

Meningitis vaccines: then, now, the future ...

Simon Kroll
January 2013

Major invasive bacterial pathogens

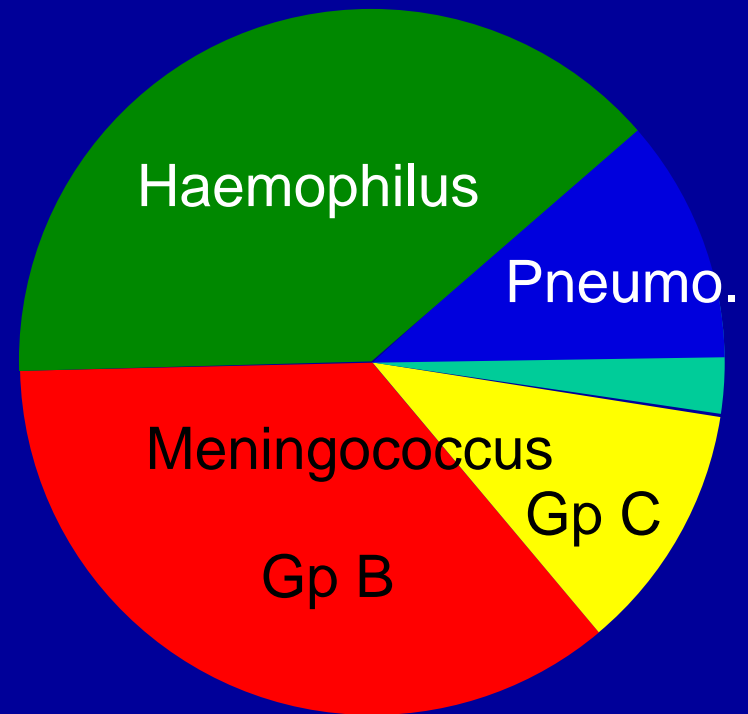
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Streptococcus pneumoniae*

- *Escherichia coli*
- *Streptococcus agalactiae*

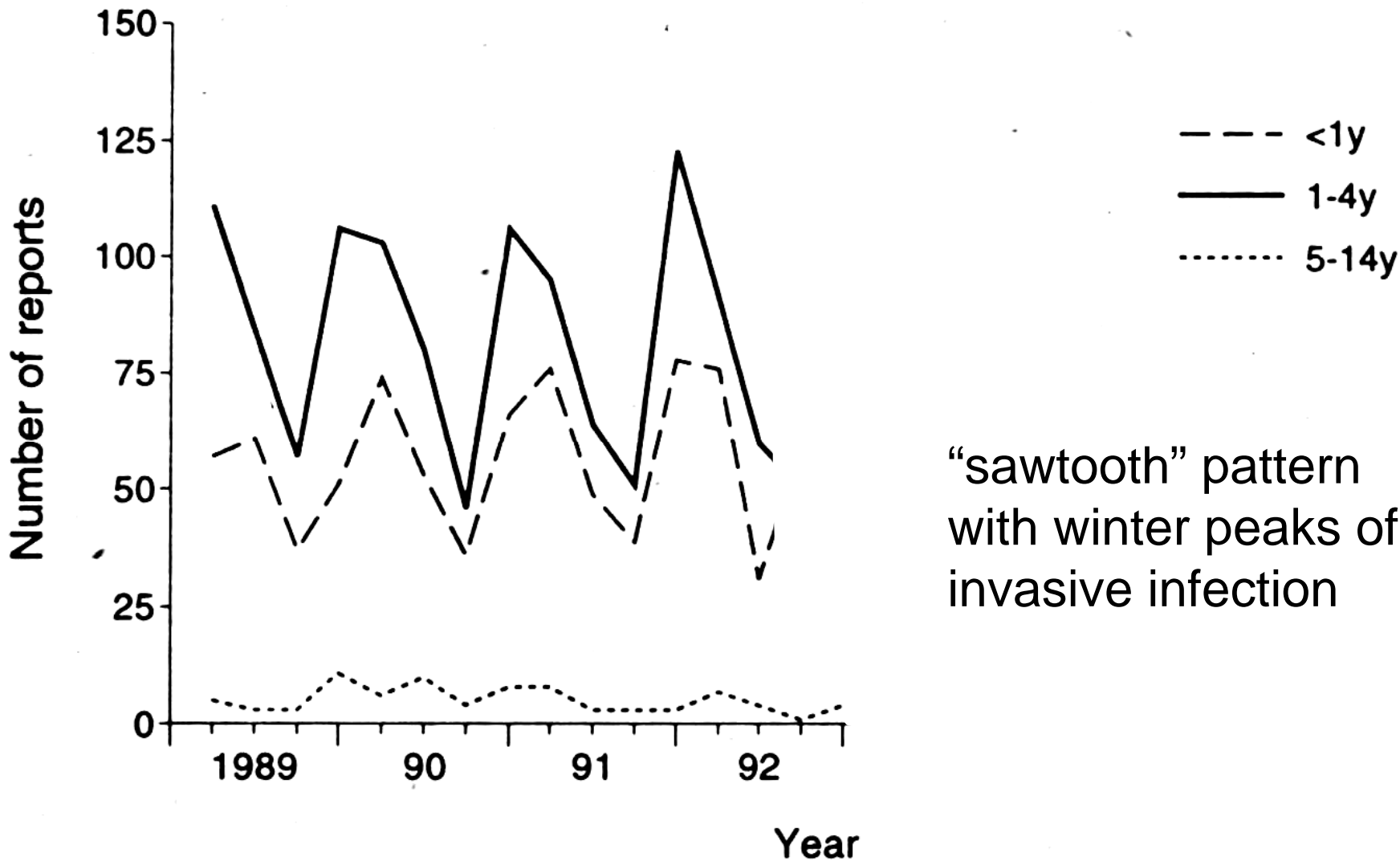
Major invasive bacterial pathogens

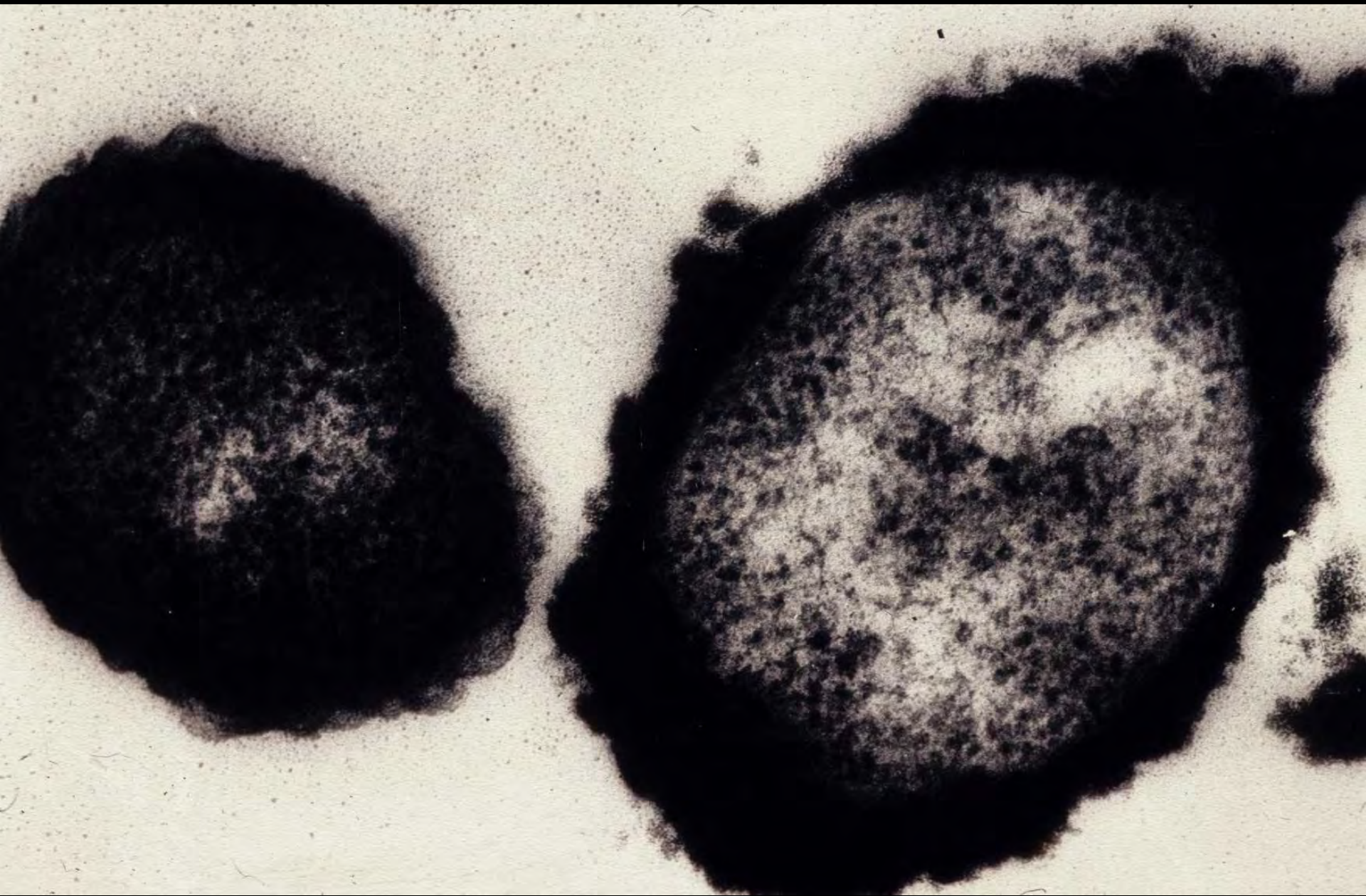
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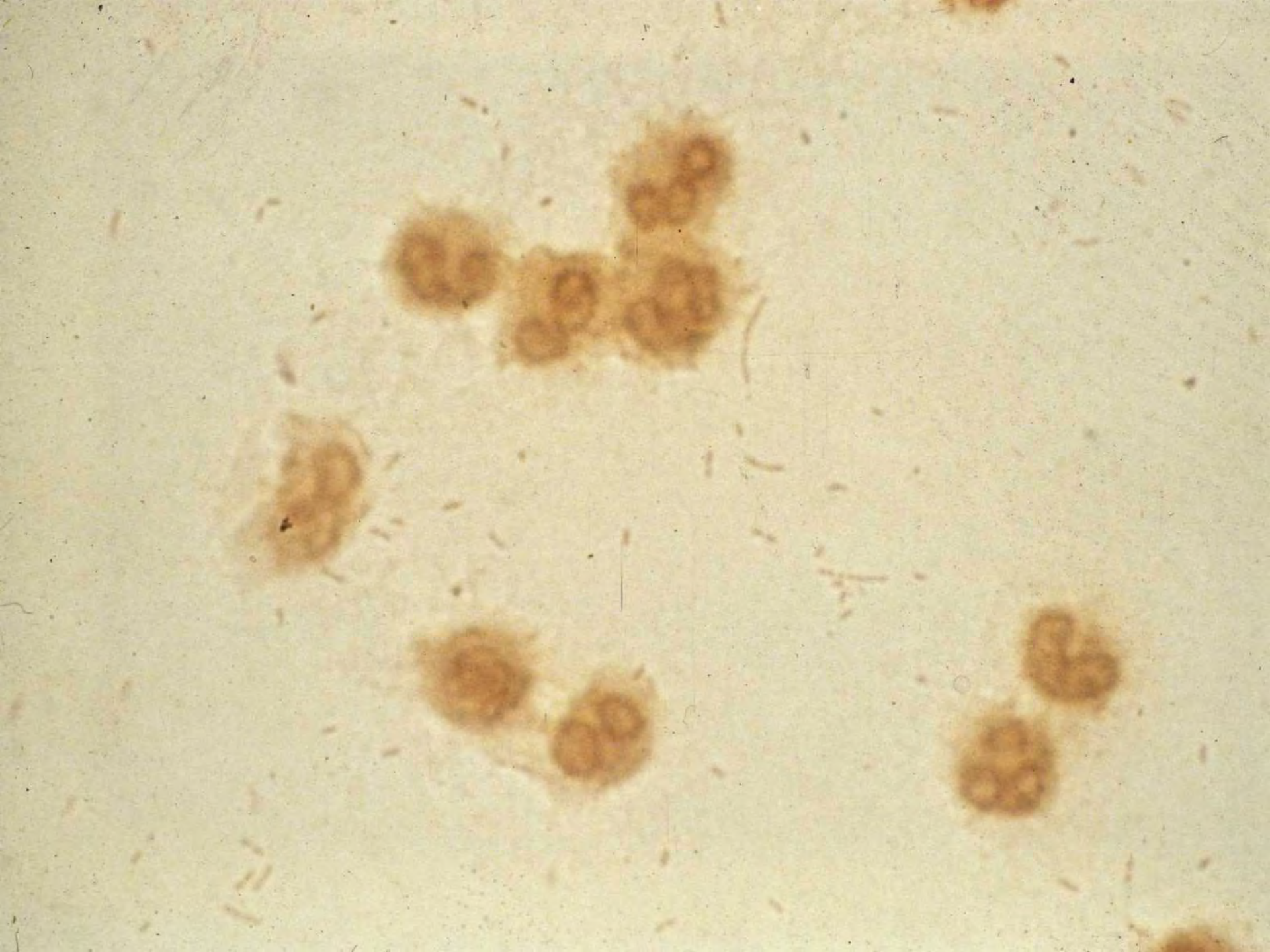
- *Escherichia coli*
- *Streptococcus agalactiae*



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



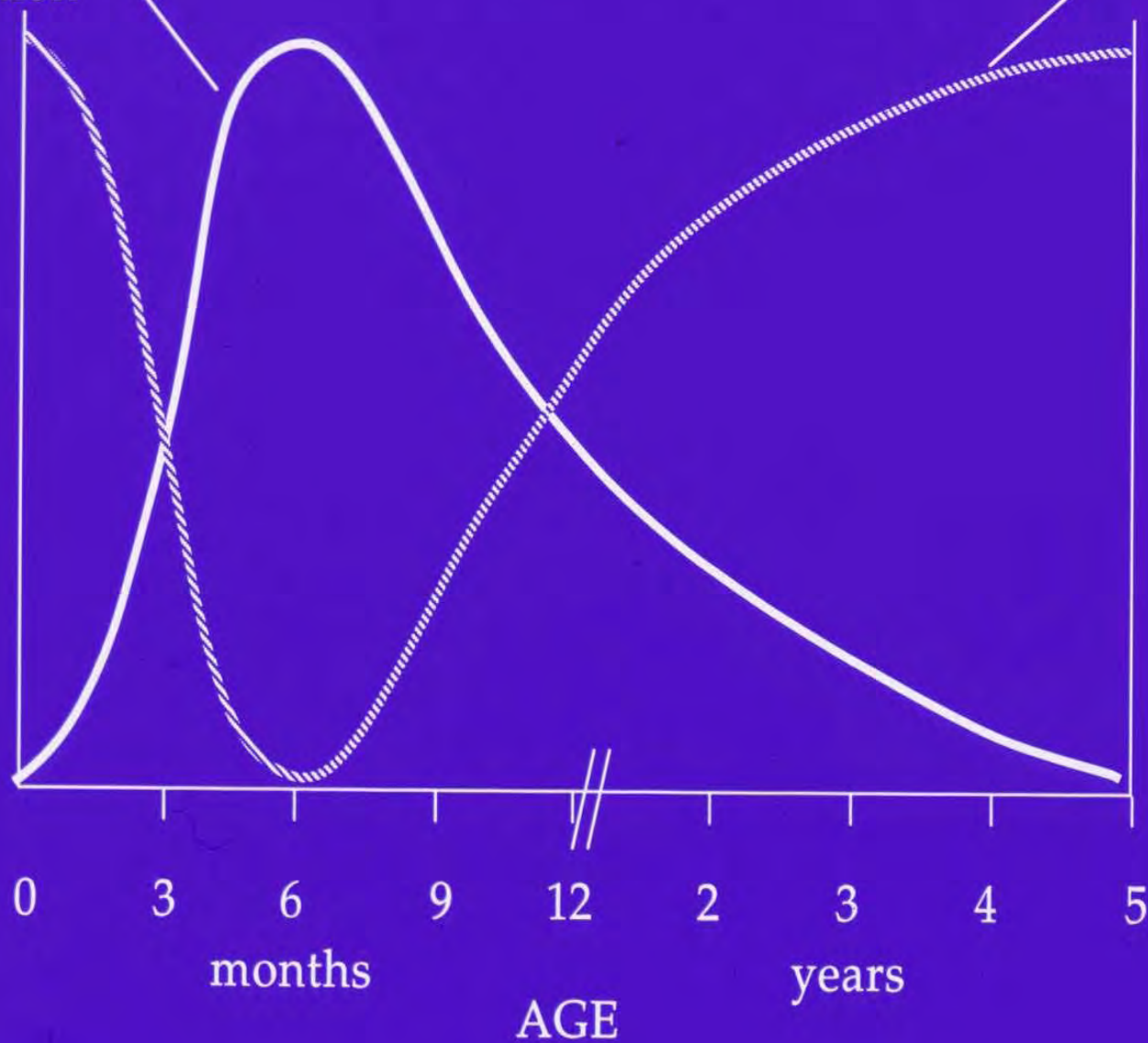


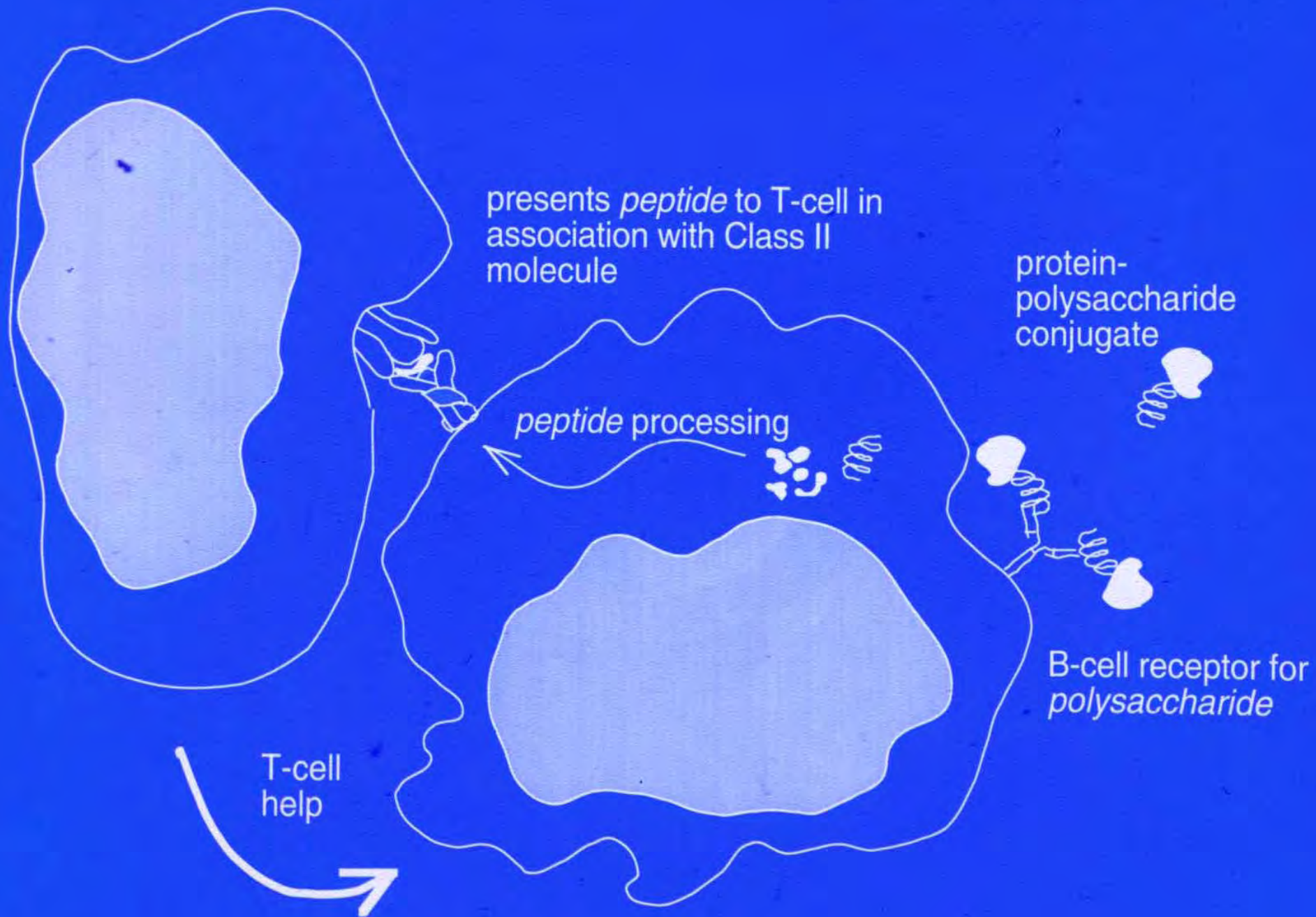


Susceptibility
to systemic
Haemophilus
infection

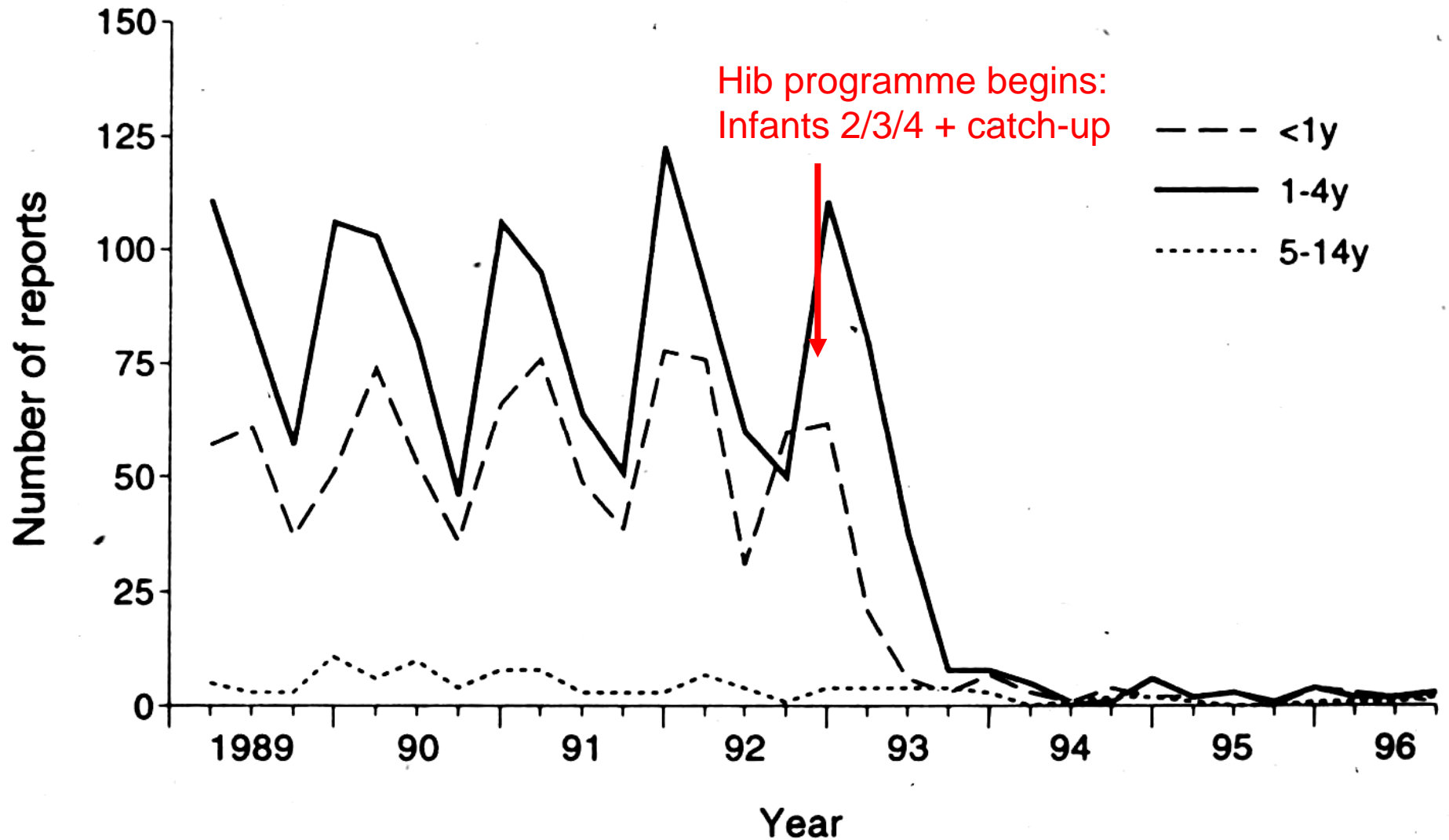
Bactericidal antibody

100% adult level





Post-neonatal *H. influenzae* meningitis eradicated by Hib polysaccharide conjugate vaccine



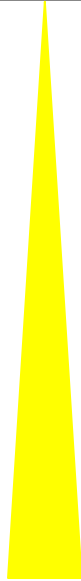
Meningococcal disease, E&W, 1984-

There has been a steady increase in meningococcal disease each year since 1984 but it is not possible to predict whether this trend will continue.

	1984	1985	1986	1987	1988
Group A	20	11	33	49	21
Group B	300	377	573	679	852
Group C	125	180	392	442	464
Other groups	15	15	17	19	16
Total	460	583	1015	1189	1353

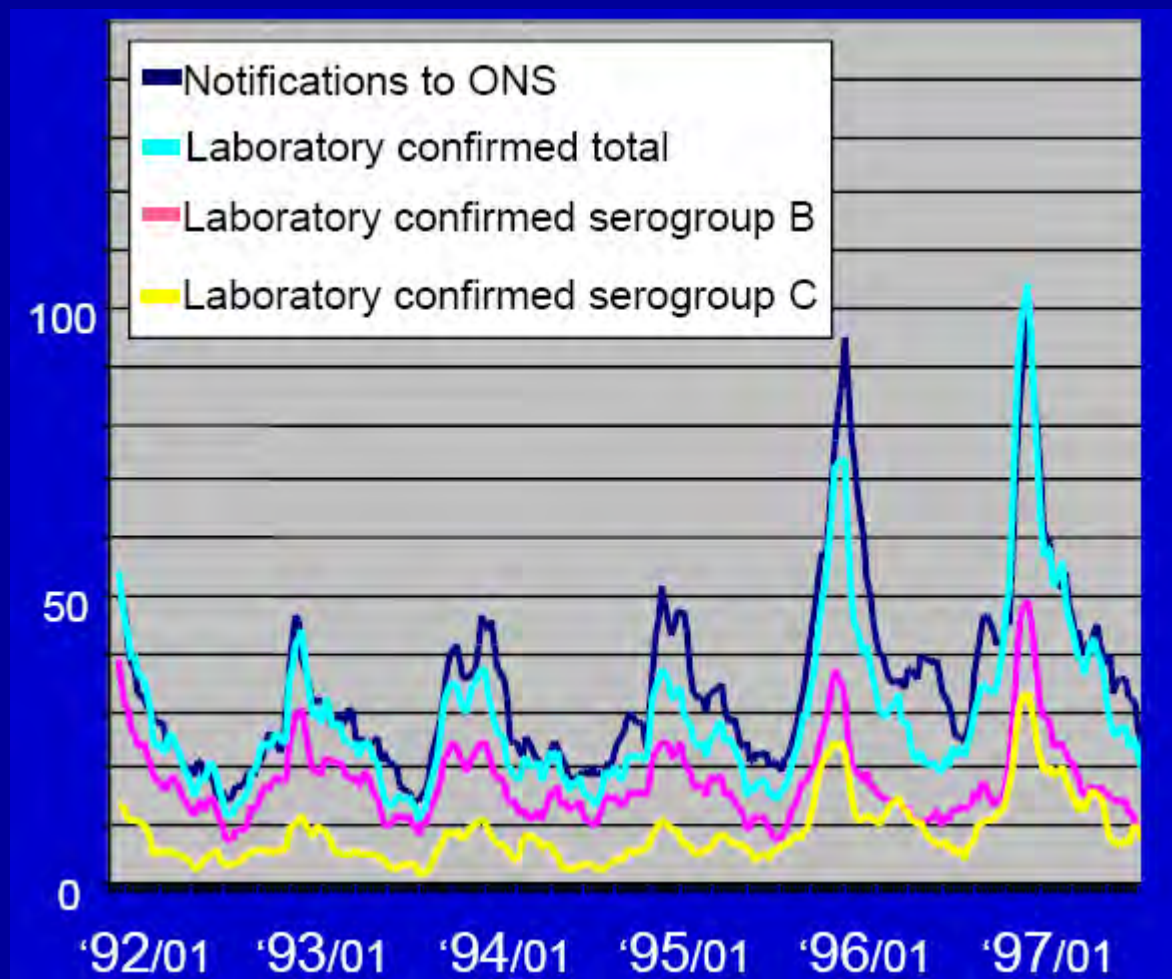
Numbers of cases of meningococcal disease reported 1989 - 1995

Year	Meningitis	Septicaemia	Total
1989	1133	229	1362
1990	1138	277	1415
1991	1117	273	1390
1992	1067	277	1344
1993	1053	398	1451
1994	938	430	1368
1995	1142	705	1847



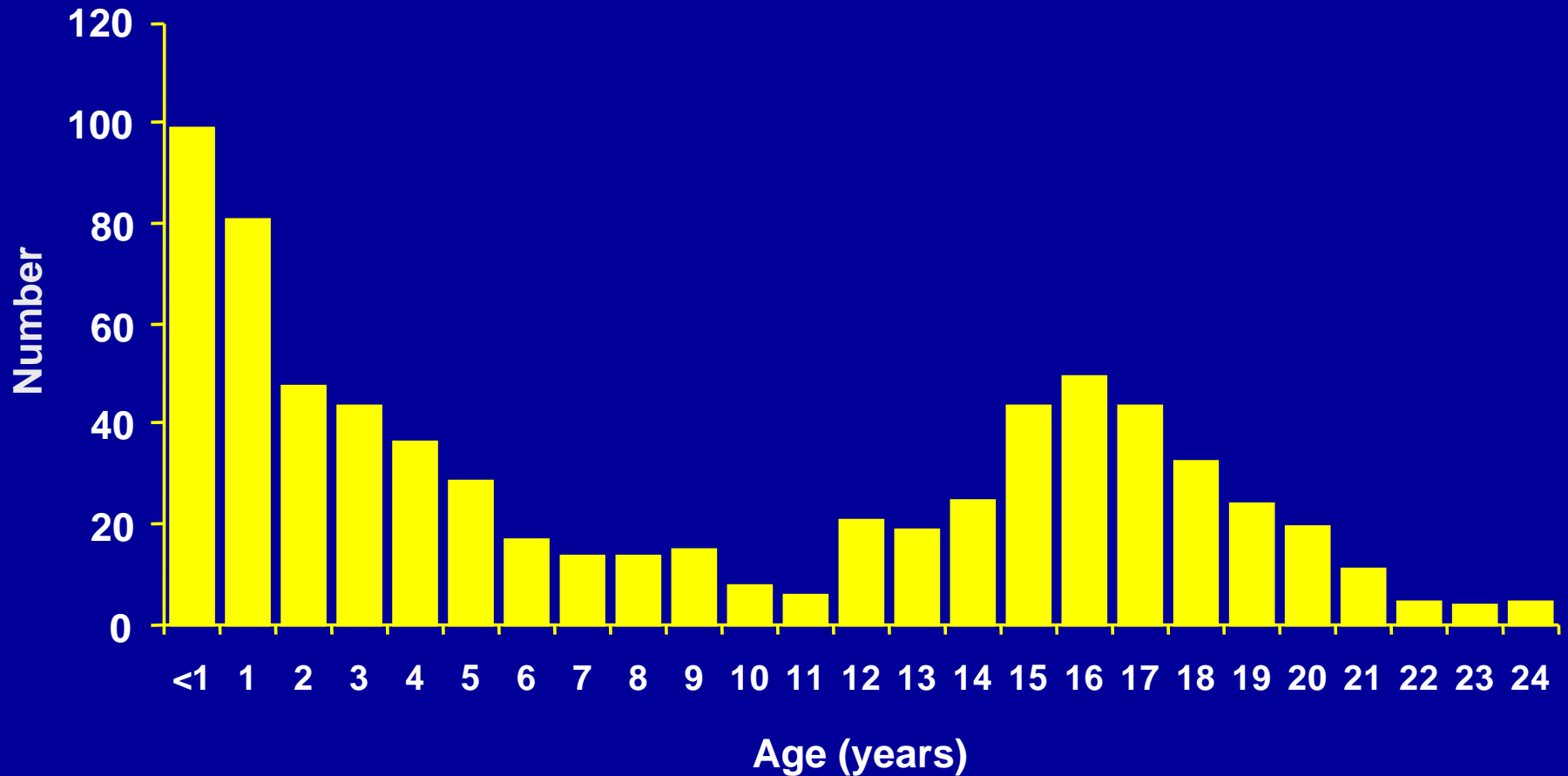
Changing patterns of case ascertainment and trends in meningococcal disease in England and Wales. *M Ramsay, E Kaczmarski, M Rush, R Mallard, P Farrington, J White.* CDR Review 7 (4) 4th April 1997

Cases of Meningococcal Disease England & Wales - 5-weekly moving averages 1992 to 1997



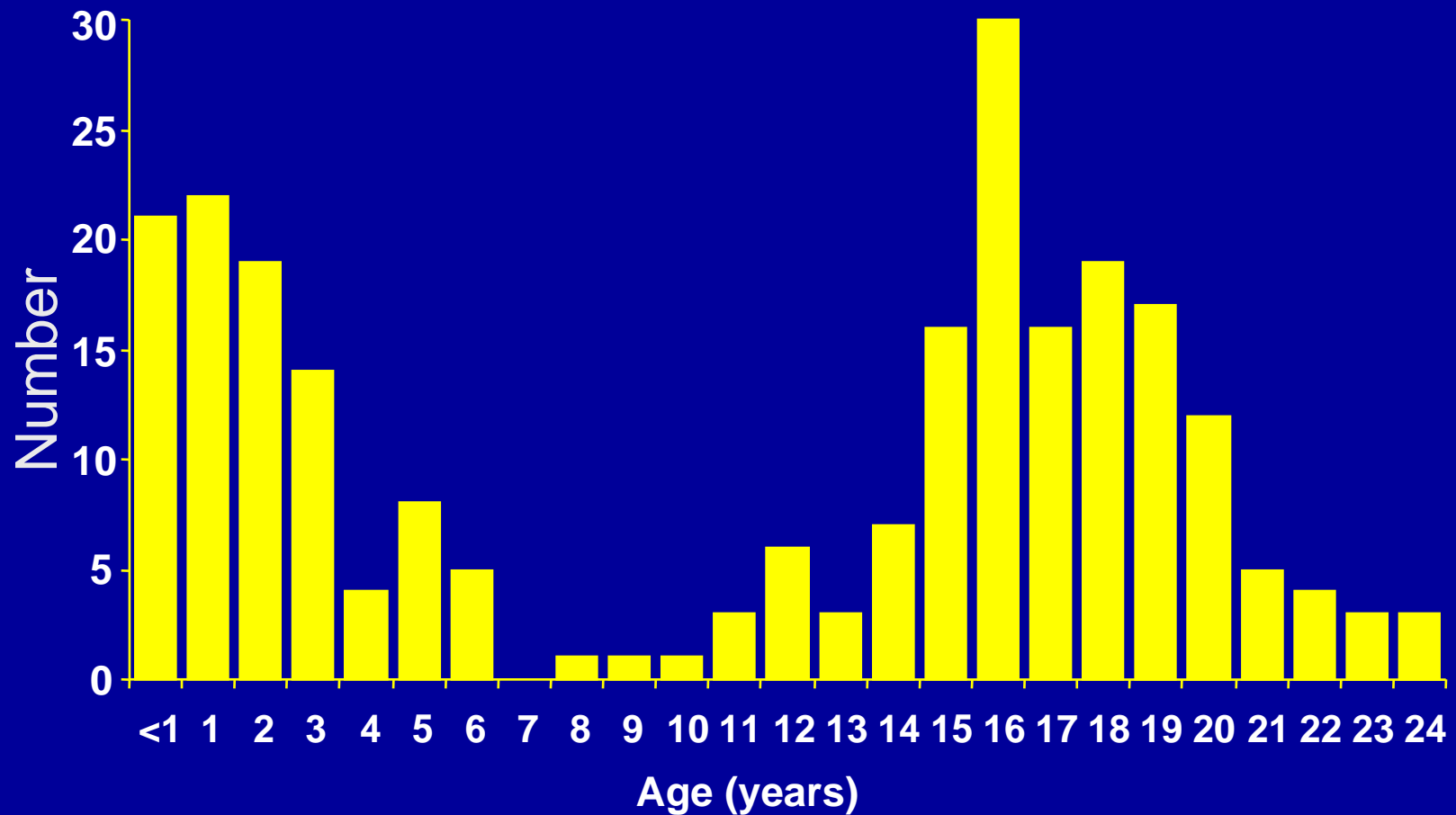
Serogroup C meningococcal infection by age

Isolates referred to PHLS, 1998/9

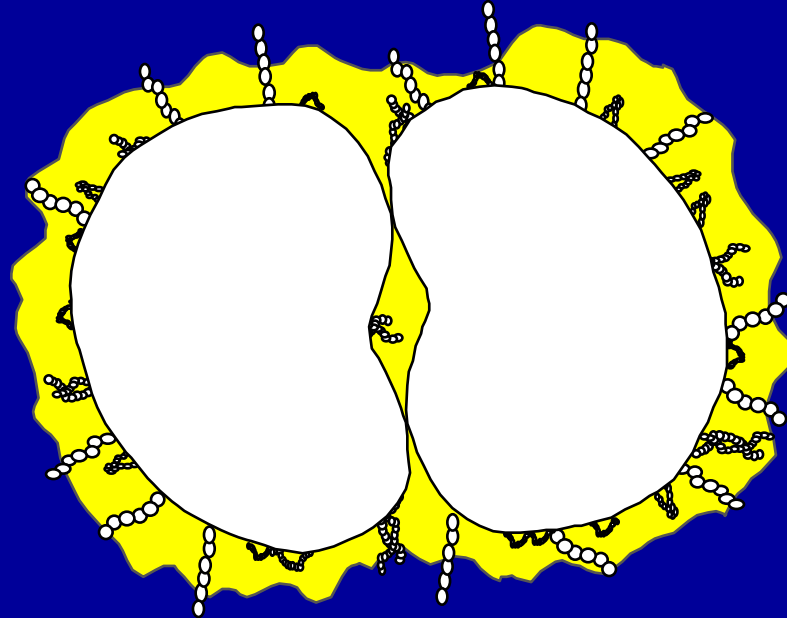


Serogroup C meningococcal deaths by age

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



N. meningitidis serogroup C



- Capsule: (α2→9)-linked polysialic acid

Join Femal's campaign to save pashminas from the style snobs

SEE PAGES 20-21



Millions to be protected from killer

MENINGITIS VACCINE FOR ALL CHILDREN

MILLIONS of children and teenagers are to be protected against meningitis C for the first time this winter.

It will be the most ambitious vaccination programme ever, potentially saving scores of lives.

Britain will be the first country in the world to routinely provide a vaccine against meningitis C to the babies, toddlers and students who are at highest risk of the deadly brain infection.

The scheme is being rushed through in time for the winter peak of the disease, which is the country's biggest killer of young children. Last year it affected more than 1,300 people, 100 of whom died. Fatal outbreaks brought fear to several college campuses.

The decision to fast-track the programme came after the Daily Mail

By **JENNY HOPE**
Medical Correspondent

revealed exclusively that trials of new vaccines had proved them safe and effective for long-term protection.

Health Secretary Frank Dobson, announcing the move, said it could halve the death toll. Immunisation will begin in October, a year ahead of schedule. As stocks of vaccine will be limited at first, it will be restricted to groups in most danger. But eventually all children will be protected.

Professor Liam Donohue, the Government's Chief Medical Officer, said the programme was an international breakthrough. It will end the reign of terror that group C has wrought on our population in recent years.

The cost to the NHS has yet to be established, but officials say it will be "tens of millions of pounds". Babies up

to 13 months will be the first to receive the vaccine, mainly as part of their routine NHS immunisation schedule.

There will be a catch-up programme in schools for children of 11, 14 and 17 who are particularly vulnerable to infection in their first weeks at college or university.

The first year of the programme is expected to provide protection for 15 million youngsters, although its speed will depend on the flow of supplies from vaccine manufacturers.

But experts warned that parents and young people should stay alert for meningitis symptoms as there is still no vaccine against the B strain of the disease which killed 130 people last year. The immunisation programme in schools will also come too late to protect students starting college later this year. They are being advised to ask their GPs for older vaccines which

Turn to Page 2, Col. 8.

EXCLUSIVE: Henman to marry



TIM HENMAN is to marry his long-time girlfriend Lucy Henman (left). The couple, who live together in South-west London, are believed to have just returned from holiday in Turkey where Britain's number one tennis player popped the question. However, his night

Turn to Page 4, Col. 1.

July 21st 1999

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

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

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)

Department of Health press release

Biggest vaccination drive for 40 years smashes Meningitis C disease

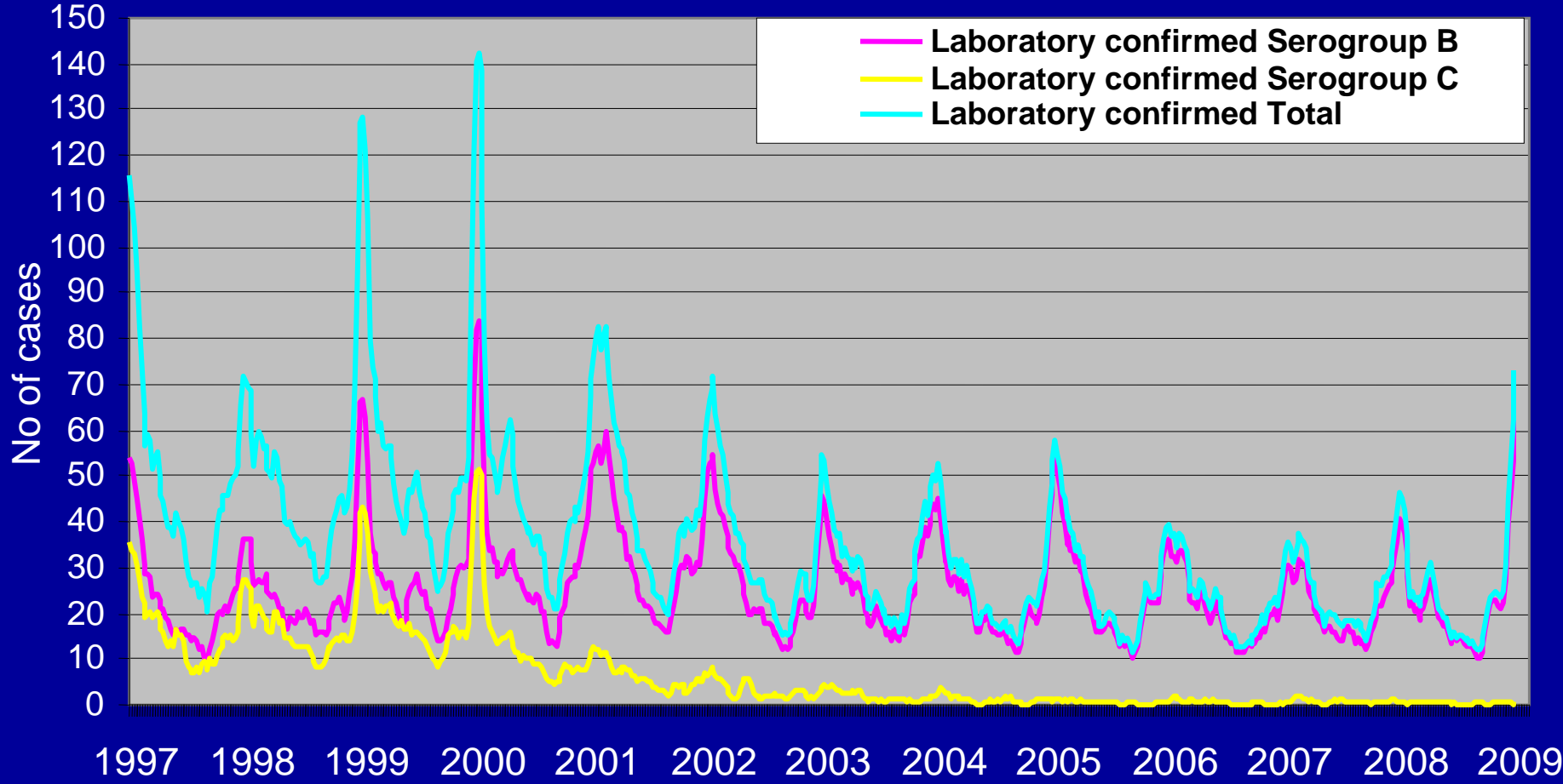
Published date: 3 January 2001

“UK the first country in the world to develop, fund and introduce MenC vaccines.”

Vaccination started in **November 1999**, and by January 2001:

- 90% drop in cases in <1y and 15-17y age groups first immunised
- 500 cases of MenC disease, and 50 deaths, estimated to have been avoided
- 75% drop overall, with increased impact anticipated ...

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





Meningitis claims 6th victim

Meningitis has claimed its sixth victim in the Gloucestershire village of Stonehouse.

The sixth victim was a 10-year-old boy, who died of meningitis on August 1st. The boy had been ill for several days before he died. His mother said that he had been very tired and had a fever. The boy's death is the sixth in the village since the outbreak began in June.

Meningitis tests find 70 carriers

Health Service Correspondent

Health Service Correspondent reports that 70 carriers of meningitis have been identified in Stonehouse. The carriers are people who have the meningitis bacteria in their throats but do not have any symptoms. The carriers are being treated with antibiotics to prevent the bacteria from spreading.

Faces of fear in a town haunted by meningitis

A junior health official attended a public meeting in Stonehouse last night to explain the meningitis outbreak. The official said that the outbreak was caused by a strain of meningitis bacteria that is highly contagious. The outbreak has caused a great deal of fear in the town.



New meningitis vaccine to be tested in Britain

A new meningitis vaccine is to be tested in Britain. The vaccine is made from a weakened strain of meningitis bacteria. It is expected to be available in the next few years.

Call to end spread of meningitis
By Christine Phillips
The outbreak of meningitis in Stonehouse has caused a great deal of concern. Health officials are calling for an end to the spread of the disease.

Tempers flare over meningitis outbreak

Tempers have flared over the meningitis outbreak in Stonehouse. Some people believe that the outbreak was caused by a contaminated water supply. Others believe that it was caused by a contaminated swimming pool. The outbreak has caused a great deal of anger and frustration in the town.

The nightmare of Strain B-15

Strain B-15 is the most dangerous strain of meningitis. It is highly contagious and can be fatal. The outbreak of Strain B-15 in Stonehouse has caused a great deal of fear in the town. Health officials are warning people to avoid contact with anyone who has been ill with the disease.

Action over meningitis

Action is being taken over the meningitis outbreak in Stonehouse. Health officials are testing people for meningitis and treating those who are found to be carriers. They are also taking steps to prevent the disease from spreading further.

Getting to grips with meningitis

Stonehouse have died from meningitis this year. Now the Gloucestershire village of Stonehouse will become the home of a new laboratory for meningitis research.

West and north bear brunt of meningitis wave

The west and north of England are bearing the brunt of a meningitis wave. The outbreak is caused by a strain of meningitis bacteria that is highly contagious. The outbreak has caused a great deal of fear in these areas.



Boy's meningitis death takes Stroud toll to six

A boy's death from meningitis has taken the toll in Stroud to six. The boy was 10 years old and had been ill for several days before he died. His death is the sixth in Stroud since the outbreak began in June.



70 have harmful meningitis strain

Seventy people have been found to have the harmful meningitis strain in Stonehouse. The strain is highly contagious and can be fatal. The people who have the strain are being treated with antibiotics to prevent the disease from spreading.

Tests on vaccine for meningitis

Tests are being carried out on a new vaccine for meningitis. The vaccine is made from a weakened strain of meningitis bacteria. It is expected to be available in the next few years.

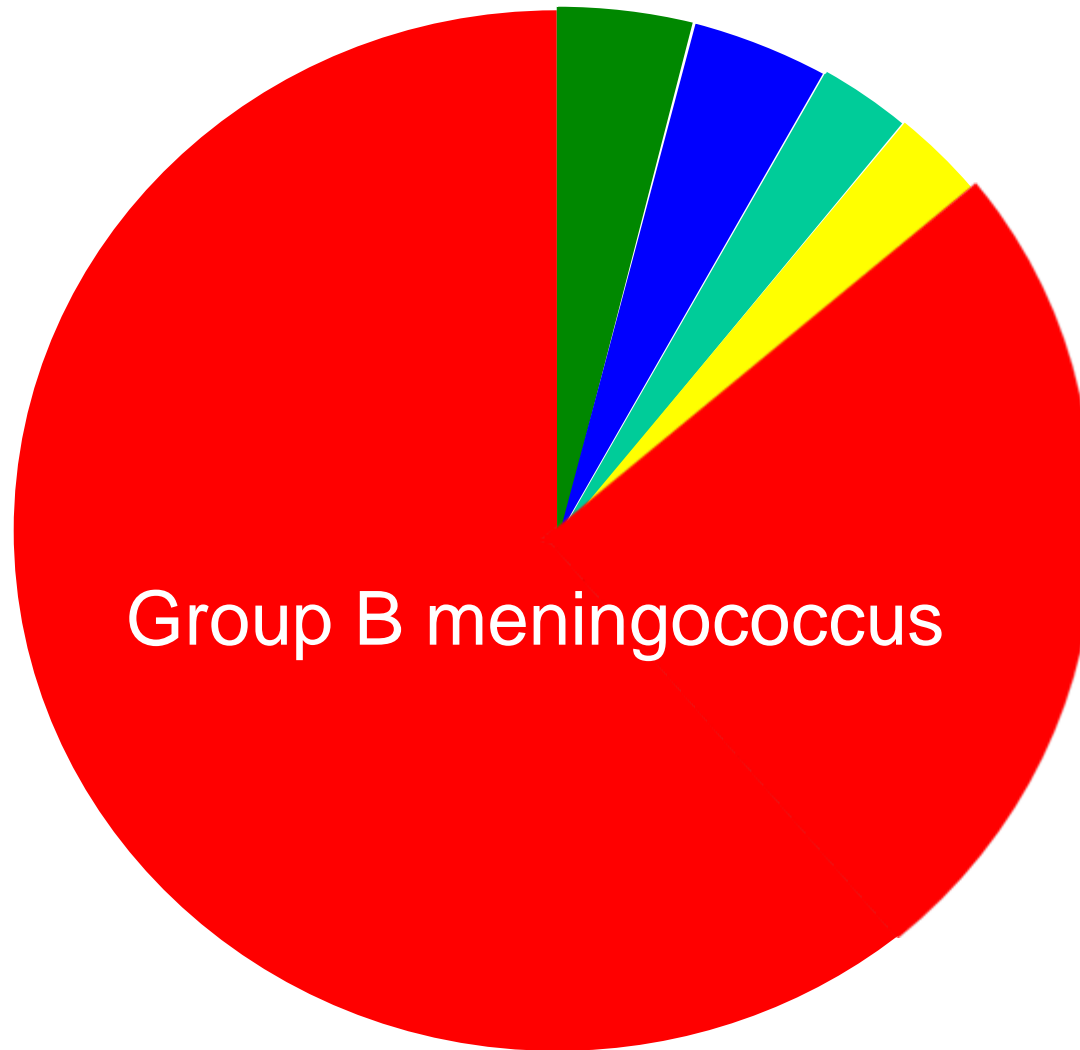
Meningitis blood tests start in stricken area

Blood tests for meningitis are starting in the stricken area of Stonehouse. The tests are being carried out to identify people who are carriers of the disease. The tests are expected to help health officials control the outbreak.

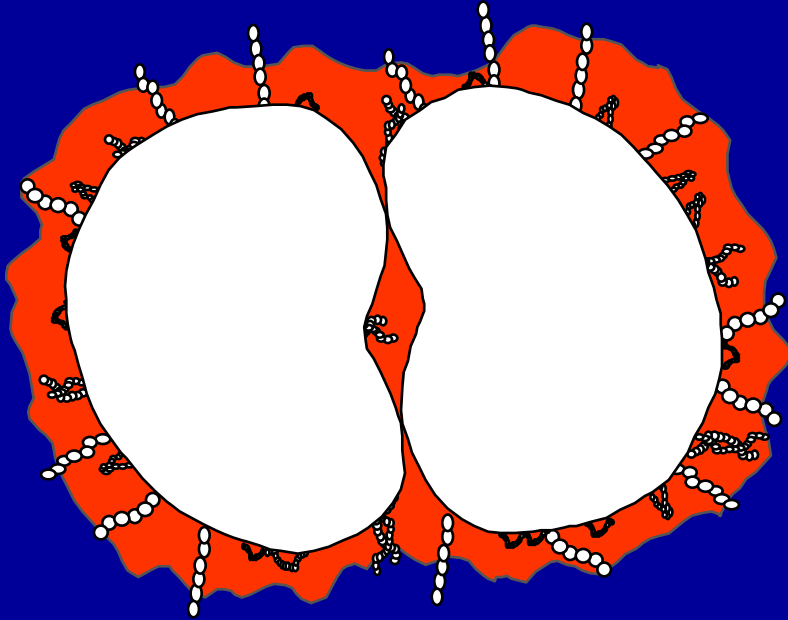


Dr Short starting the mass project with Danielle Smith, aged 13 months, and her parent (Photograph: Rex Dicks)

Post-neonatal bacterial meningitis in the UK 2008

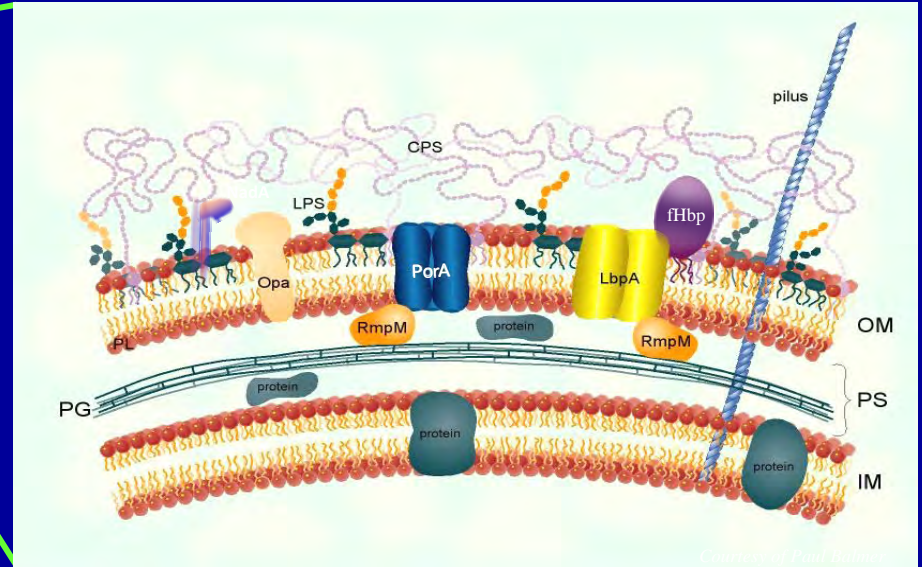
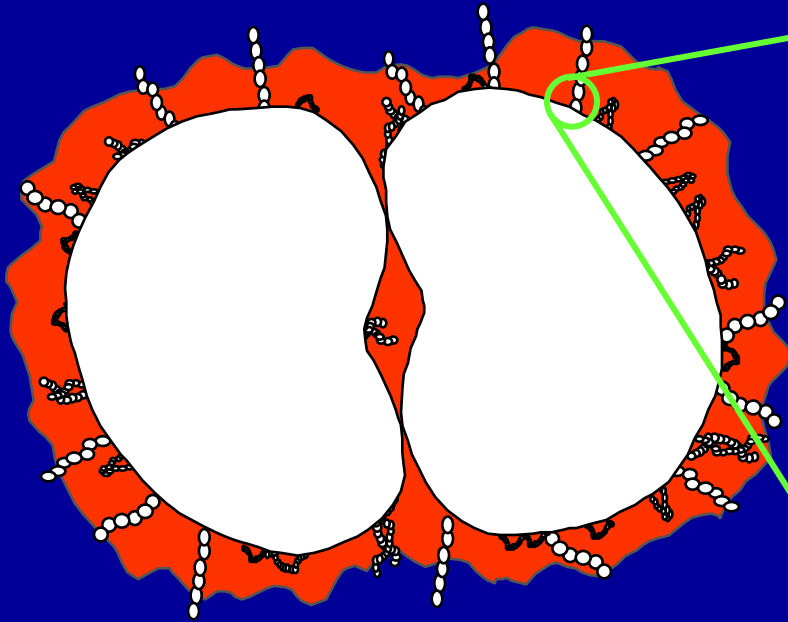


N. meningitidis serogroup B



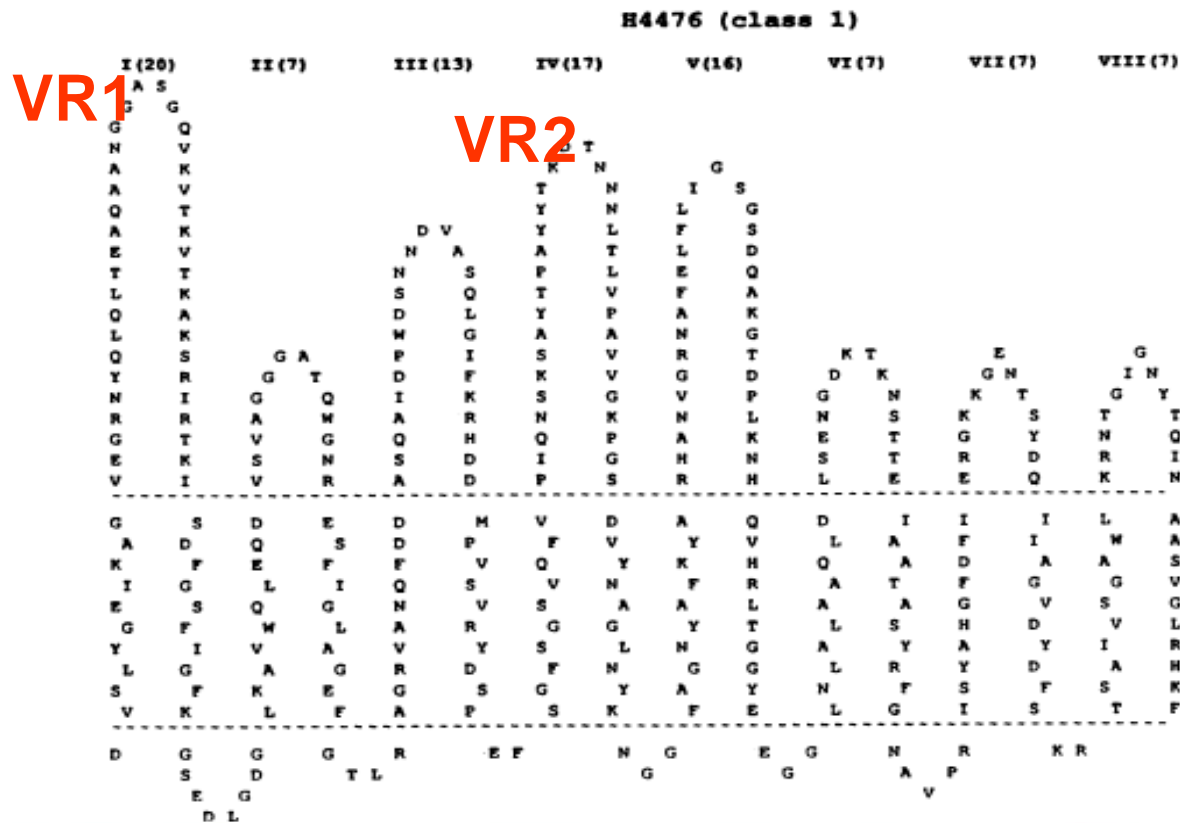
- Capsule: ($\alpha 2 \rightarrow 8$)-linked polysialic acid
 - invariant; **BUT** self-antigen

N. meningitidis serogroup B

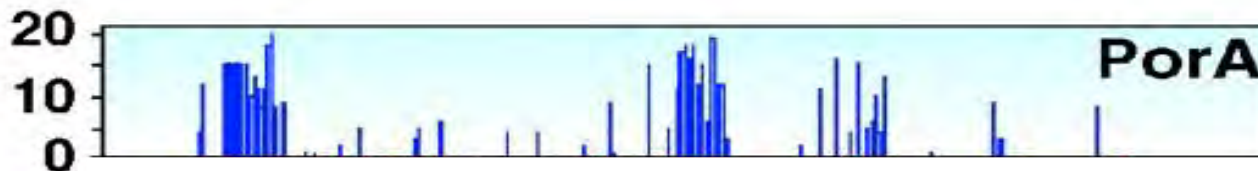


- Capsule: ($\alpha 2 \rightarrow 8$)-linked polysialic acid
 - invariant; **BUT** self-antigen
- Outer membrane proteins (OMPs)
 - many of high diversity - variable expression
 - immune selection

PorA (P1) – serosubtyping antigen VR1-VR2 typing



Bacterial
outer
membrane

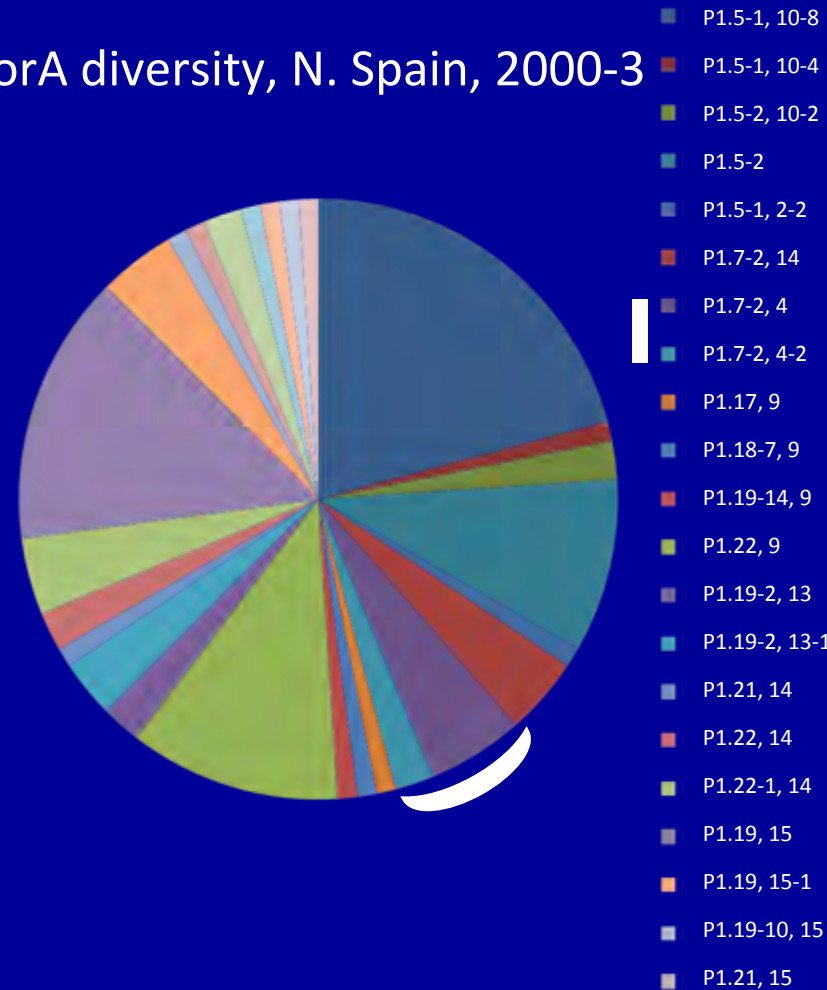


Seq variability
in 22 strains

Vaccines for endemic meningococcal B disease challenging strain diversity

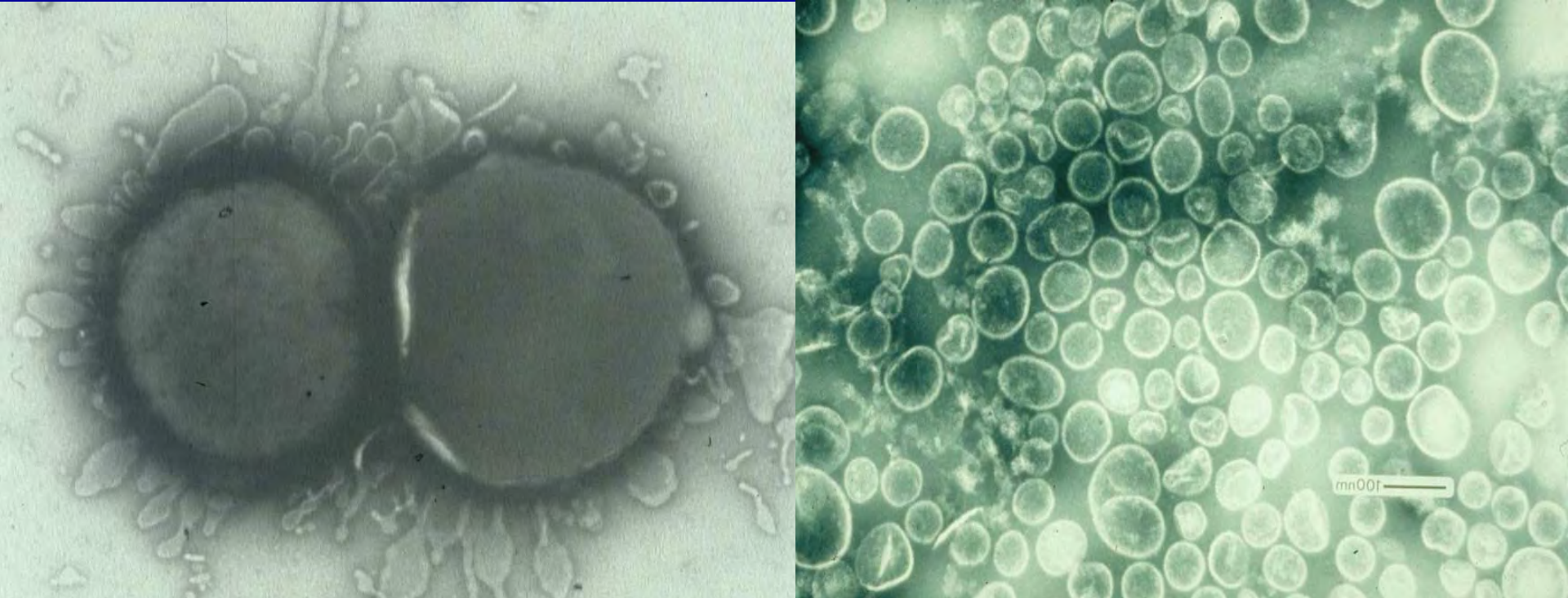
- immunodominant PorA is hypervariable
- Are there invariant OMPS?

PorA diversity, N. Spain, 2000-3





OMVs and vesicle vaccines – 1980s



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



Cuba ~ 90%

Brazil 74%

Norway 54%

Group B meningococcal OMV vaccines

The New Zealand experience - MeNZB

Pre-1991	~ 50 cases of meningococcal disease annually
1991	Epidemic began: 80% B-4 (PorA: P1.7-2,4)
2001	651 cases (>200 per 100,000 children less than 1 year of age in 2004)

Group B meningococcal OMV vaccines for epidemics

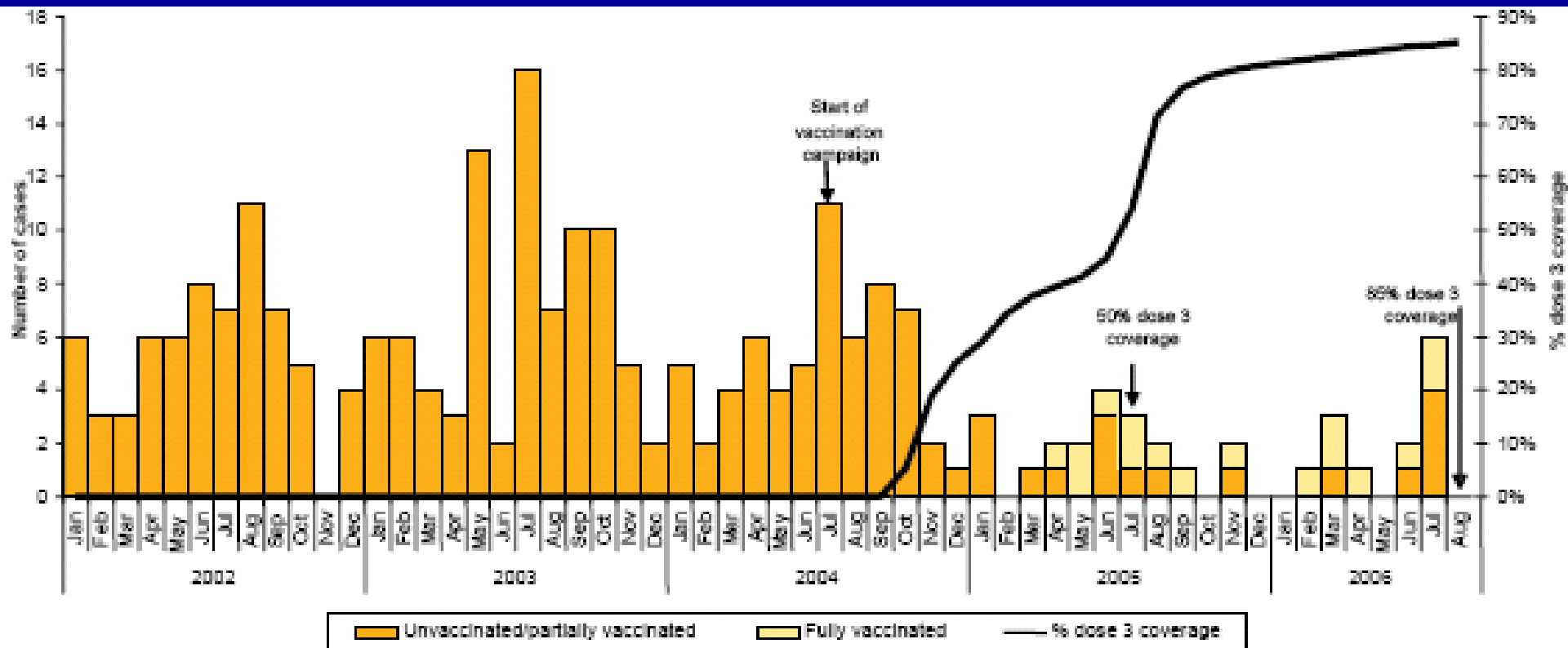
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Novartis MeNZB OMV vaccine in New Zealand

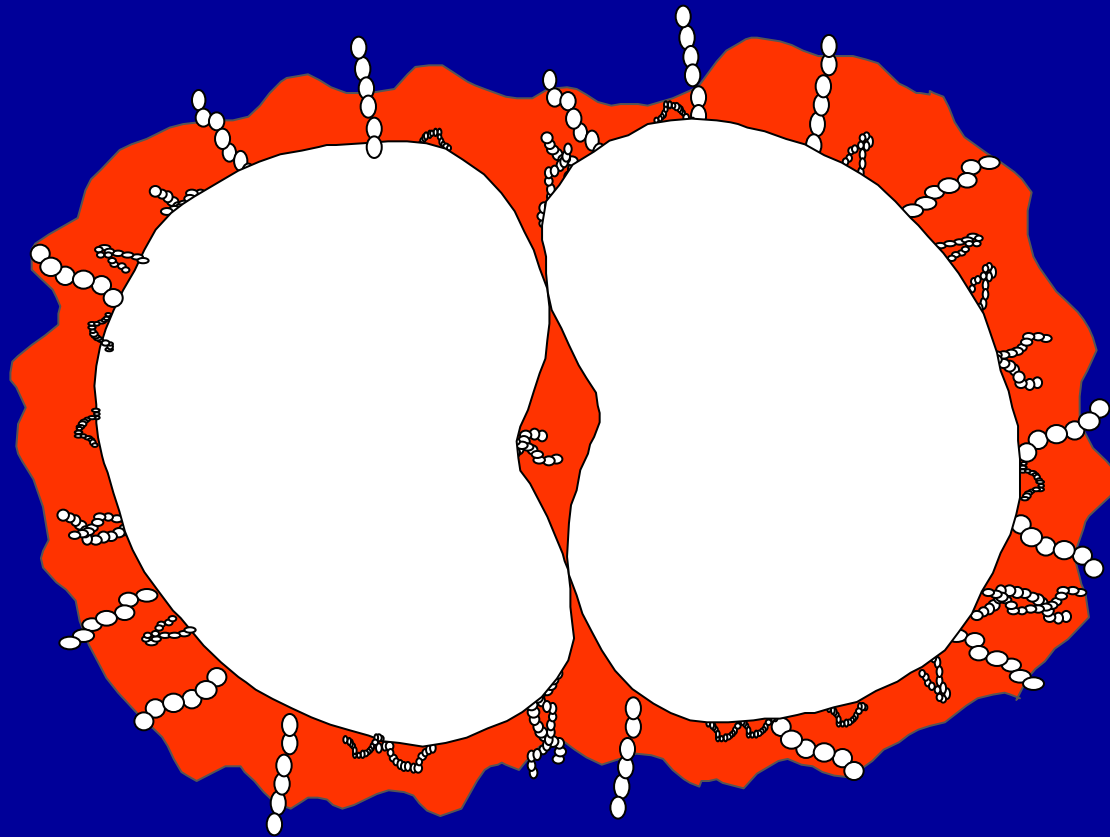
~ 1M under-20s; roll-out 2004-6

Impact on the New Zealand epidemic



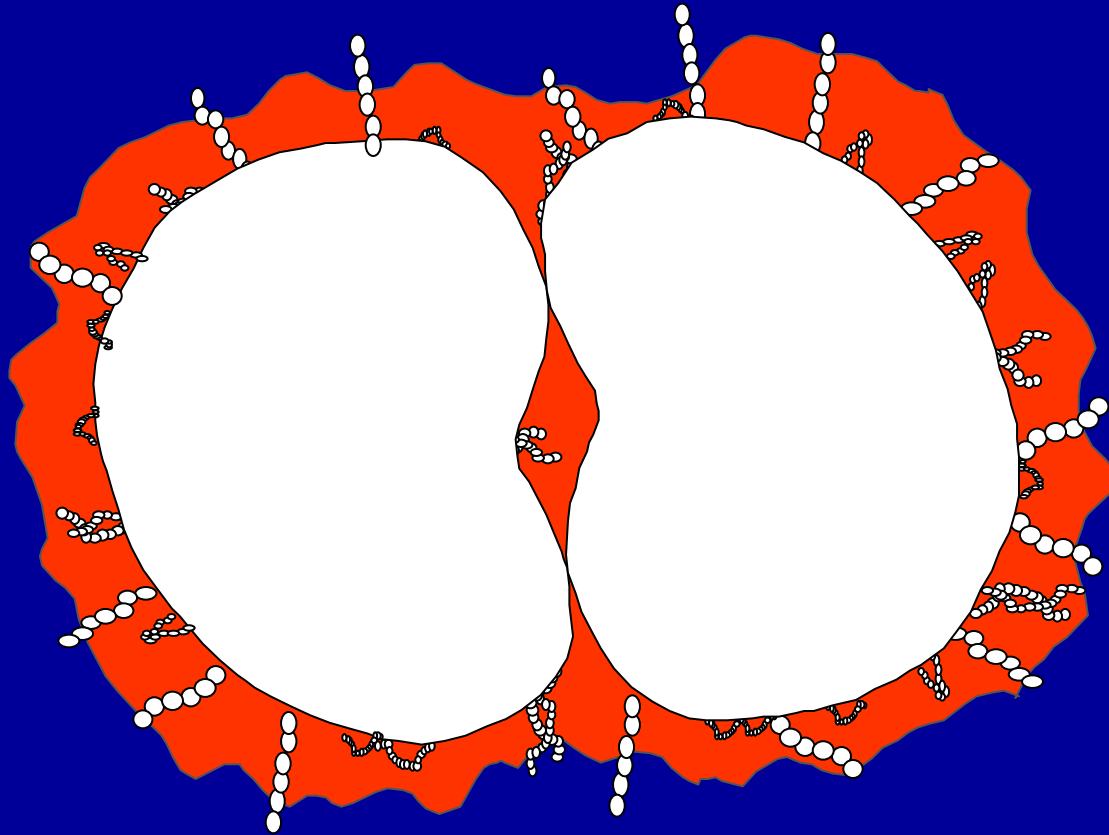
78% vaccine effectiveness ages 2 months – 18 years

Discovering elusive conserved proteins of meningococcus B



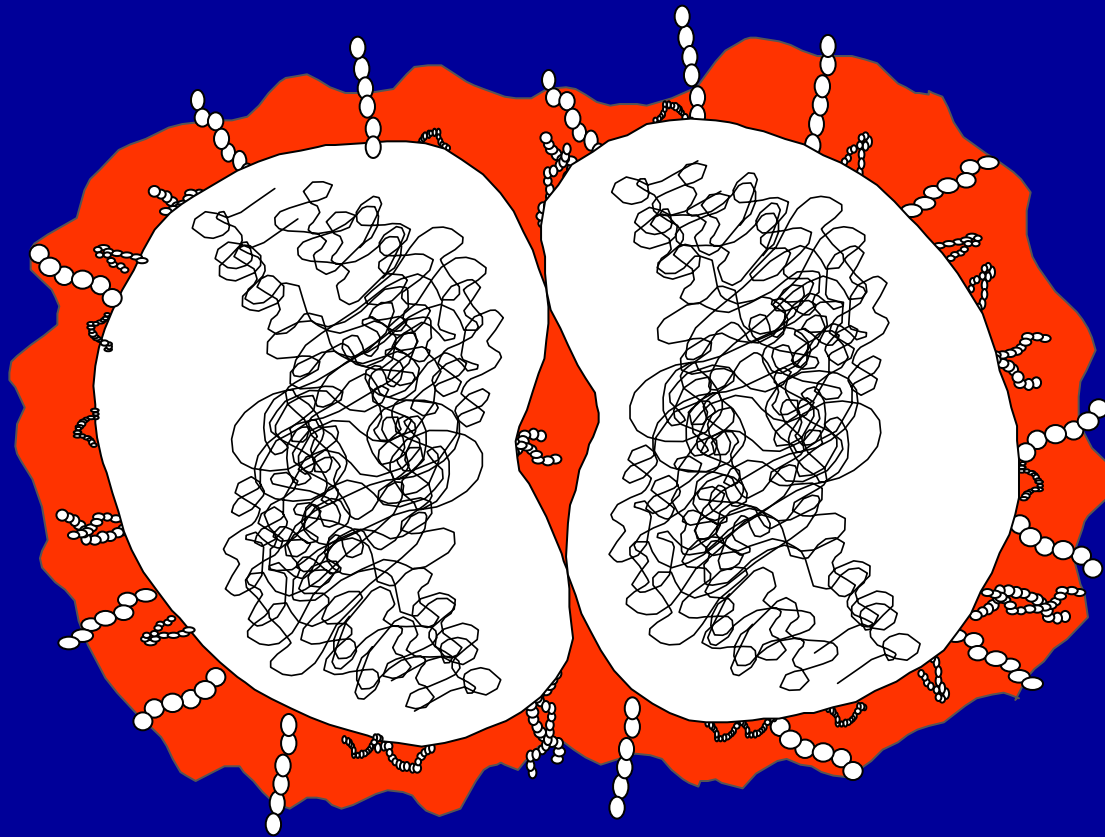
Discovering elusive conserved proteins of meningococcus B

A vaccine for endemic disease?



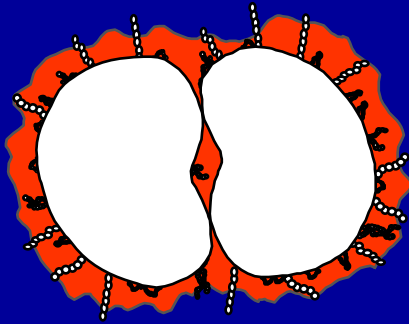
Discovering elusive conserved proteins of meningococcus B

“Reverse Vaccinology” – from genes to vaccines



A universal vaccine for serogroup B meningococcus

Giuliani MM *et al.* 2006.



- NadA – adhesion protein
- fHbp – Factor H binding protein
- NHBA – heparin-binding antigen
- + PorA sero-subtype P1.4

“... 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.

4CVMenB - investigational Novartis MenB vaccine

NadA, fHbp, NHBA + PorA P1.4

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 strains used to make the vaccine:

100%, 100%, 98%, & 93%, + evidence of immune memory
fHbp NHBA NadA P1.4

THE INDEPENDENT

(Ireland, €1.10) 80p

Thursday 15 May 2008
www.independent.co.uk

Today
**.education
& careers**

40-page
supplement
inside



Hollywood's longest feud

Two stars and the family row that won't go away PAGES 18&19



MENINGITIS: DEFEATED AT LAST?



Parents live in fear of this infection. It targets the young and strikes with horrific speed. One in 10 dies, and many others suffer permanent disabilities. But yesterday scientists revealed a startling breakthrough

FULL REPORT PAGE 2 PLUS 'THE DAY IT STRUCK MY CHILD', BY FRANK KANE

Janet Street-Porter

Rise up
against the
eco-towns!

Comment
page 34



Cooper Brown

Hits the
Côte d'Azur

Extra
Page 7



The best
**Portable
DVD
players**

Extra
Page 24



The Independent, London. 15th May 2008

4CVMenB - investigational Novartis MenB vaccine

NadA, fHbp, NHBA + PorA P1.4

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Does it work?

Insights from

genotyping

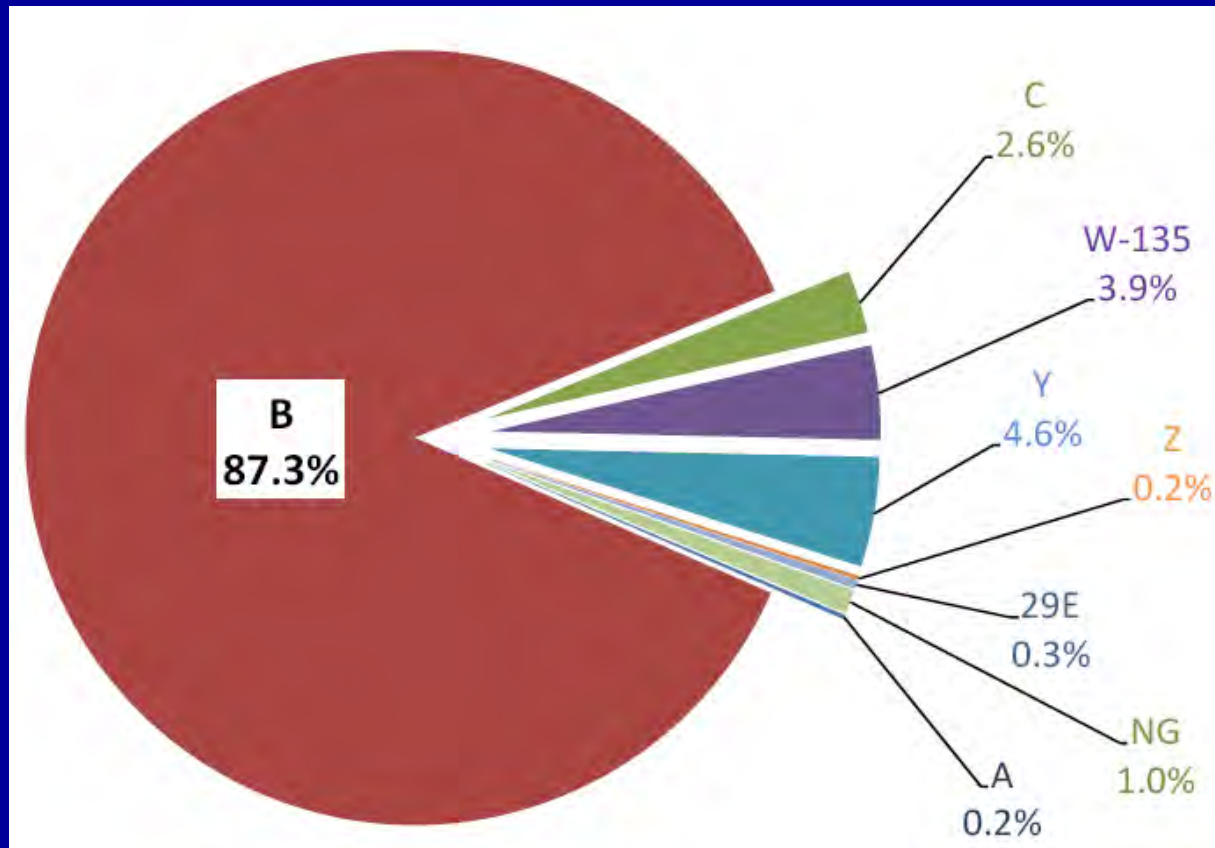
meningococcal strains

Strain collection for vaccine appraisal in UK

HPA Meningococcal Reference Unit, Manchester

All invasive meningococcal isolates submitted Jul '07- Jun '08

Capsular serogrouping (n = 613)



Data courtesy of Professor Ray Borrow, HPA

Strain collection for vaccine appraisal in UK

HPA Meningococcal Reference Unit, Manchester

Genotyping of Men B strains submitted Jul '07- Jun '08

for 4CVMenB coverage

- PorA (P1.4) 22% +ve
- NadA 9.5% +ve
- fHbp 65% +ve
- NHBA ~100% +ve



but gene expression uncertain . . .

Does it work?

Insights from
immuno-phenotyping
meningococcal strains

Immuno-phenotyping for “vaccine preventability”

1. Bacterial antigens extracted for antibody inhibition ELISA, using pooled sera from adult and infant vaccinees.
2. Results correlated with bactericidal assay using standard strains
3. 124 serogroup “international” B strains:
Meningococcal Antigen Typing correlated with killing (the “MATS assay”).
 - 3 vaccine Ags above threshold, 100% killed by pooled adult sera
 - 2 vaccine Ags above threshold, 94% killed by pooled adult sera
 - 1 vaccine Ag above threshold, 85% killed by pooled adult sera
4. UK strain collection → estimated coverage high 70s %

15th November 2012

European Medicines Agency,

Committee for Medicinal Products for Human Use.

“Positive Opinion” for BEXSERO

*for active immunisation of individuals >2 months old
against invasive infection caused by
Neisseria meningitidis serogroup B*

Meningitis B vaccine gets European licence

By Michelle Roberts

Health editor, BBC News online

22 January 2013 Last updated at 09:58

A vaccine to protect children against one of the most common and deadly forms of meningitis has been licensed for use in Europe.

The Bexsero vaccine licensed by the European Commission is the first to cover meningococcal B meningitis - until now vaccines had protected against only some of the bacterial types involved.

About 1,870 people contract meningitis B each year and one in 10 die.

The UK is yet to roll out the jab.

The Joint Committee on Vaccination and Immunisation (JCVI) which provides vaccination advice to the government plan to meet in June when they will discuss the vaccine and whether to add it to the list of vaccines routinely offered to young children.

Meningitis UK said: "We urge the JCVI and UK government to introduce the new MenB vaccine to the childhood immunisation schedule as soon as possible. Every day of unnecessary delay in introducing this vaccine will cost lives. We must not allow children to die from this disease if it can be prevented."

Now it is licensed in the UK and other EC countries, it could potentially be bought and used by healthcare providers.



The vaccine is not currently recommended in the UK

Related Stories

[Meningitis jab 'protection hope'](#)

[Parents back meningitis warnings](#)

[Meningitis B trials 'encouraging'](#)

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Novartis Bexsero Meningitis Shot Wins EU Agency's Backing

By Eva von Schaper - Nov 16, 2012 4:58 PM GMT

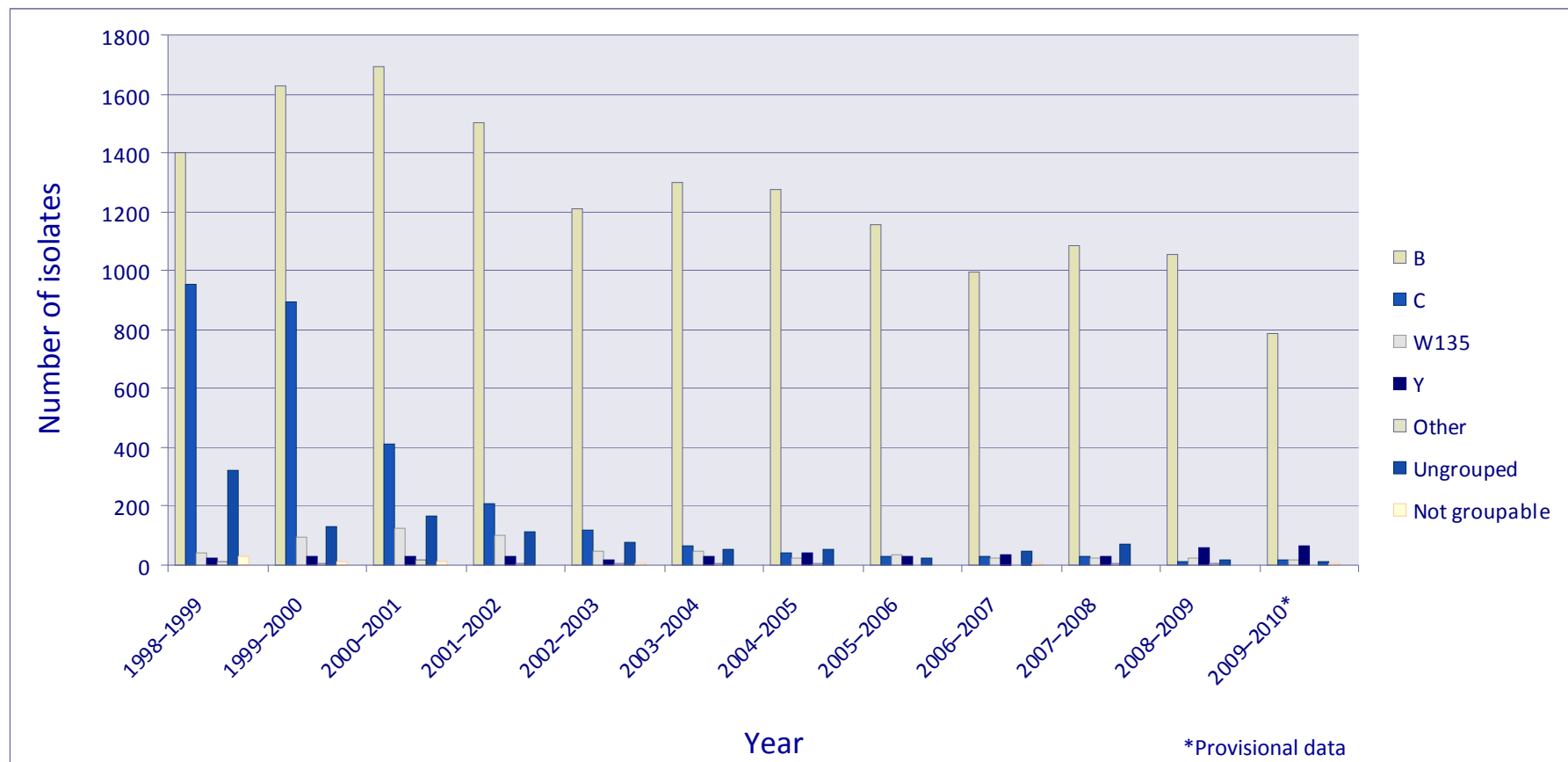


Basel, Switzerland-based Novartis, Europe's largest drugmaker by sales, must still convince national health agencies to recommend that parents give their children the shot and governments to pay for it.



Basel, Switzerland-based Novartis, Europe's largest drugmaker by sales, must still convince national health agencies to recommend that parents give their children the shot and governments to pay for it.

Neisseria meningitidis (Meningococcal Disease) Isolates by Serogroup in England and Wales 1989–2010¹



- Similar trend in Scotland of a reduction in total number of cases²

1. Health Protection Agency. Meningococcal Disease. Epidemiological Data. Serogroup breakdown 1998–1999 to 2009–2010. http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1234859711901.

2. Health Protection Scotland. Immunisation and vaccine preventable disease. Meningococcal disease. <http://www.hps.scot.nhs.uk/immvax/meningococcaldisease.aspx>.

