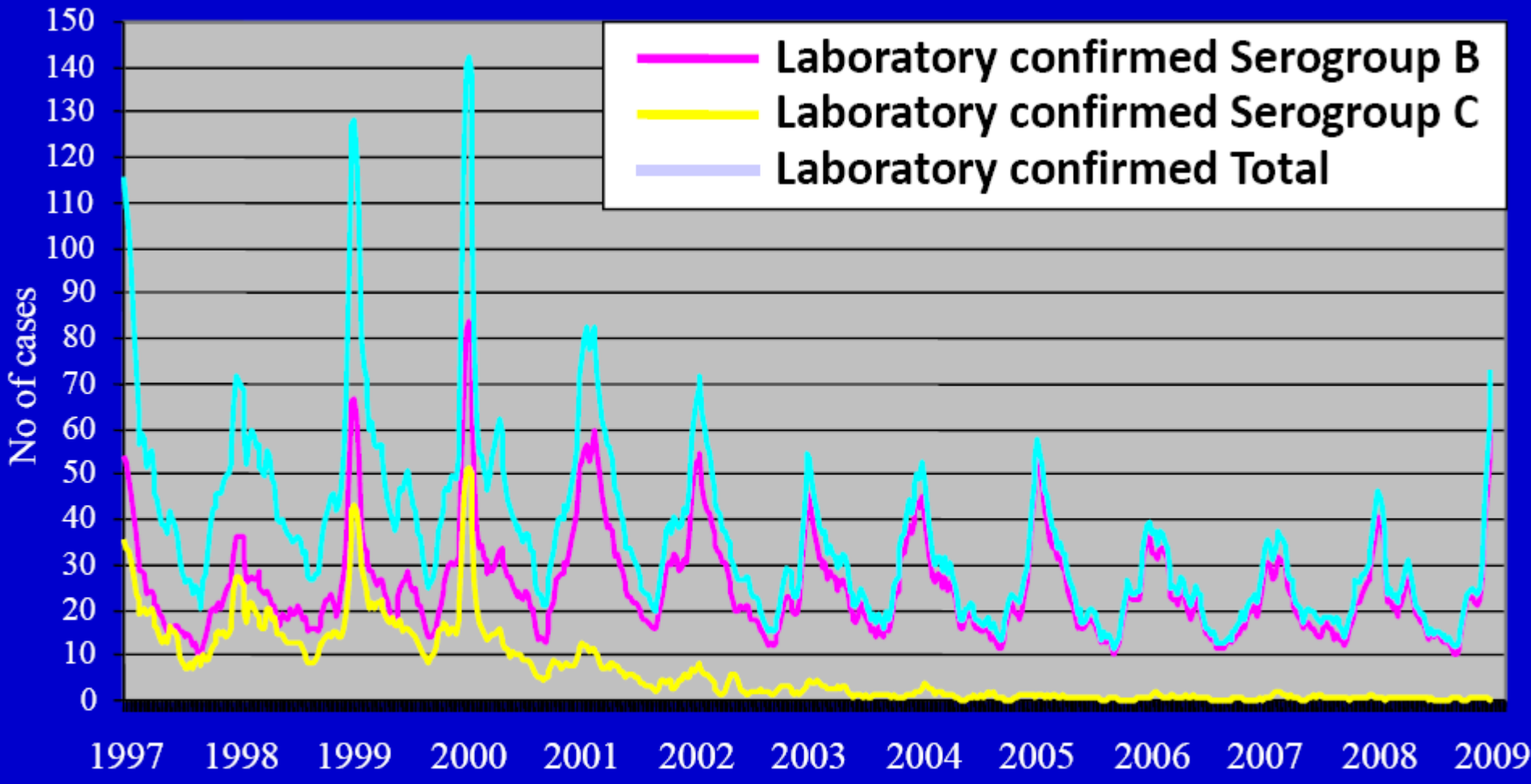
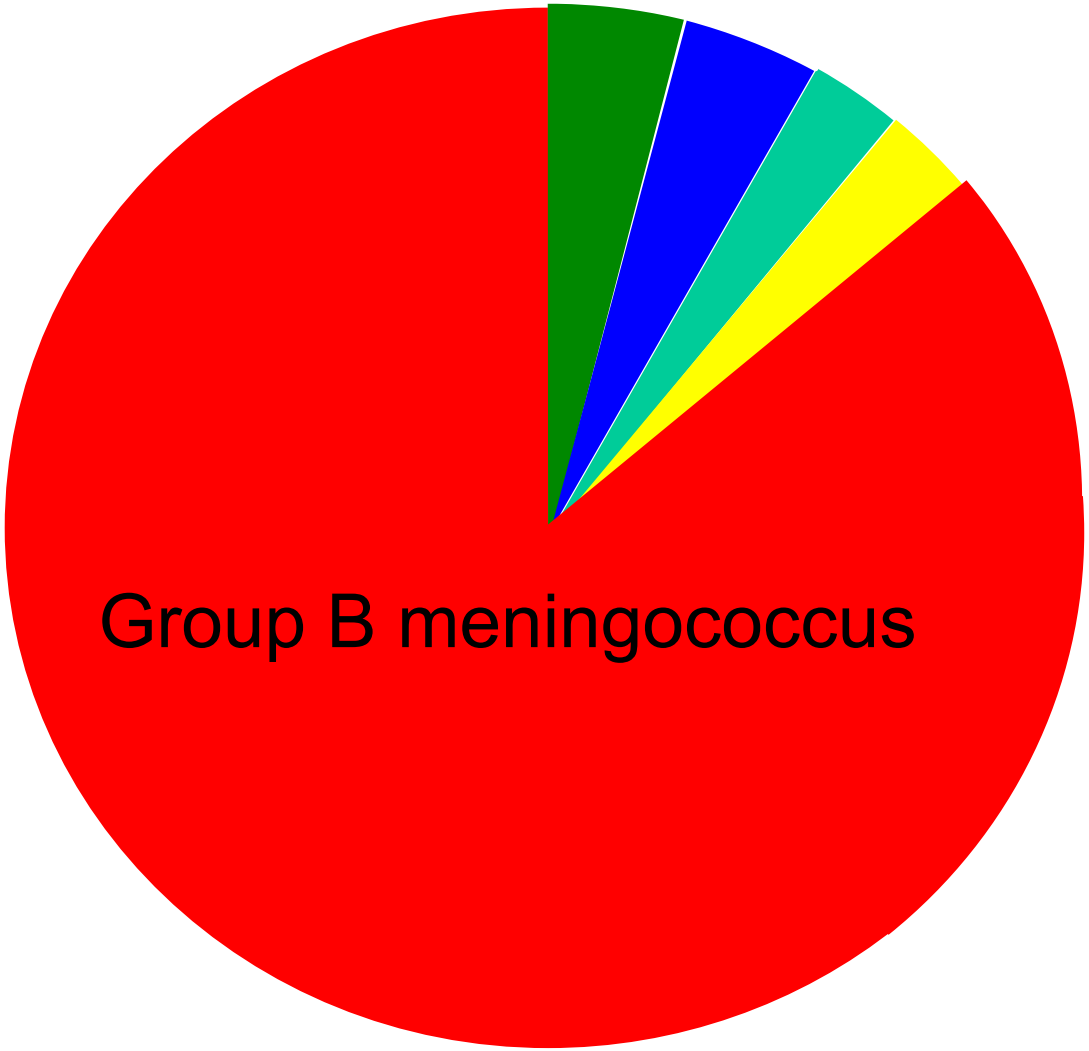
early Nov 1999	15-19 year olds (single dose)
late Nov 1999	infants (multiple doses)
Jan 2000 -	10-14, 1-4, 5-9 (single dose)

Laboratory Confirmed Cases of Meningococcal Disease England & Wales, 5-weekly moving averages, to 07/01/09



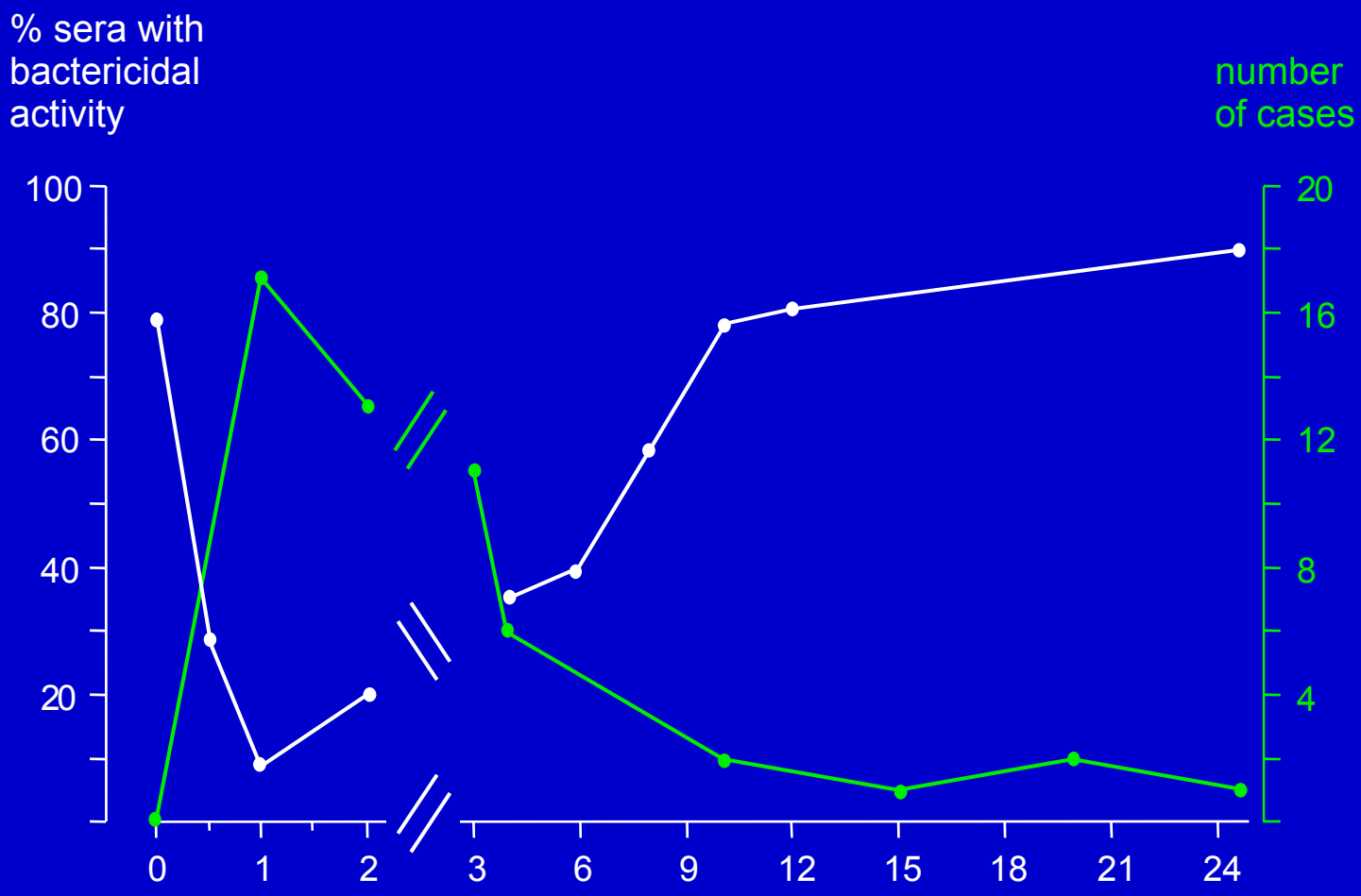
Meningococcal Reference Unit, Health Protection Agency

Bacterial meningitis in the UK after MenC

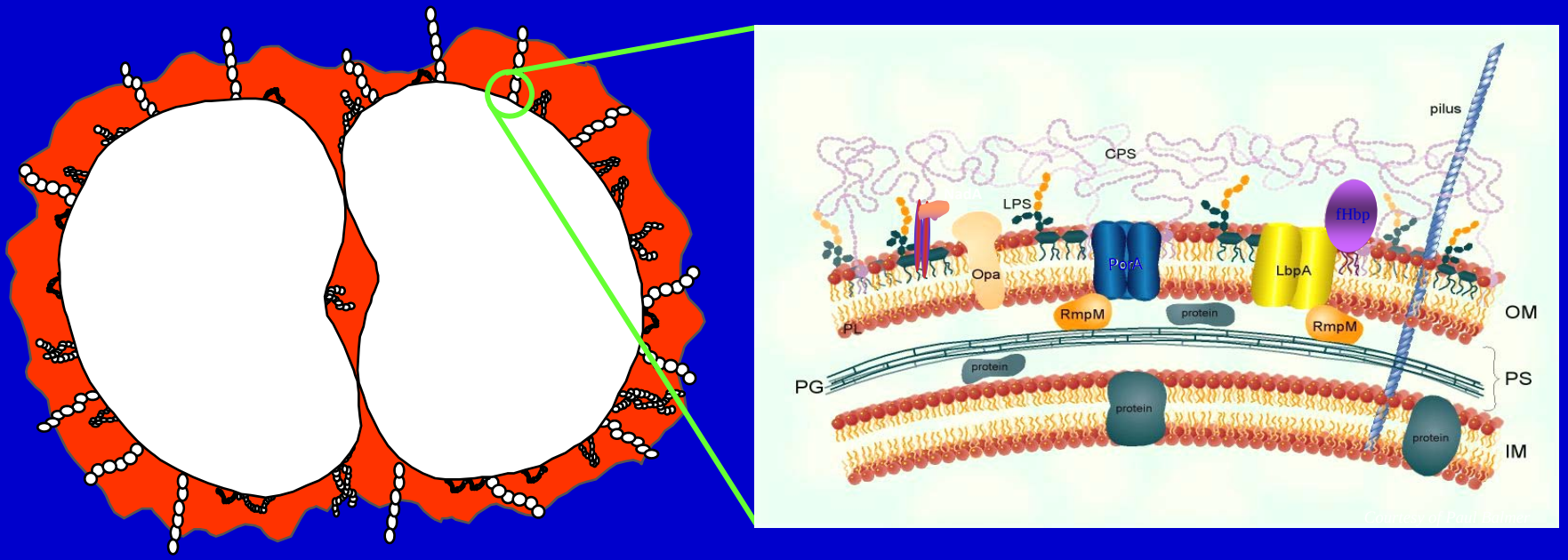


Meningococcal disease: age-specific bactericidal activity and incidence

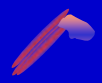
after Goldschneider, 1969



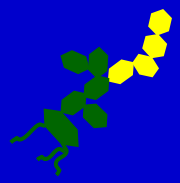
N. meningitidis serogroup B



- Capsule: (α2→8)–linked polysialic acid
  - invariant; ***BUT*** self-antigen



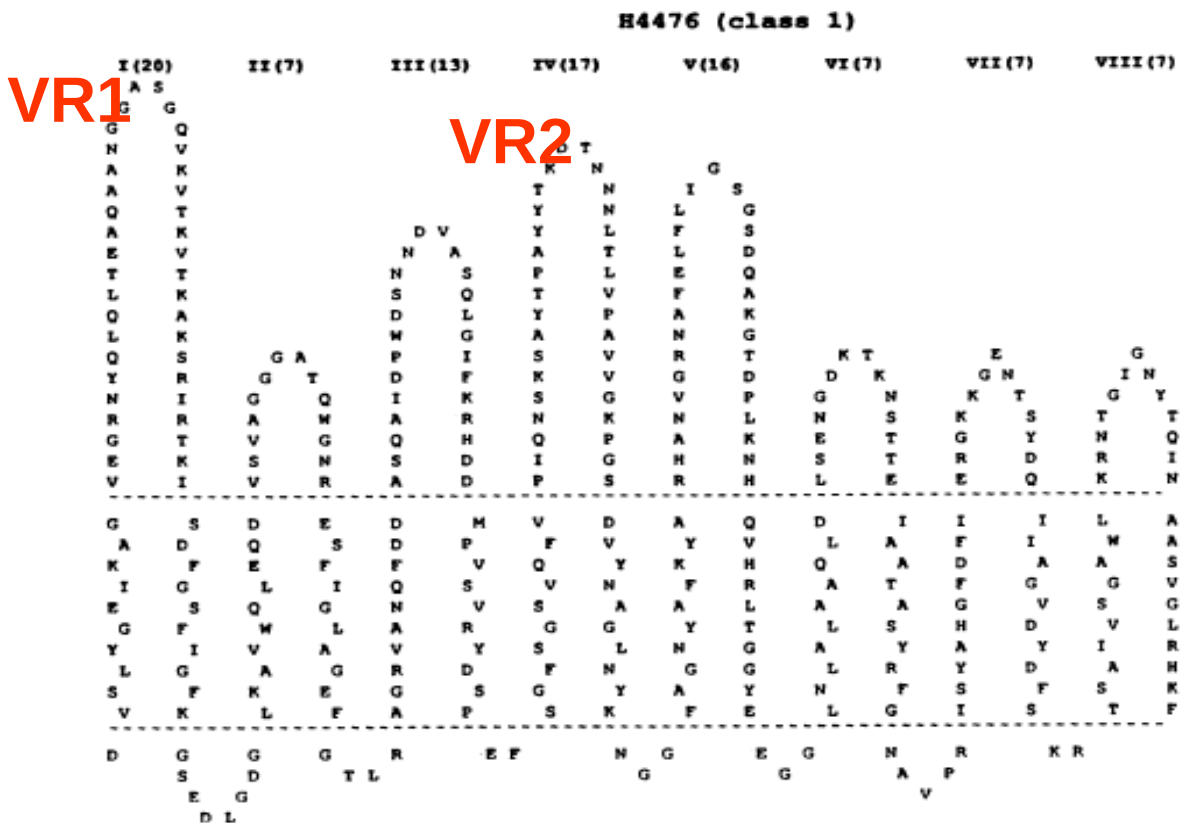
- OMPs
  - many of high diversity



- LPS
  - complex phase variation

- variable expression
- immune selection

PorA (P1) – serosubtyping antigen VR1-VR2 typing

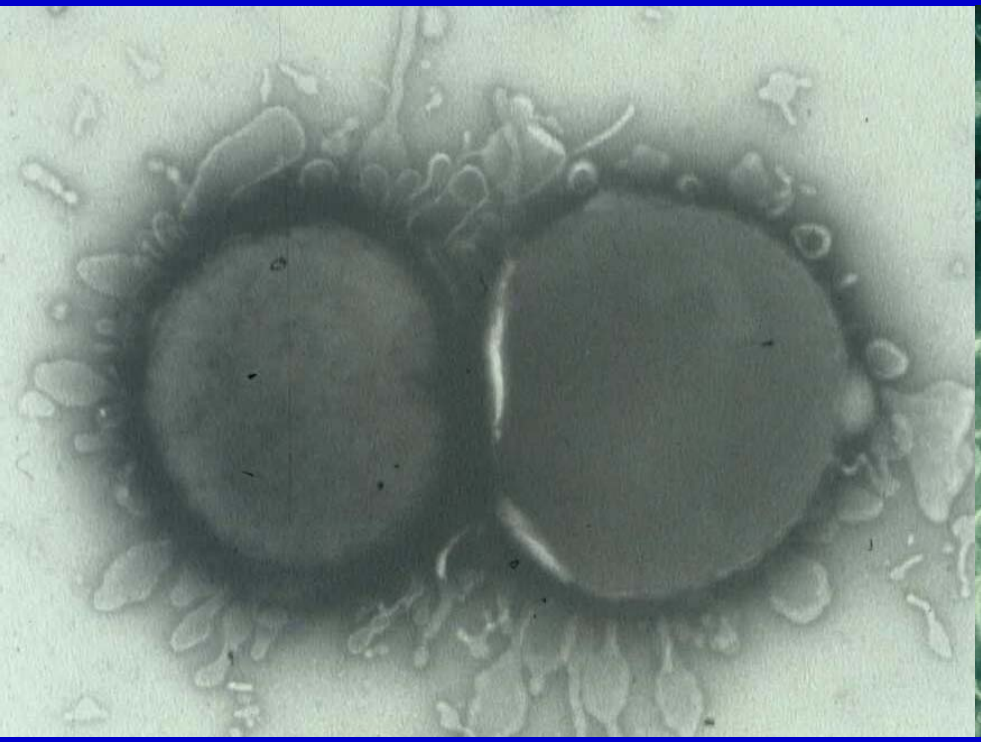


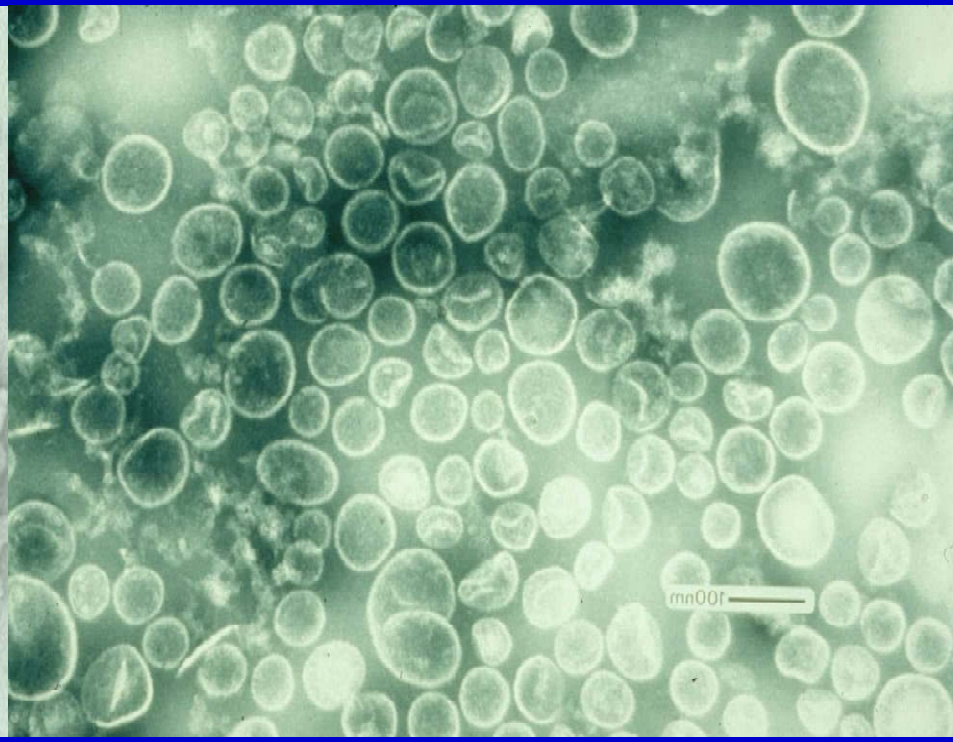
Bacterial outer membrane

Seq variability in 22 strains

data of Van der Ley et al., 1991; Pizza et al., 2000

OMVs and vesicle vaccines – 1980s





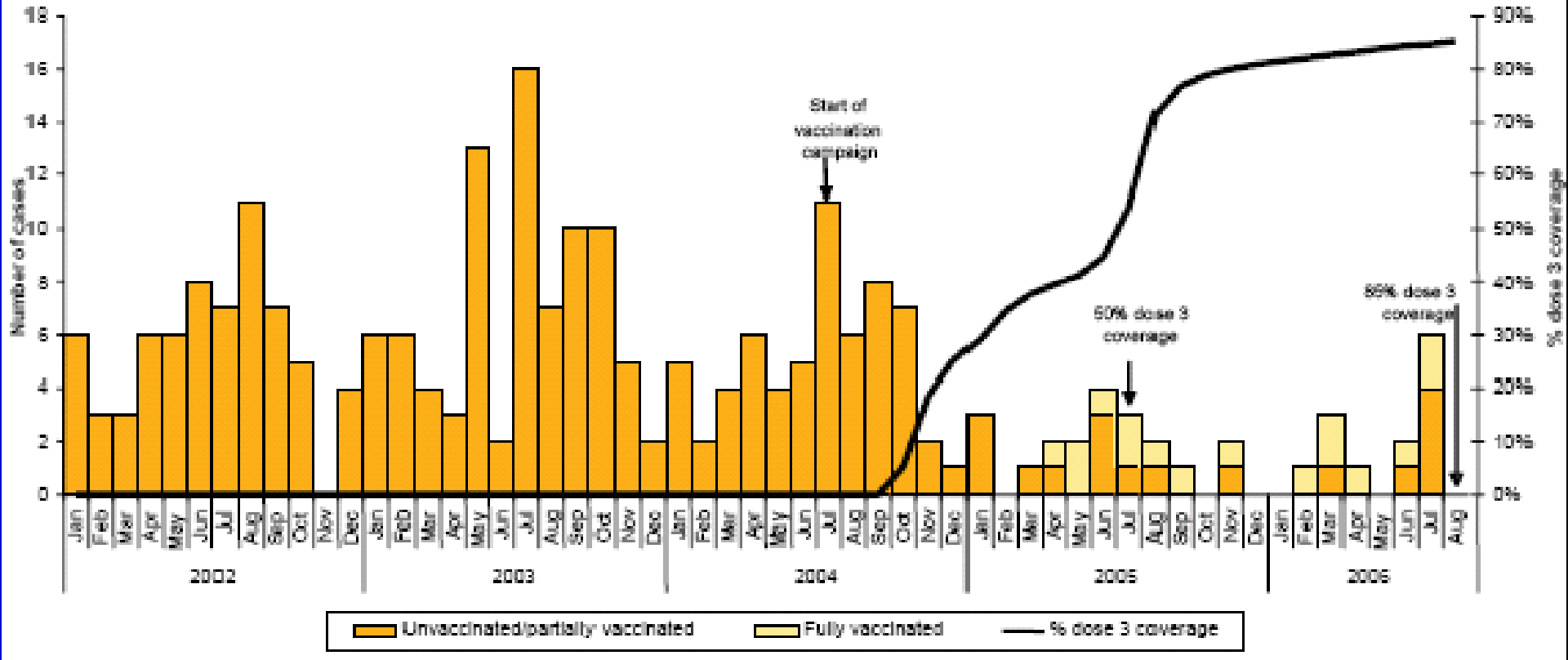
- OMVs potentially contain all surface-exposed antigens *BUT*
- PorA immunodominance

Group B meningococcal OMV vaccines for epidemics

The New Zealand experience - MeNZB

Pre-1991	~ 50 cases of meningococcal disease annually
1991	Epidemic began: 80% B-4 (PorA: P1.4)
2001	651 cases (>200 per 100,000 children less than 1 year of age in 2004)

Novartis MeNZB OMV vaccine in New Zealand
~ 1M under-20s; roll-out 2004-6
Impact on the New Zealand outbreak

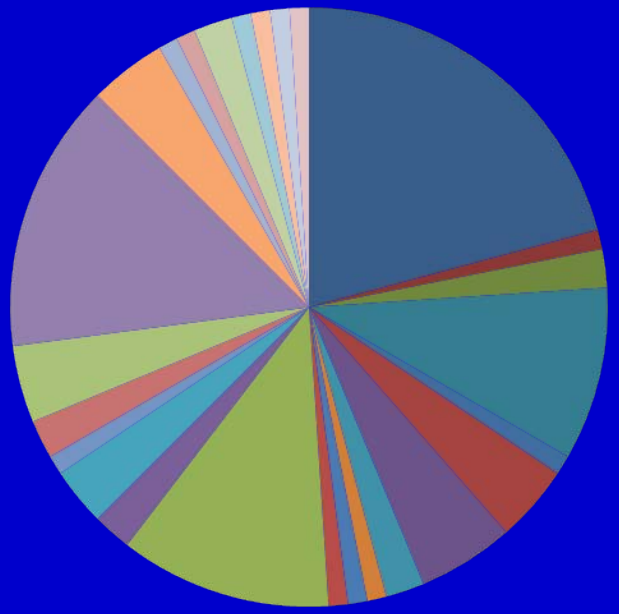


78% vaccine effectiveness ages 2months – 18 years

Vaccines for endemic meningococcal disease

- Challenging strain diversity
- Modifying vesicles?
  - Walter Reed Army Inst. of Research, USA
    - NOMVs to preserve LPS antigens
    - ***Multiple PorAs***
- Invariant outer-membrane proteins?

PorA diversity, N. Spain, 2000-3



P1.5-1,10-8
P1.5-1,10-4
P1.5-2,10-2
P1.5,2
P1.5-1,2-2
P1.7-2,14
P1.7-2,4
P1.7-2,4-2
P1.17,9
P1.18-7,9
P1.19-14,9
P1.22,9
P1.19-2.13
P1.19-2,13-1
P1.21,14
P1.22,14
P1.22-1,14
P1.19,15
P1.19,15-1
P1.19-10,15
P1.21,15

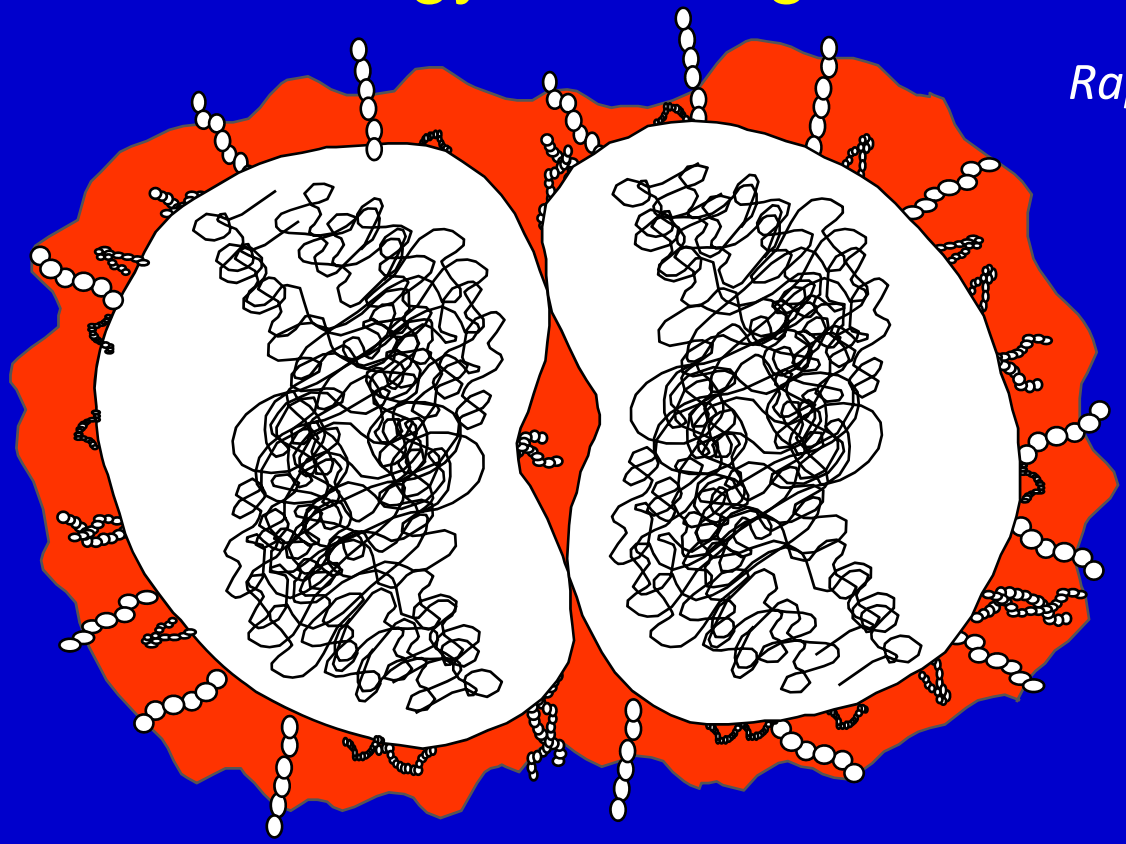
Diego Vicente et al, 2005

Discovering elusive conserved proteins of meningococcus B

A cross-protective vaccine for *endemic* disease?

"Reverse Vaccinology" – from genes to vaccines

Rappuoli et al 2000 -

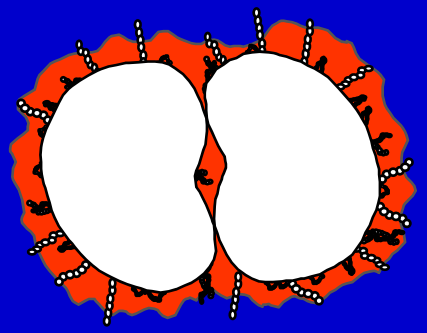


PNAS

Proceedings of the National Academy of Sciences of the United States of America www.pnas.org

A universal vaccine for serogroup B meningococcus

Giuliani MM *et al*. 2006.



- NadA - adhesion/invasion protein
- Factor H binding protein (fHbp)
- Neisserial heparin-binding antigen (NHBA)

"In marked contrast to the OMV vaccines … the vaccine induced broad protection that was not sero-subtype-specific and covered most of the population diversity".

NadA

OM-anchored trimeric adhesin

strong bactericidal response, protective after passive immunization of infant rat

Unknown function.
Definitely not essential for viability / pathogenic behaviour (null alleles)

Several subtypes, → cross-protective immune response.
But n.b. those null alleles.

fHbp

Surface-exposed lipoprotein

strong bactericidal response, protective after passive immunization.

Binds Factor H (key regulator of Complement activation *via* the Alternative Pathway).
? Essential for full pathogenic behaviour; variable expression level.

Three genetic variants;
1 & 2/3 are poorly cross-reactive.

after Bambini et al 2009

4CVMenB - investigational Novartis MenB vaccine

NadA, fHbp, NHBA + P1.4 PorA

Immunogenicity studies in UK infants, reported in May 2008

injections at 2/3/4 m, + 12 m booster.

1 month post booster, protective levels against 3 strains used to make the vaccine:

100%, 98%, & 93%, + evidence of immune memory

fHbp NadA PorA

Strain collection for vaccine appraisal in UK

HPA Meningococcal Reference Unit, Manchester

Genotyping of ~600 MenB strains submitted Jul '07- Jun '08

for 4CVMenB coverage

- PorA (P1.4) 22% +ve
- NadA 9.5% +ve
- fHbp 65% +ve

==========

- ≥ 1 Ag gene 73%

but gene expression uncertain . . .

MenB vaccines – where are we now?

These are not "MenB vaccines" – they are vaccines against a range of MenB strains

- 4CVMenB has established immunogenicity in infants, with evidence of memory.
  (European license application in progress)
- *but* potentially serious problems with UK strain coverage . . .
- . . .and worrying potential for replacement

Conclusions

- Hib, pneumococcus and meningococcus are accidental meningitis pathogens living a complex, colonising existence in the URT.
- Effect of vaccination on carriage – and so on invasive infection risk – may be crucial and is unpredictable.
- Vaccination schedule changes have unforeseen consequences.
- Strain replacement – not if but when . . .