Benefits of the pneumococcal immunisation programme in children in the United Kingdom 2006-2014

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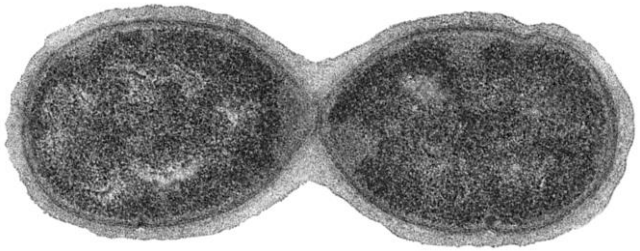

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Disclosure of interest

The presenter has received honoraria from

Pfizer, GlaxoSmithKline Biologicals & Merck

as a speaker and member of advisory boards

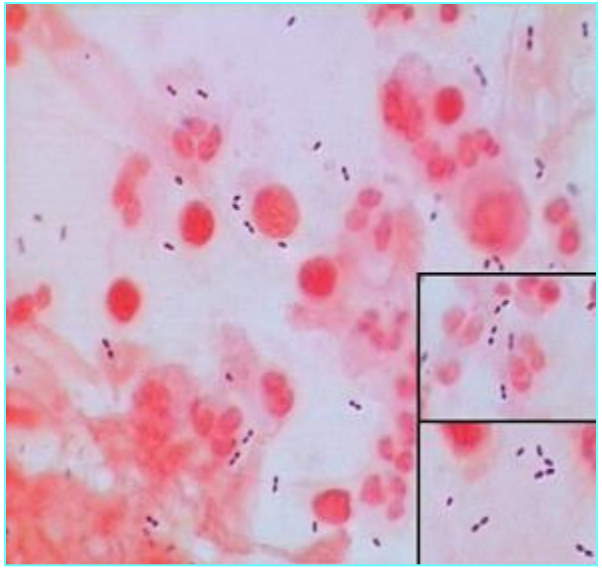
and funding to attend scientific meetings/conferences

Streptococcus pneumoniae

- Gram-positive diplococci
- More than 90 capsular types

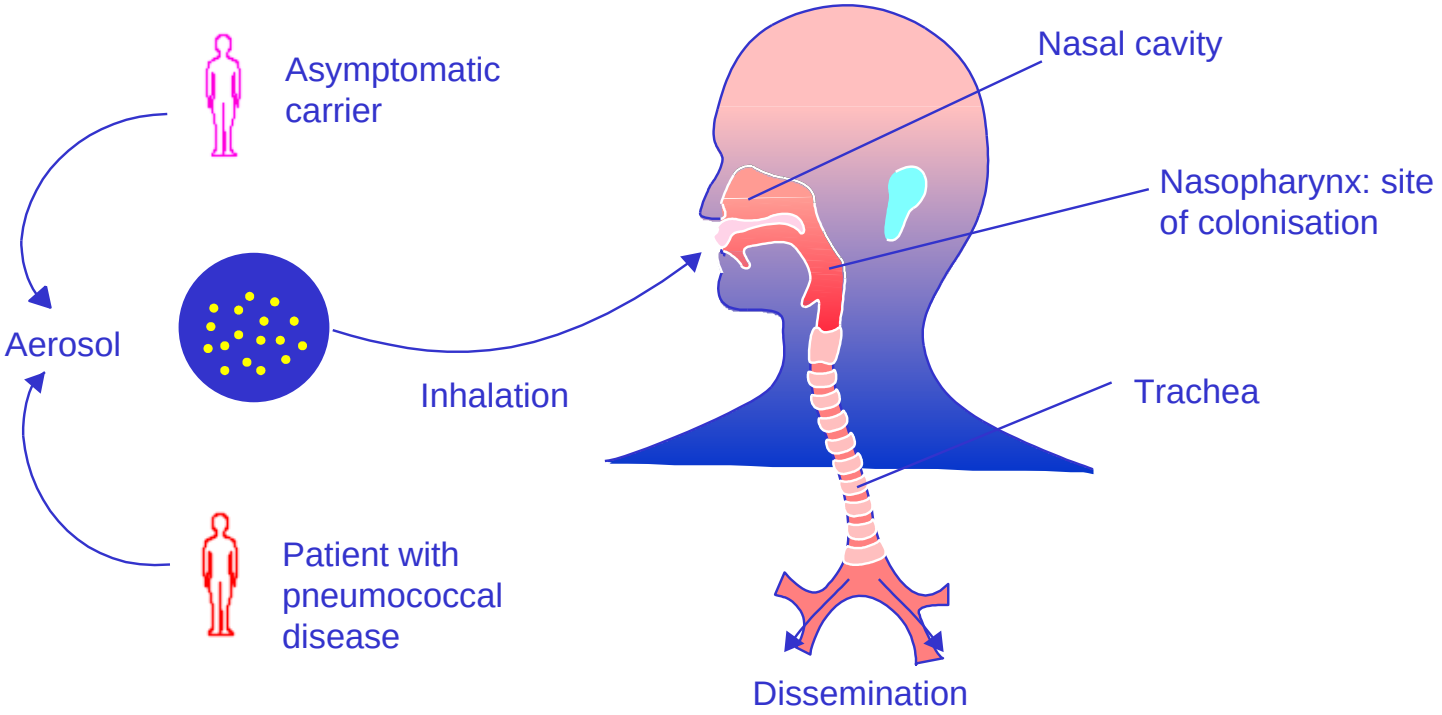
- Geographical, temporal and age-related differences in distribution of serotypes

Pneumococci with visible capsule

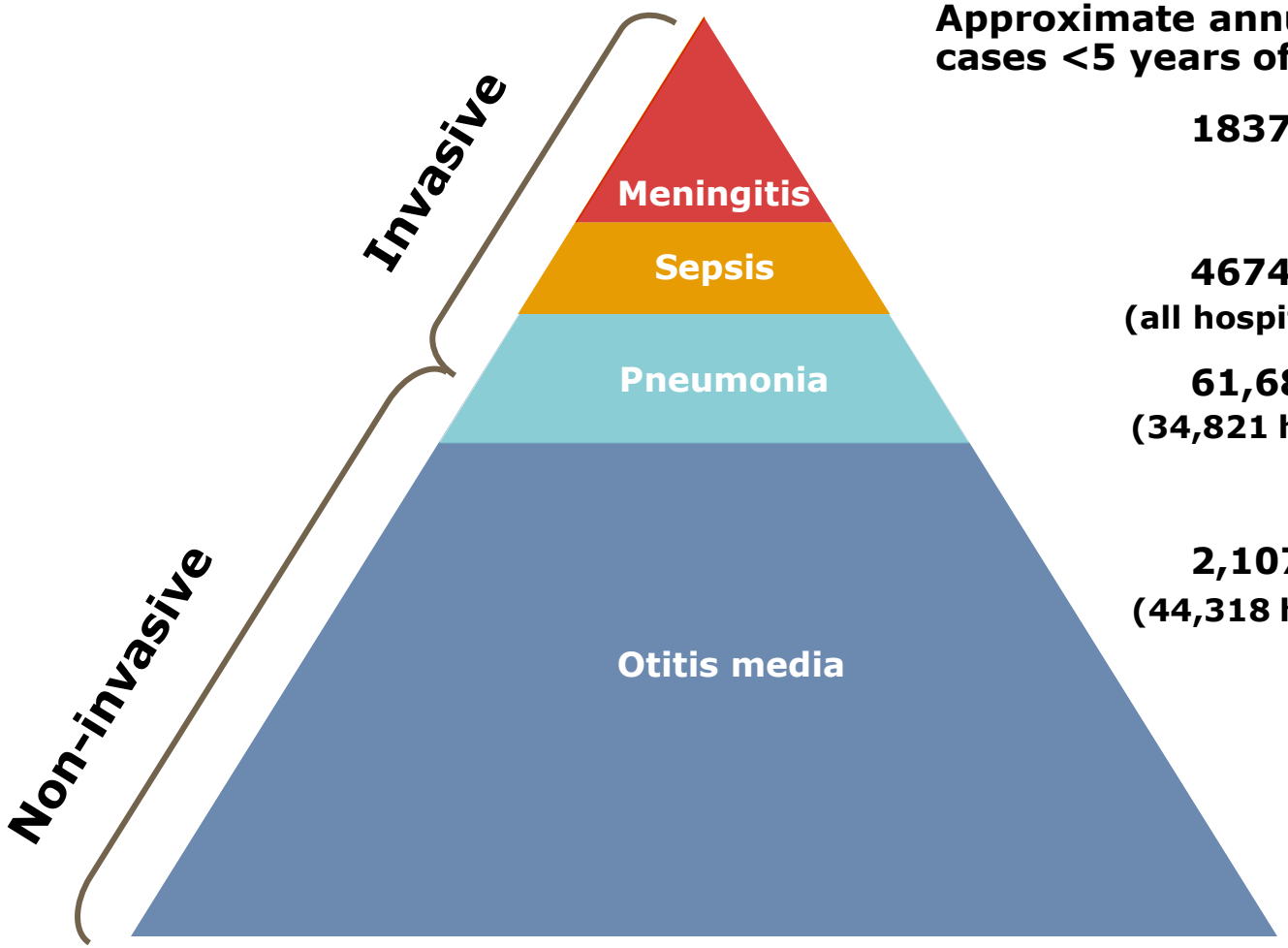


Pneumococcal Carriage

Nasopharyngeal carriage may occur in up to 60% of healthy pre-school children and up to 30% of healthy older children and adults



Pneumococcal disease spectrum (EU)



Approximate annual number of cases <5 years of age*

1837

156 deaths

4674

(all hospitalised)

61,684*

(34,821 hospitalised)

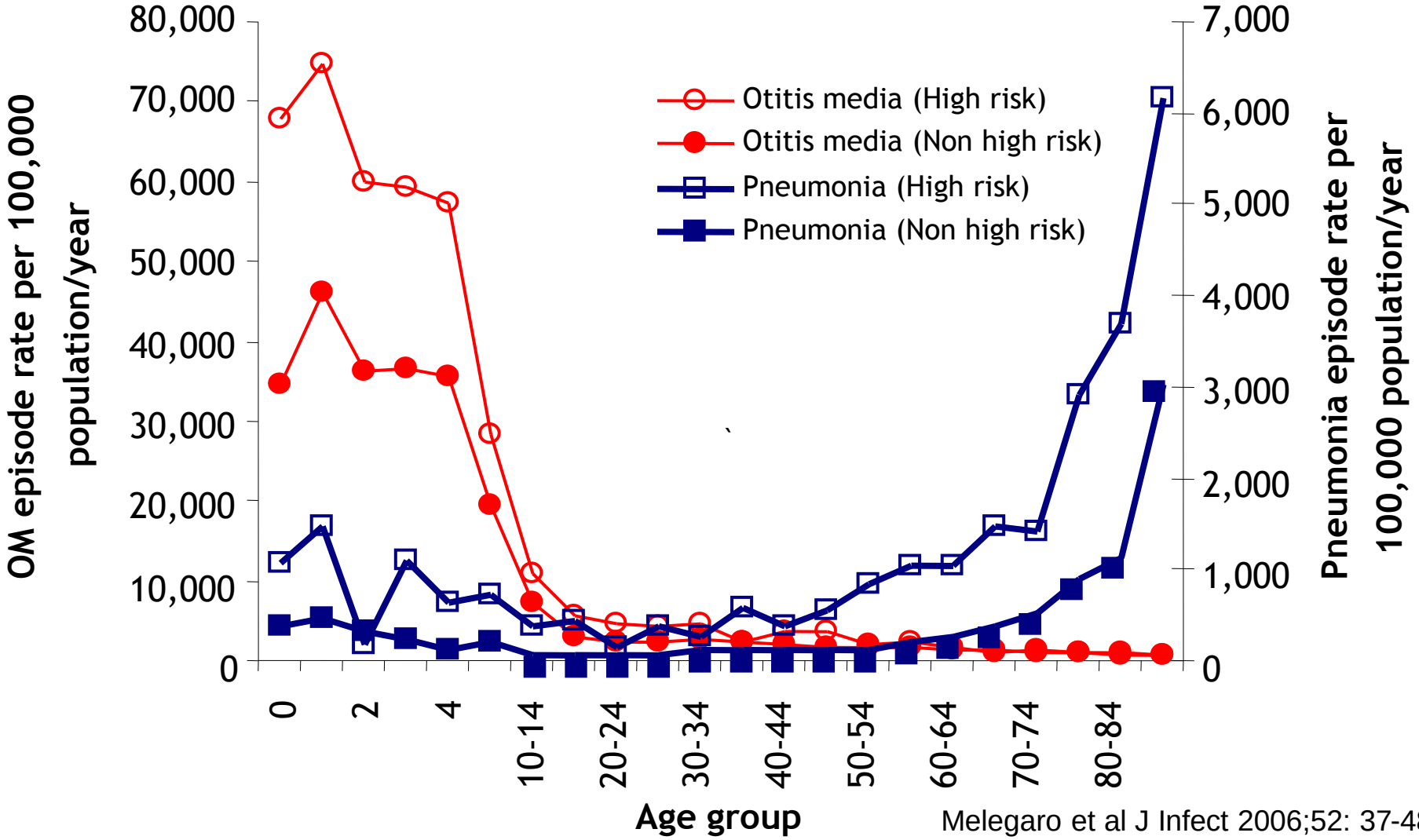
2,107,741**

(44,318 hospitalised)

*26% of all CAP assumed to be due to pneumococcus
**23% of all AOM assumed to be due to pneumococcus
AOM = acute otitis media. CAP = community-acquired pneumonia.
Melegaro A, et al. *J Infect* 2006;52:37–48

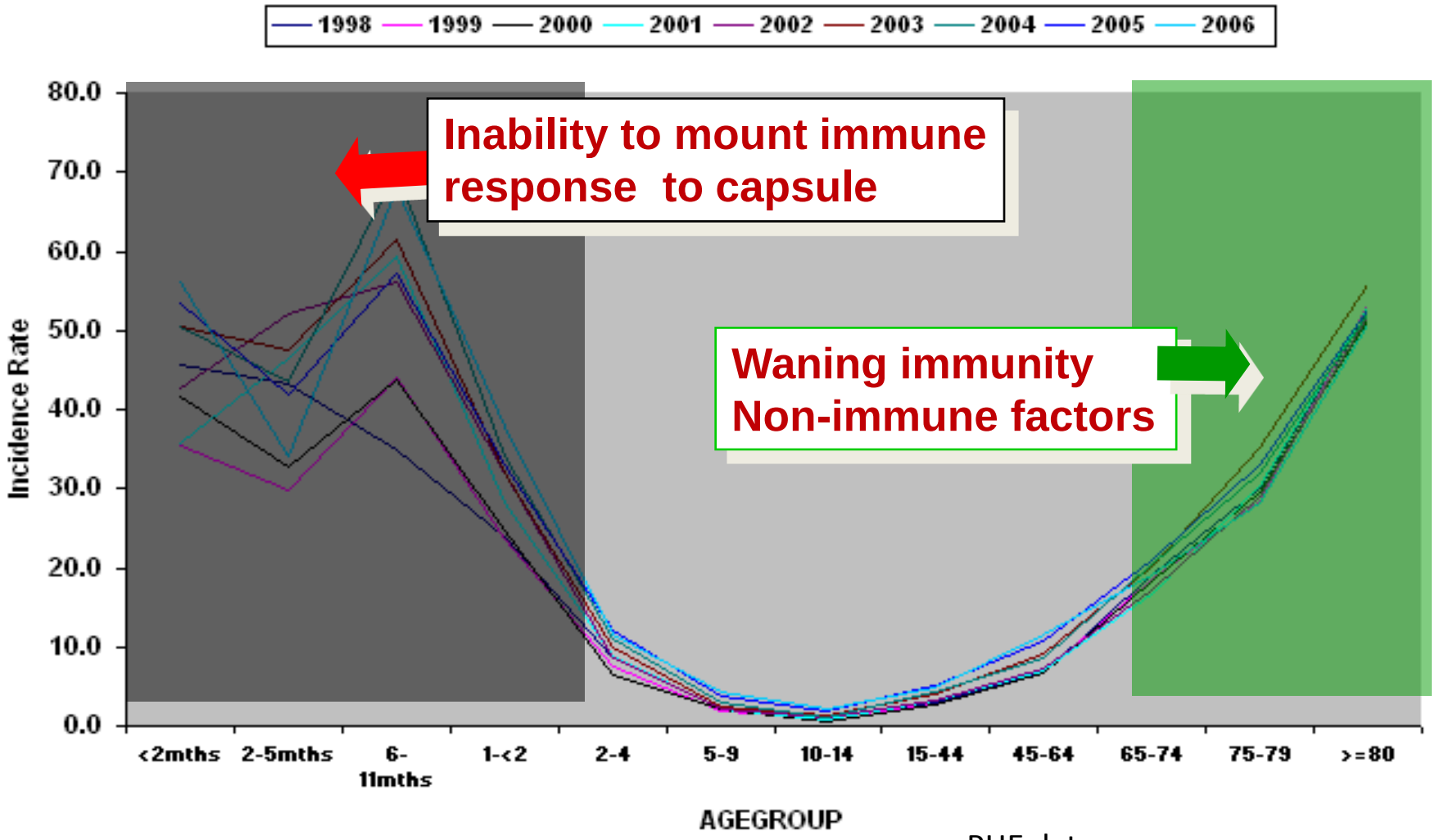
Burden of Pneumococcal disease

GP consultation rate for CAP and OM



Melegaro et al J Infect 2006;52: 37-48

Annual incidence per 100,000 of invasive pneumococcal infection England & Wales by age group & year 1998-2006



PHE data

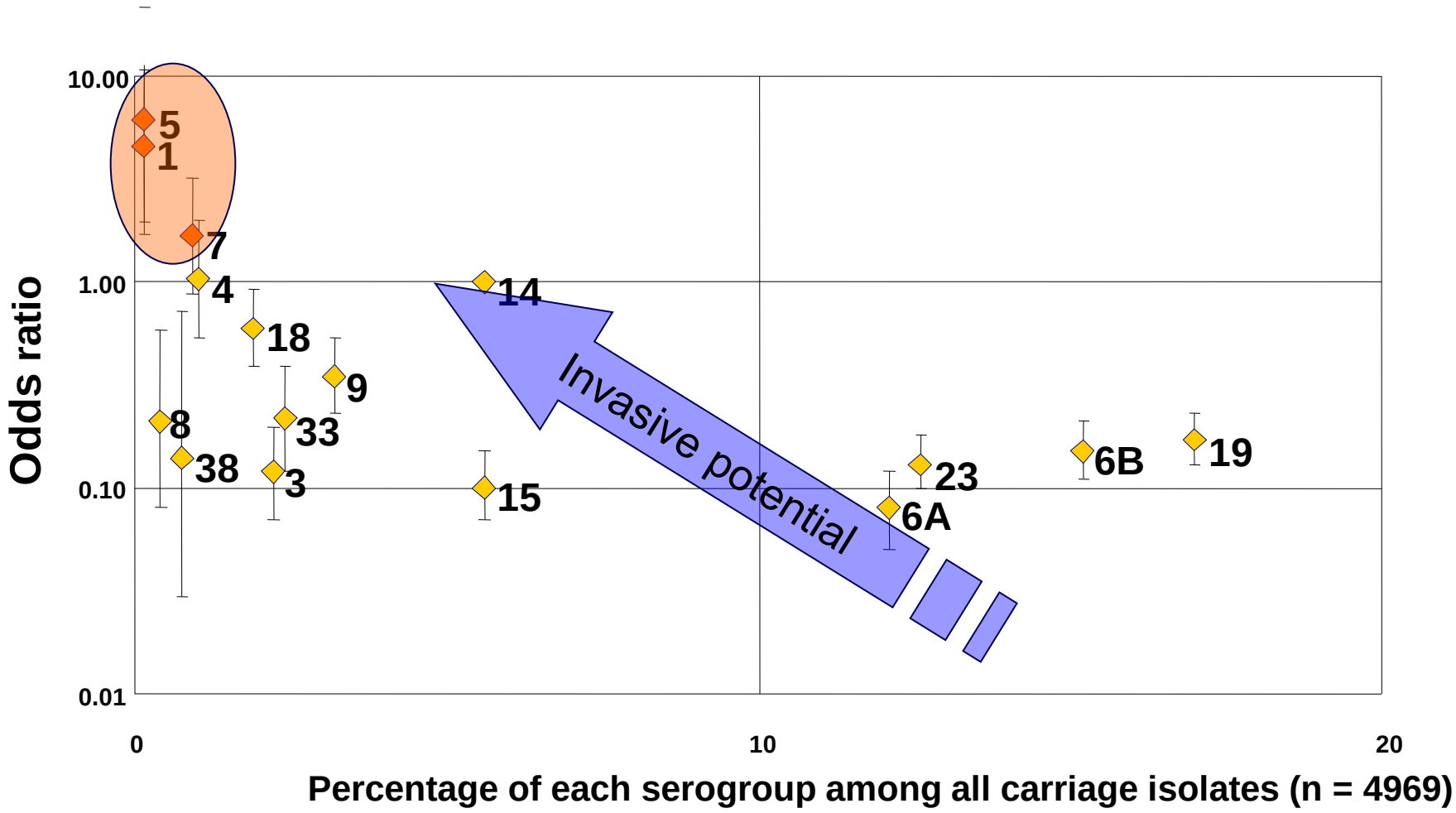
Burden of invasive pneumococcal disease (IPD) in Europe

- Prior to Pneumococcal Conjugate Vaccine (PCV7) introduction in Europe*
  - Mean annual incidence IPD = 44.4/100,000 children <2y
  - Mean case fatality rate for IPD = 3.5%

- Most common serotypes were 14, 6B, 19F, 23F (all in PCV7)

*Isaacman et al Int J Inf Dis 2010;14: e197-209

Serotypes 1, 5 and 7F are invasive serotypes



A. Brueggemann, Pneumococcus Book Chapter, 2007

Antibiotic susceptibility in Europe before PCV7

	Mean
Penicillin (2y): 0% (Finland) to 48% (Slovakia)	23%
Penicillin (5y): 5% (Denmark) to 55% (Slovakia) [49% (Spain)]	29%
Erythromycin (2y): 26% (Germany) to 59% (Belgium)	41%
Erythromycin:(5y): 7%(Denmark) to 53% (Spain)	35%
3rd gen Ceph (5y): 0% (France) to 36% (Slovakia) [7% (Spain)]	9%

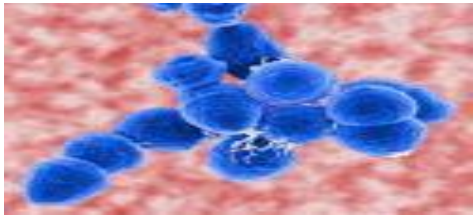
Isaacman et al Int J Inf Dis 2010; 14: 197

Pneumococcal Vaccines

- Two types of pneumococcal vaccines currently available:

Plain Polysaccharide : PPV(23V)	Conjugate: PCV (13V, 10V)
•not effective in under 2y olds	•effective in under 2y olds
•does not induce immunologic memory	•induces immunologic memory
•does not protect against non-invasive disease (e.g. otitis media and nonbacteraemic pneumonia)	•protects against non-invasive disease
•does not reduce nasopharyngeal carriage so no herd protection	•reduces carriage thus induces herd protection

Pneumococcal vaccines



There are over 90 serotypes of *Streptococcus pneumoniae*

7-valent pneumococcal conjugate vaccine (PCV7) contains serotypes

14 18C 19F 23F 4 6B 9V

Additional serotypes in PCV10

1 5 7F

Additional serotypes in PCV13

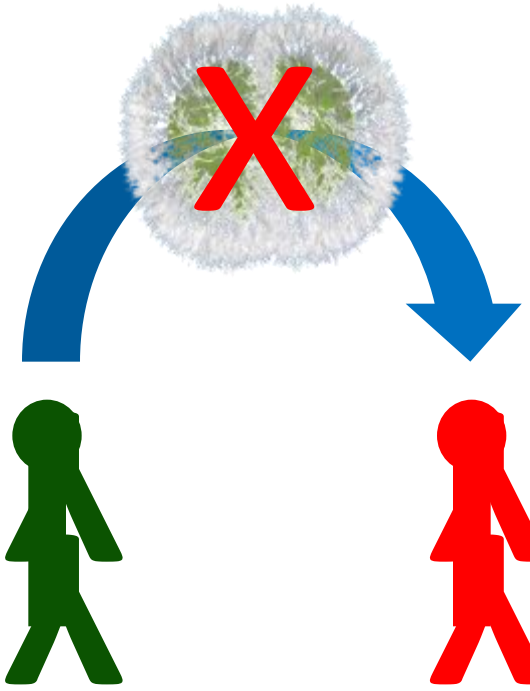
1 3 5 6A 7F 19A

The 23 valent plain polysaccharide vaccine (PPV 23) contains

1 2 3 4 5 6B 7F 8 9N 9V 10A 11A 12F

14 15B 17F 18C 19A 19F 20 22F 23F 33F

Herd protection: indirect protection against disease in non-immunised individuals



Immunised **Non-immunised**

Effective vaccines provide direct protection to immunised individuals

↓

Reduced pathogen transmission; reduced risk of colonisation of new hosts and reduced carriage (less circulating pathogen)

↓

Indirect protection of non-immunised individuals (reduced carriage = reduced disease)

Trotter, C. and Maiden, M. *Exp Rev Vacc,* 2009; 8: 851–61

Evolution of pneumococcal vaccination strategy in England and Wales

- 1992 **PPV23** (23-valent pneumococcal polysaccharide vaccine) in ≥2 years of age at increased risk of IPD.
- 2002 **PCV7** for children < 2 years of age at increased risk of IPD.
- 2003 **PPV23** for ≥ 80 years of age.
- 2004 **PPV23** for ≥ 75 years of age.
- 2005 **PPV23** for ≥ 75 years of age.
- 2006 From September, **PCV7** as a 2 + 1 schedule in infant immunisation schedule. Catch- up to 2 years of age.
- 2010 From April, **PCV13** replaced PCV7, no catch-up.

Surveillance of invasive pneumococcal disease

- Establish baseline epidemiology
- Monitor impact of vaccine intervention
- Monitor serotype replacement
- Monitor epidemiological trends over time
- Monitor antimicrobial resistance

PHE Enhanced Surveillance of IPD England and Wales from 2006

All microbiology Labs in England and Wales

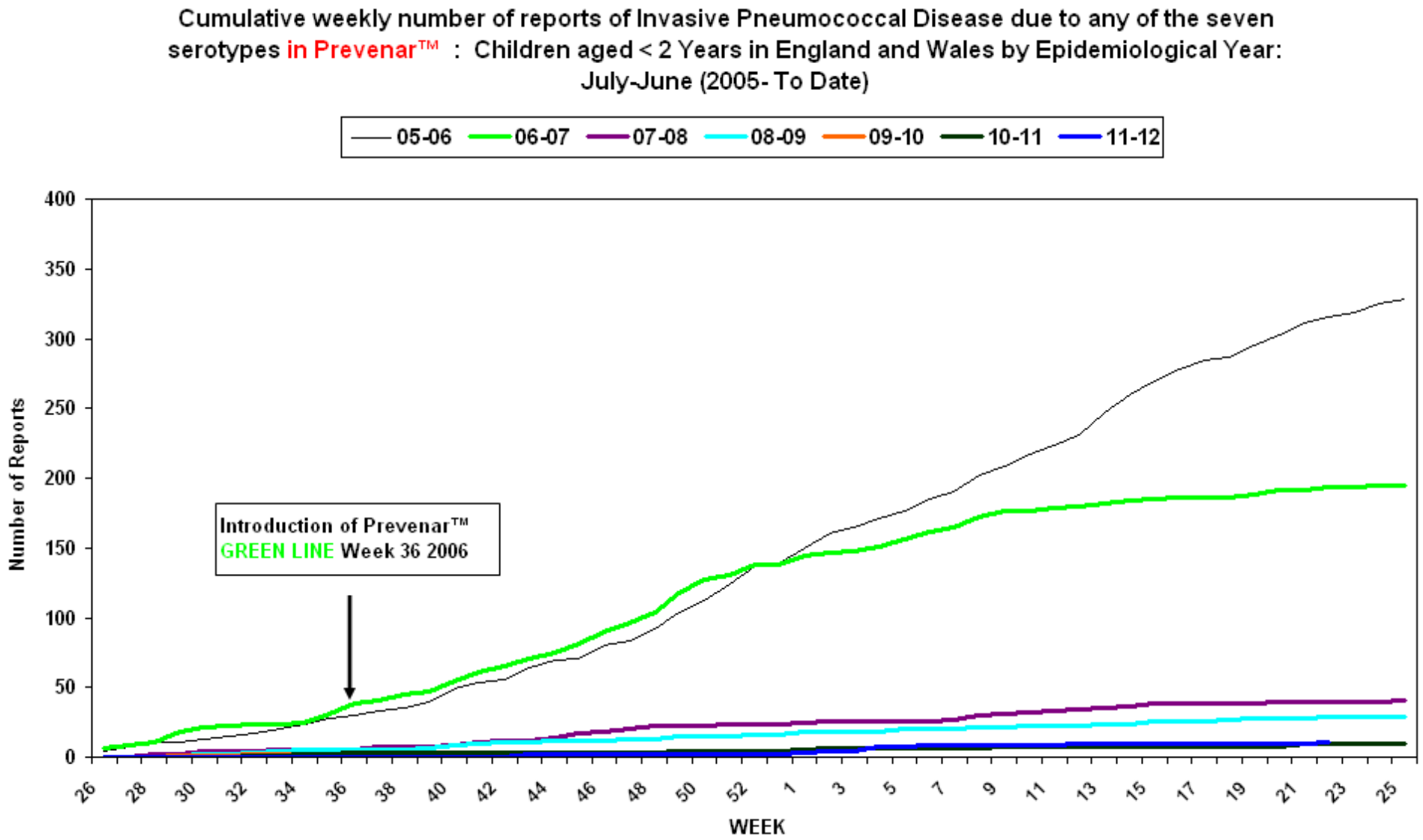
S pneumoniae **cultures sent for serotyping to Colindale**

Reports of *S. pneumoniae* isolates sent to Colindale electronically

Joint data set generated by reconciling the two data sources (approx 6000/yr)
Analysed by Epidemiological year (July to June)

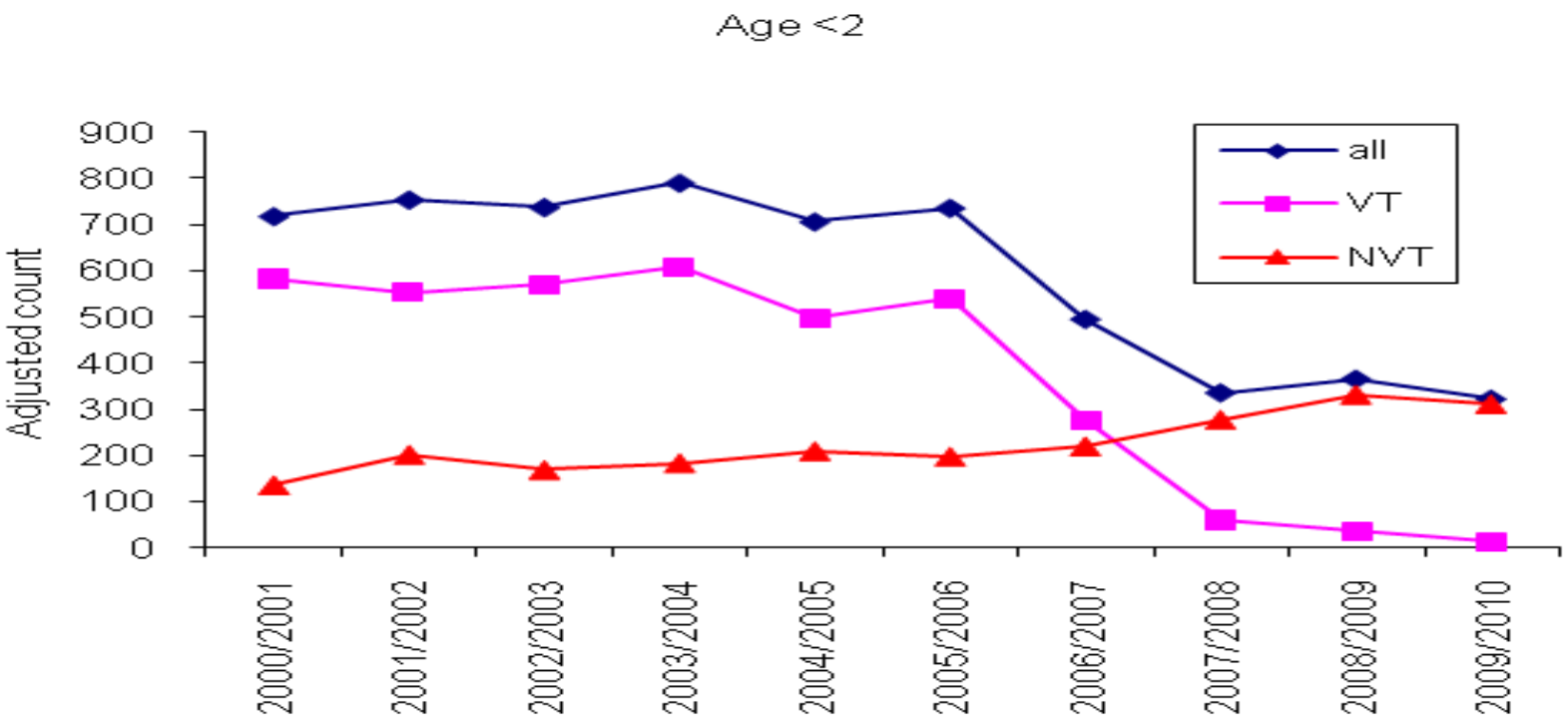
Follow up of children eligible to receive PCV (born since 4/9/04) for PCV vaccination status and clinical information from physician

What was the impact of PCV7 ?



PHE enhanced surveillance of IPD in England and Wales

Reduction in disease incidence for children < 2 and for all ages

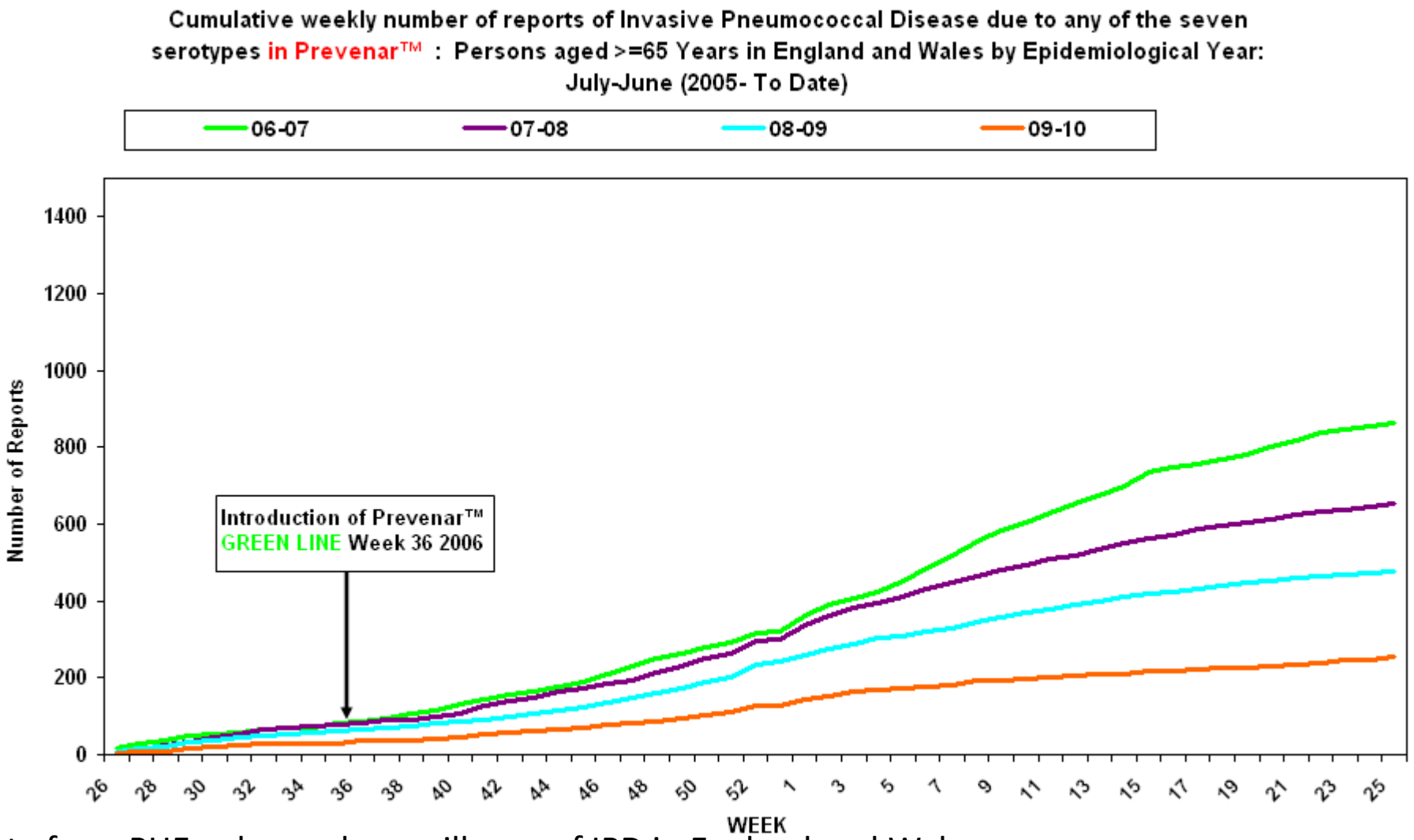


98% reduction in IPD caused by PCV7 serotypes in children aged under 2 years

OVERALL 56% reduction in this age group

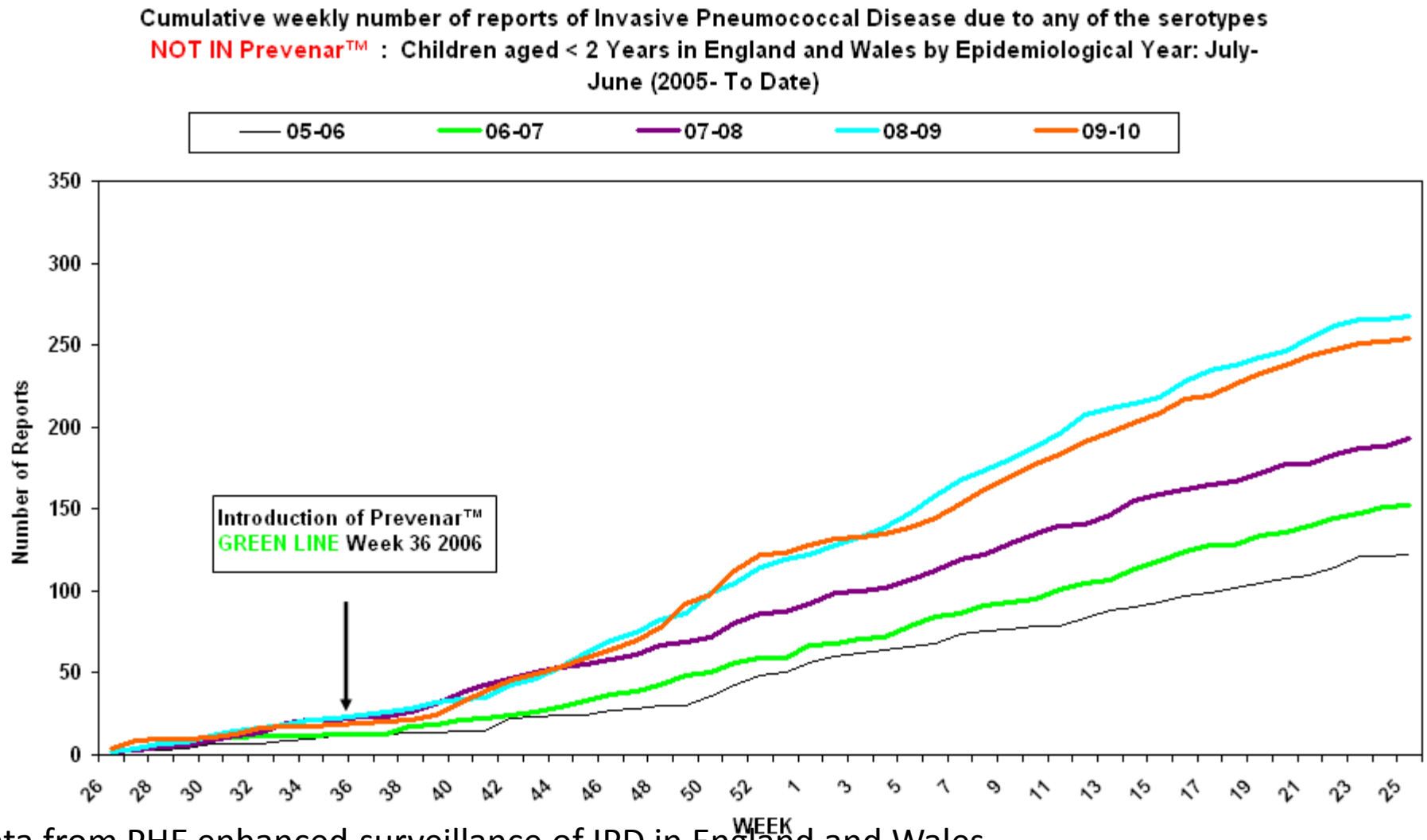
Data from PHE enhanced surveillance of IPD in England and Wales

Herd protection in age >=65 years



Data from PHE enhanced surveillance of IPD in England and Wales

Serotype replacement after PCV7



Data from PHE enhanced surveillance of IPD in England and Wales

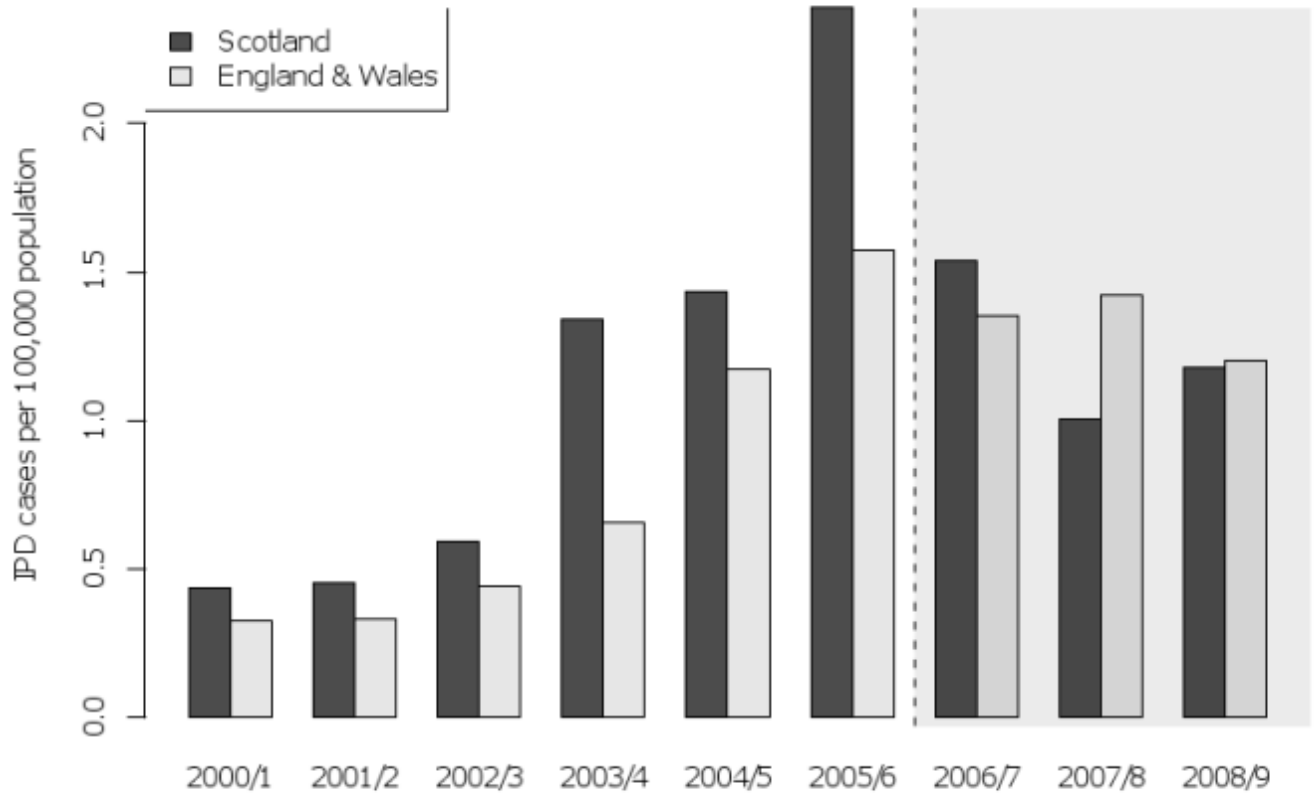
Impact of PCV7 in UK

- Significant reduction in Vaccine Type IPD in all ages for 2008-2010
- Significant increase in all age groups for

  7F, 19A, 22F IPD
- 19A increase not associated with antimicrobial resistance
- Evidence of natural secular trends with some Non Vaccine serotypes : 1,8, 9N

Data from PHE enhanced surveillance of IPD in England and Wales

Long term trends in serotypes unrelated to PCV7, for example ST 1 in UK, changes mainly in 5-64 year olds



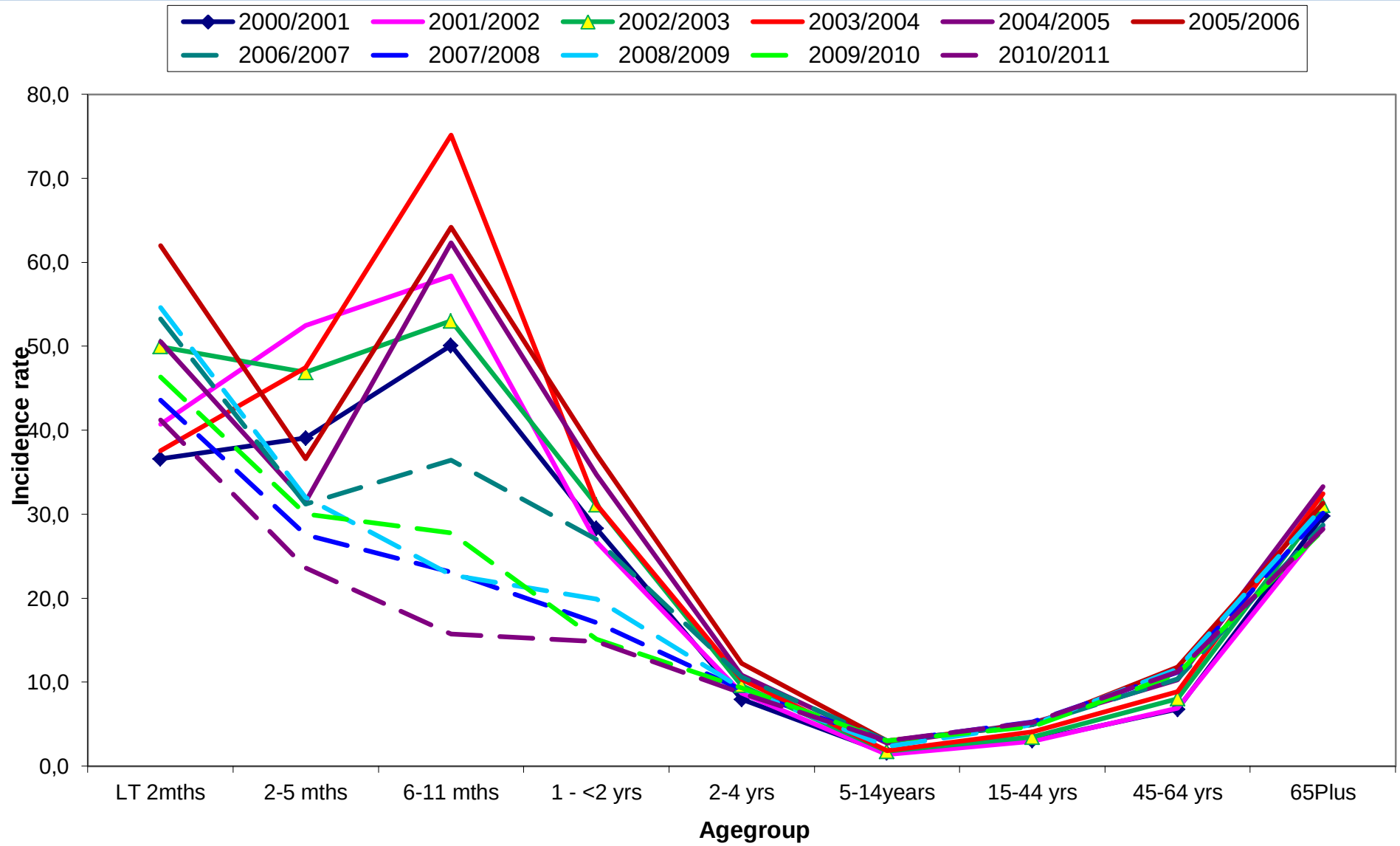
Scottish data: Flasche S, Robertson C et al. Trends in serotypes among cases of invasive pneumococcal disease (IPD) in Scotland after the introduction of PCV7. 7th International Symposium on Pneumococci and pneumococcal diseases, Tel'Aviv, Israel, March 4-18, 2010.
England & Wales data, HPA unpublished data

PCV7 Impact on antibiotic susceptibility in Europe

- Penicillin : 40% decrease in resistance rate
- Macrolides: 40% decrease
- Cephalosporins: 10% decrease

Calbo et al Clin Microbiol Infect 2006;12: 867
Aristegui et al Eur J Clin Microbiol Infect Dis 2007; 26:303
Vestrheim et al Vaccine 2008; 26:3277
Aguiar et al Clin Microbiol Infect 2008; 14: 835

Incidence of IPD/ 100,000 population by age: England & Wales 1998-2011 (PHE data)



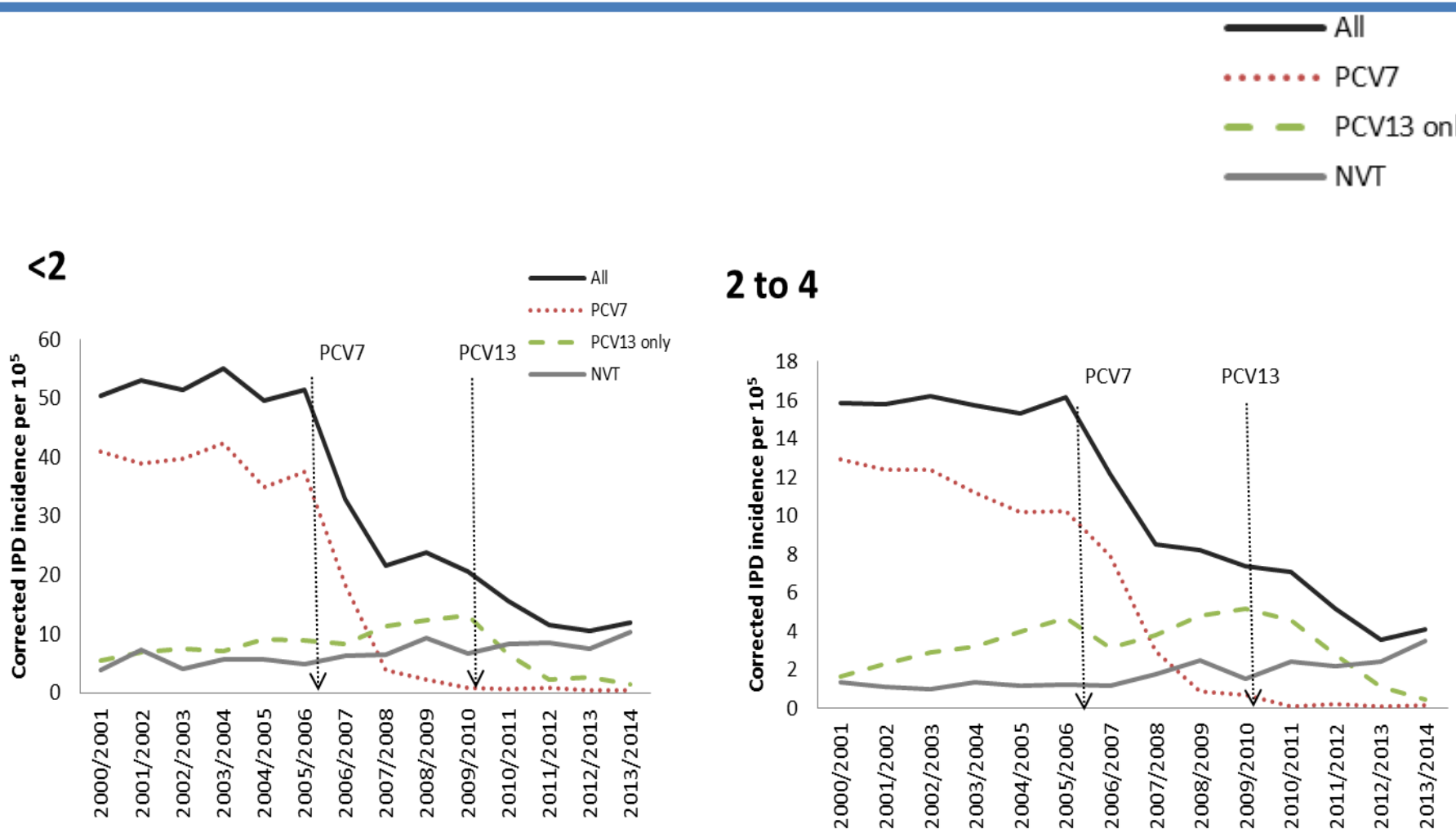
PCV7 was replaced by PCV13 in April 2010

CASES OF IPD in children FOLLOWED UP to Feb 2014 (PHE data)

- 3204 cases of IPD in children born since 04/09/2004
- 90% serotyped – i.e. Isolate sent to RSIL
  - » Remainder are from CoSurv reports to Centre For Infections but no isolate sent to RSIL for serotyping
    - Immunisation status obtained for 99.5%
    - 308 of total serotyped (19%) have a PCV7 serotype
    - 865 of total serotyped (53%) have a PCV13 (but not in 7) serotype
- Clinical risk factor information obtained for 92%

  15% of children had a risk factor for IPD
- 196 children have died
  - » Around (75%) attributable to pneumococcal sepsis
- There have been 60 PCV7 vaccine failures
- There have been 92 PCV13 vaccine failures
- 22% had pneumococcal meningitis
  - » Case fatality rate of meningitis was 13%

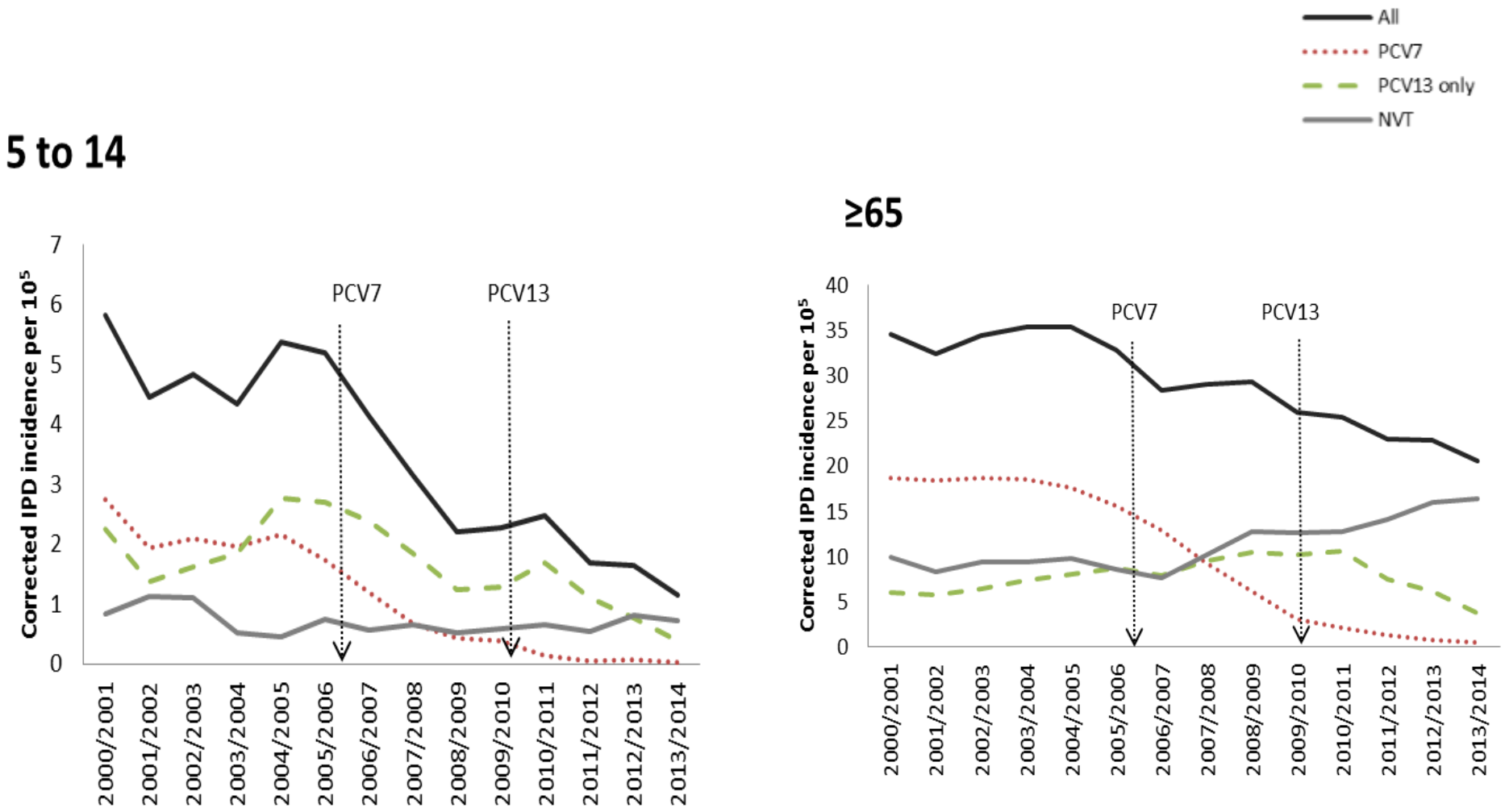
Adjusted incidence rates of IPD by year and serotype grouping



nvt = non-vaccine types

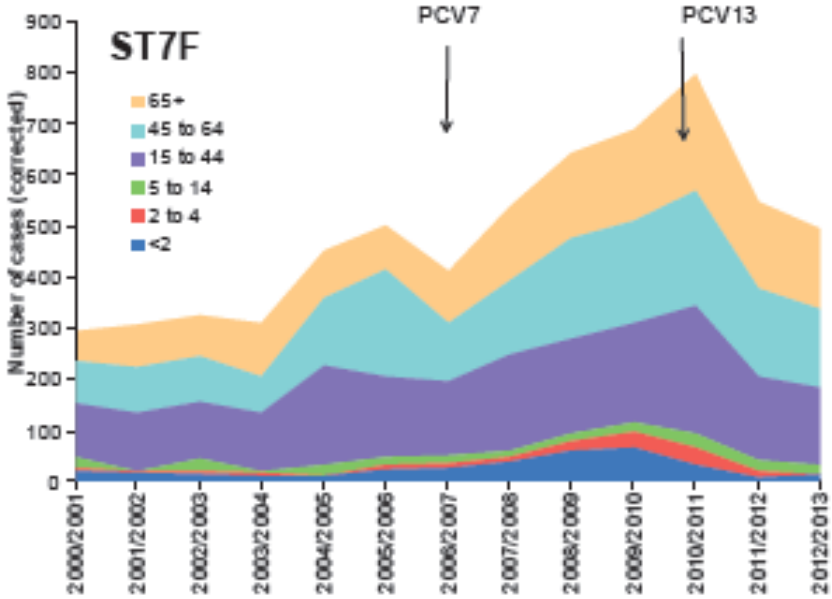
Data from PHE surveillance of IPD

Adjusted incidence rates of IPD by year and serotype grouping

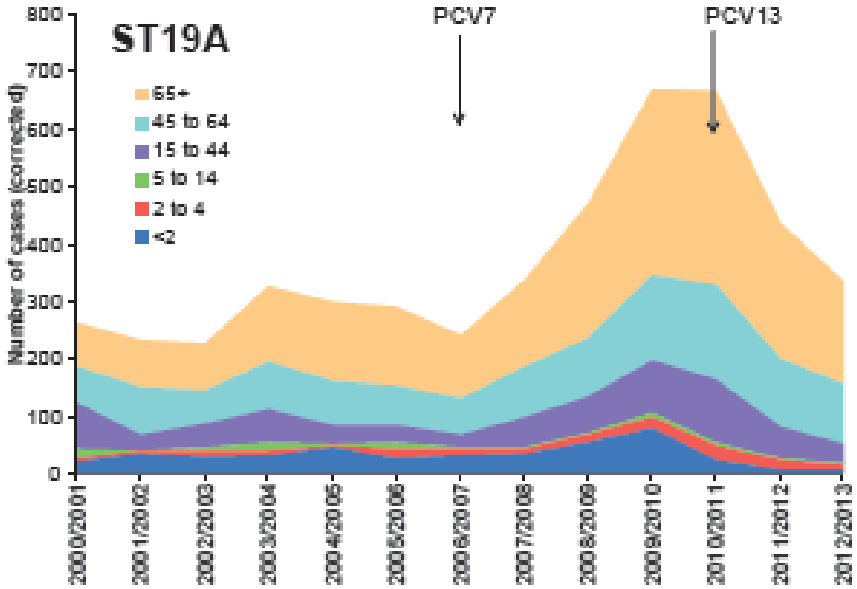


nvt = non-vaccine types

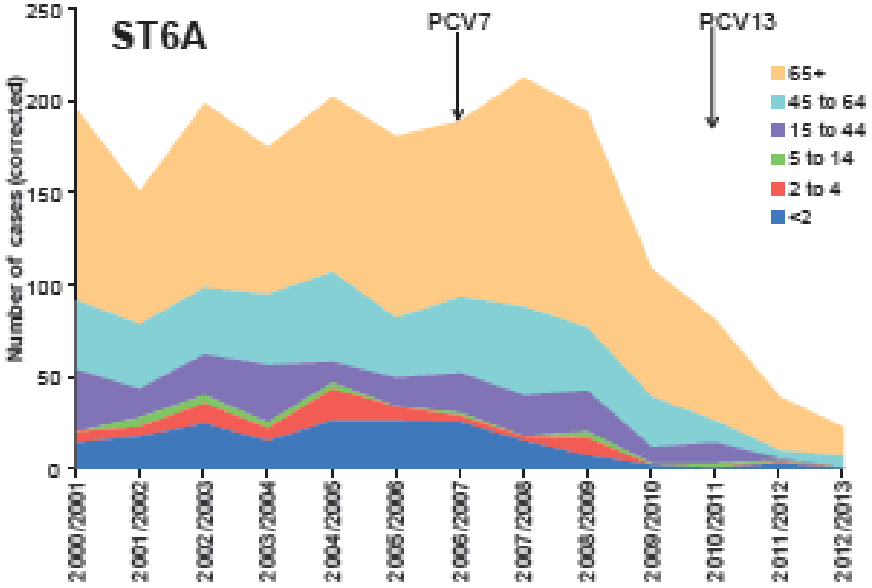
PCV13 serotypes showing a decrease (PHE data)



7F : Age 65 + years IRR : 0.92 (0.69-1.22)



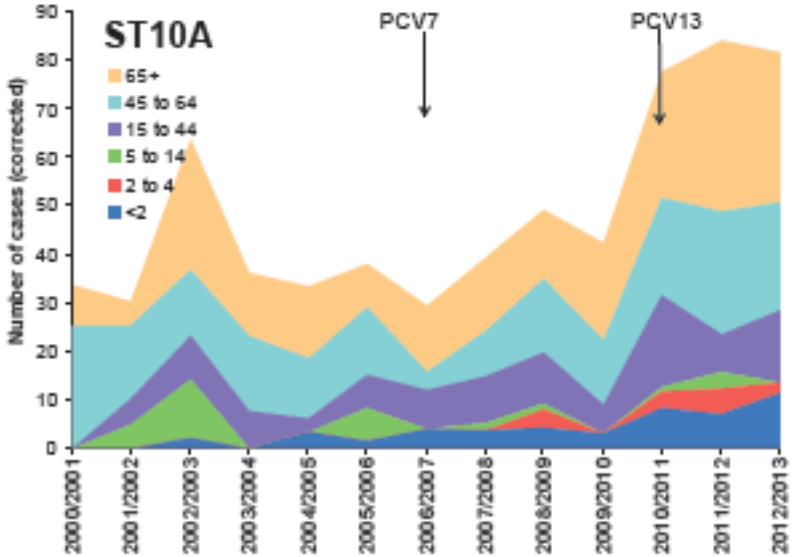
19A : Age 65 + years IRR : 0.64 (0.49-1.22)



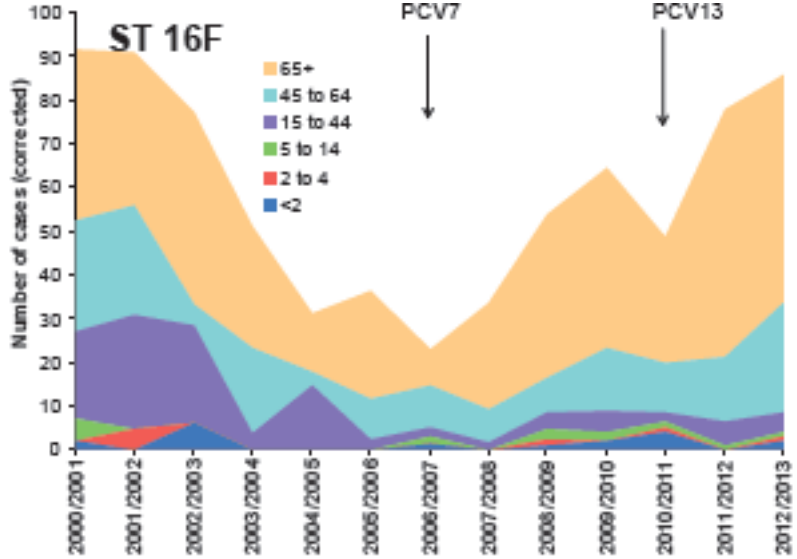
6A : Age 65 + years IRR : 0.17 (0.08.0.37)

Data from PHE enhanced surveillance of IPD in England and Wales

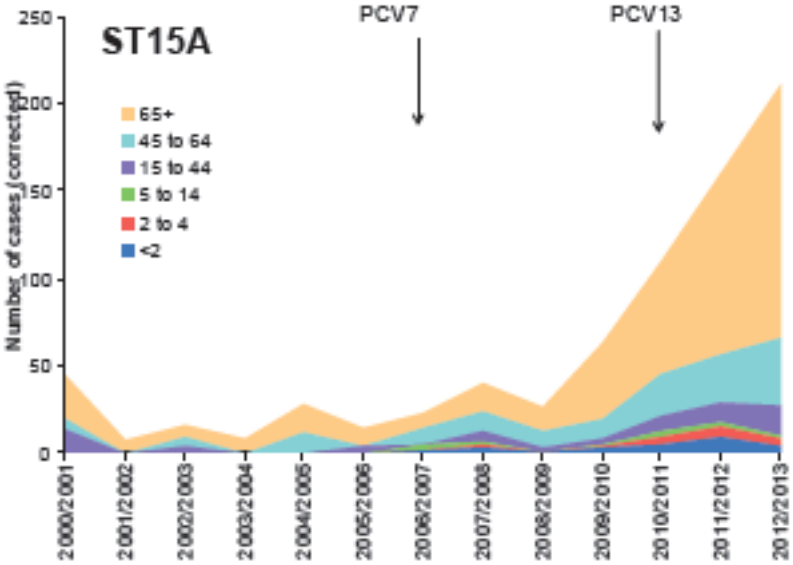
Non-PCV13 serotypes showing an increase (PHE data)



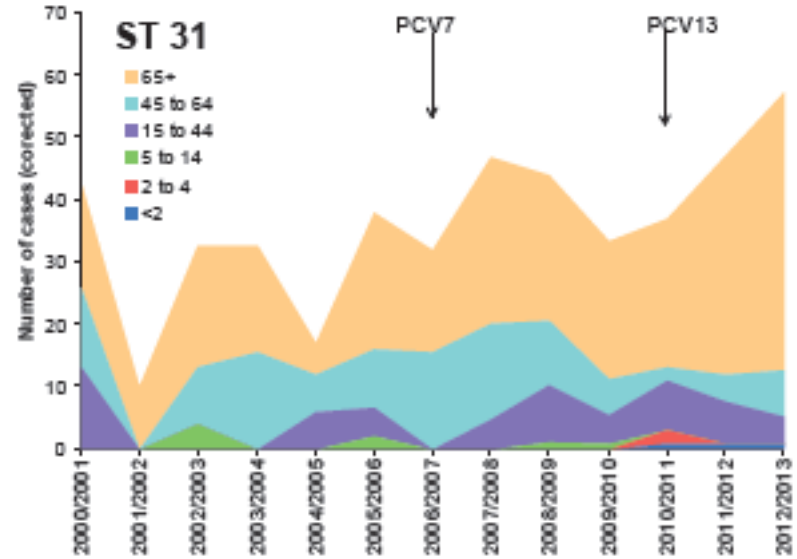
10A : Age 65 + years IRR : 1.81 (0.86-3.77)



16F : For age 65 + years IRR : 1.32 (.078-2.25)

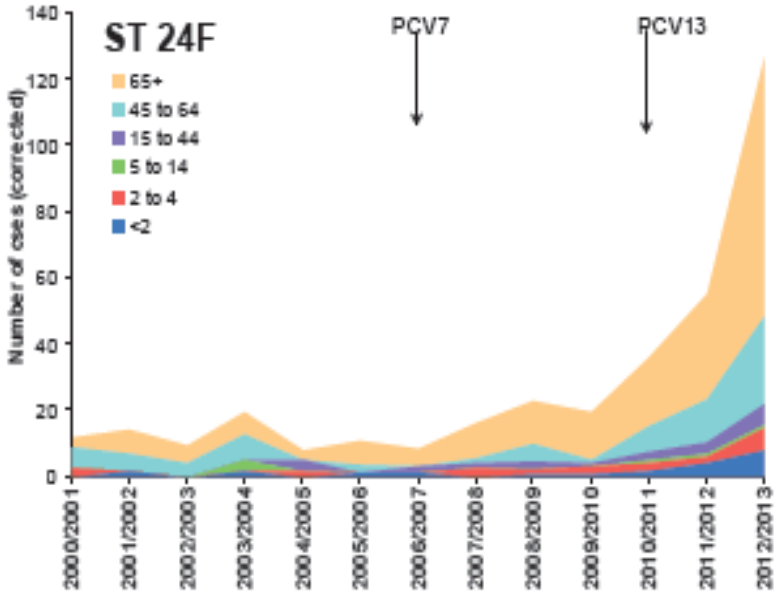


15A : Age 65 + years IRR : 5.03 (3.11-7.92)

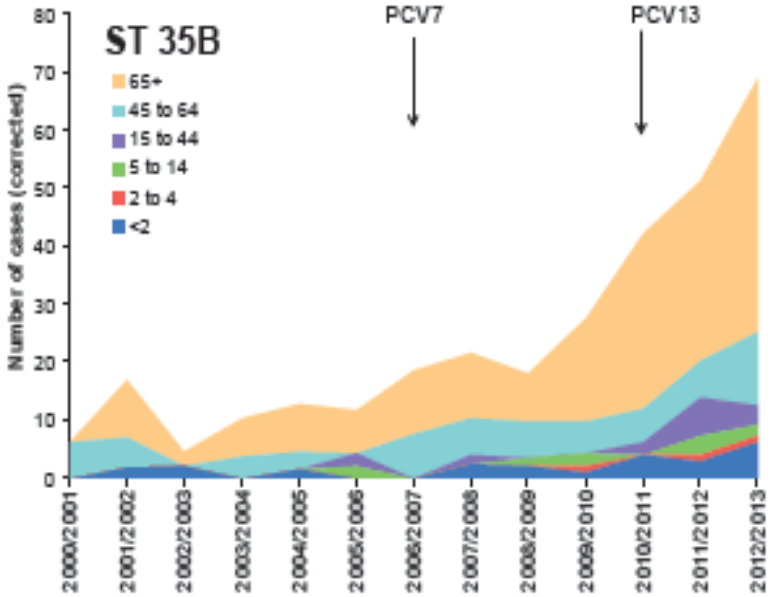


31 : For age 65 + years IRR : 1.95 (1.04-3.66)

Non-PCV13 serotypes showing an increase (PHE data)



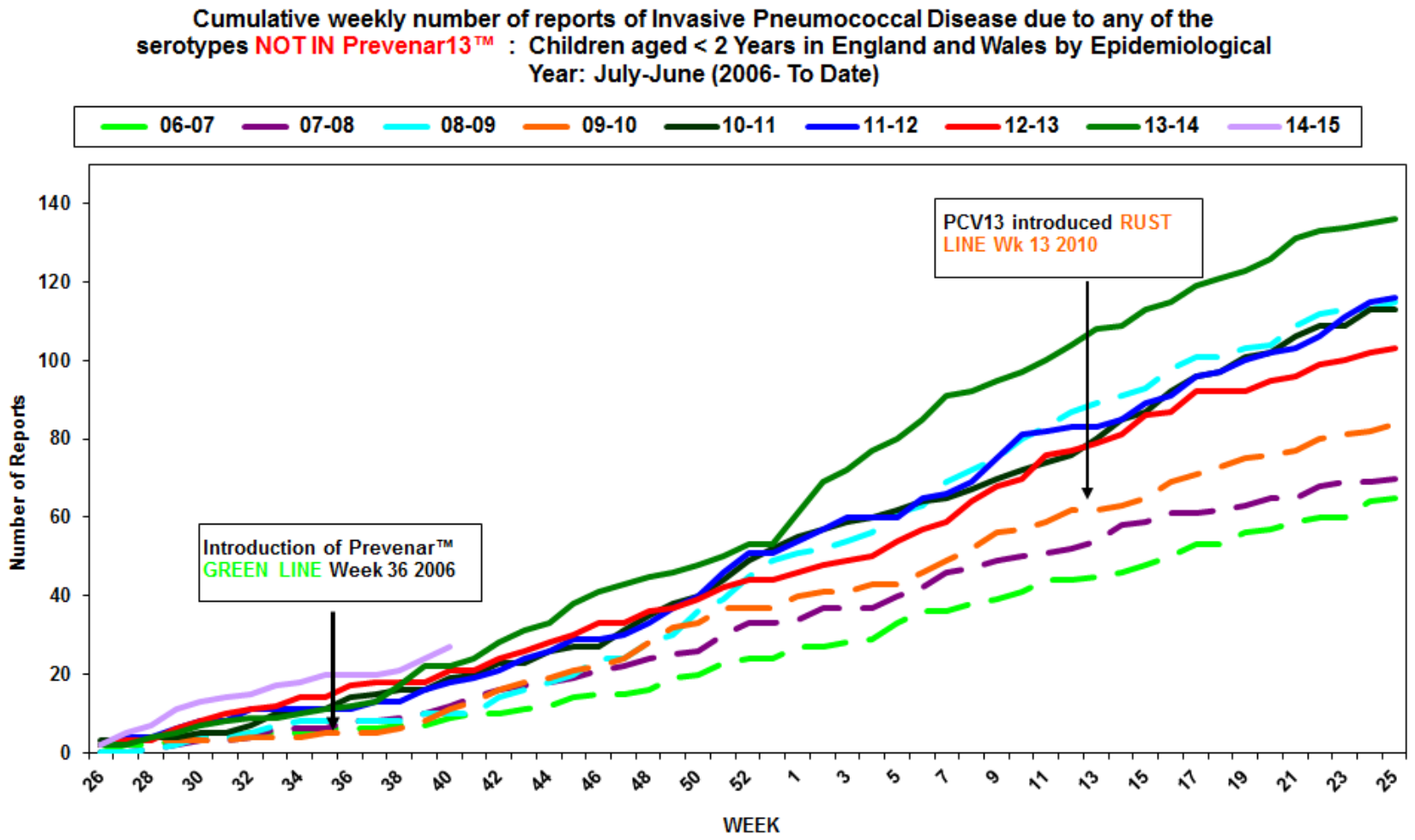
24F : For age 65 + years IRR : 5.67 (2.90-11.05)



35B : Age 65 + years IRR : 3.35 (1.58-6.96)

Data from PHE enhanced surveillance of IPD in England and Wales

Recent data shows replacement occurring in children < 2 years

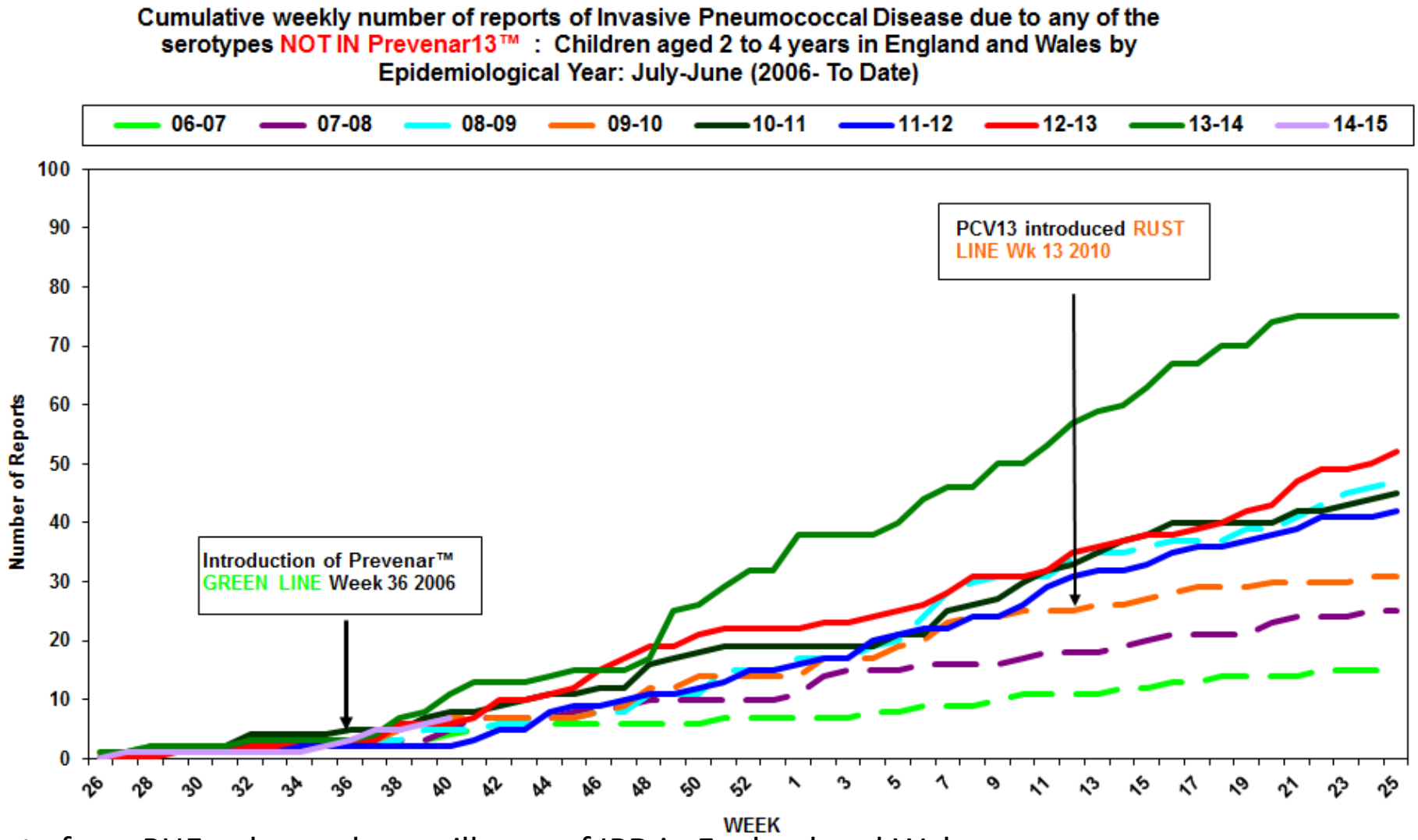


Data from PHE enhanced surveillance of IPD in England and Wales

Recent data shows replacement occurring in<5 years

Main culprits – 12F , 22F, 24F, 15B, 33F, 15A, 8, 23B

In 2-4 year olds



Data from PHE enhanced surveillance of IPD in England and Wales

Impact of PCVs on IPD in England and Wales: all ages (2013/14 vs 2000-06)

Type	change	[N* 2000/06 – 13/14]
ALL IPD	56% reduction	[8631 – 3784]
PCV7	97% reduction	[4269-111]
PCV13 only	63% reduction	[2098 – 772]
NVT	28% increase	[2264 – 2900]

* N= Corrected numbers

Data from PHE enhanced surveillance of IPD in England and Wales

Use Broome method to calculate vaccine effectiveness

Broome method (Broome 1980)

- Only requires information on proportion of vaccine serotype cases vaccinated compared to proportion of non-vaccine type cases vaccinated.

- Method is adjusted for period to allow for changes in serotype prevalence as vaccine is introduced

Effectiveness of PCV against IPD

PCV7

82% (95% CI: 72-89)

for at least 2 doses under 1 year or one dose over 1 year of age

PCV13

75% (95%CI: 55-84)

for at least 2 doses under 1 or one dose over 1

Andrews et al, Lancet ID 2014

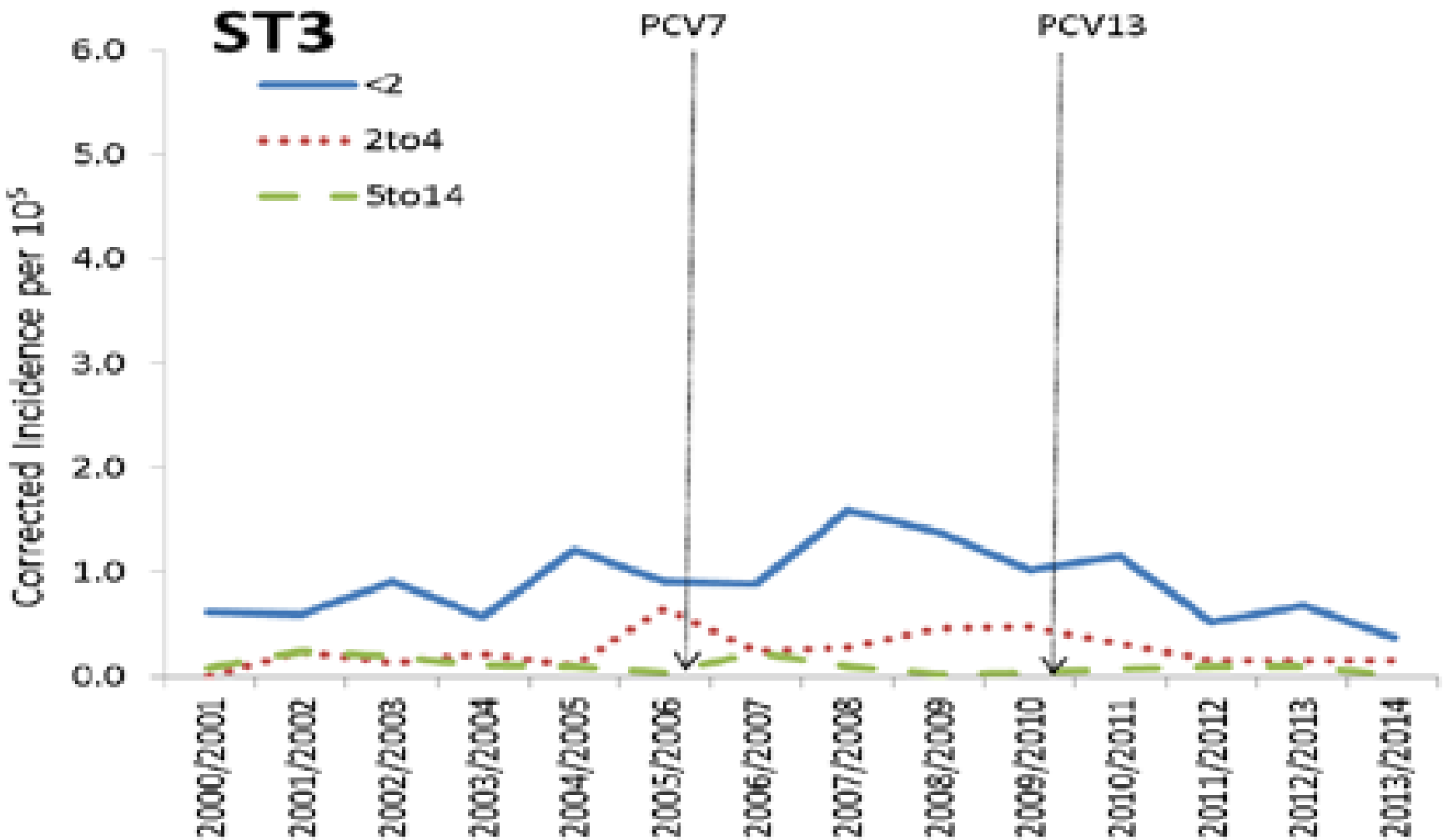
Serotype specific effectiveness of PCV13

Serotype	Adjusted VE (95% CI)
• 6A	97% (57-99)
• 7F	92% (70-98)
• 1	82% (38-95)
• 19A	70% (32-86)
• 3	-6% (-158-57)

For at least 2 doses under 1 y or 1 dose over 1 y

Impact of PCV13 on Serotype 3

(PHE data)



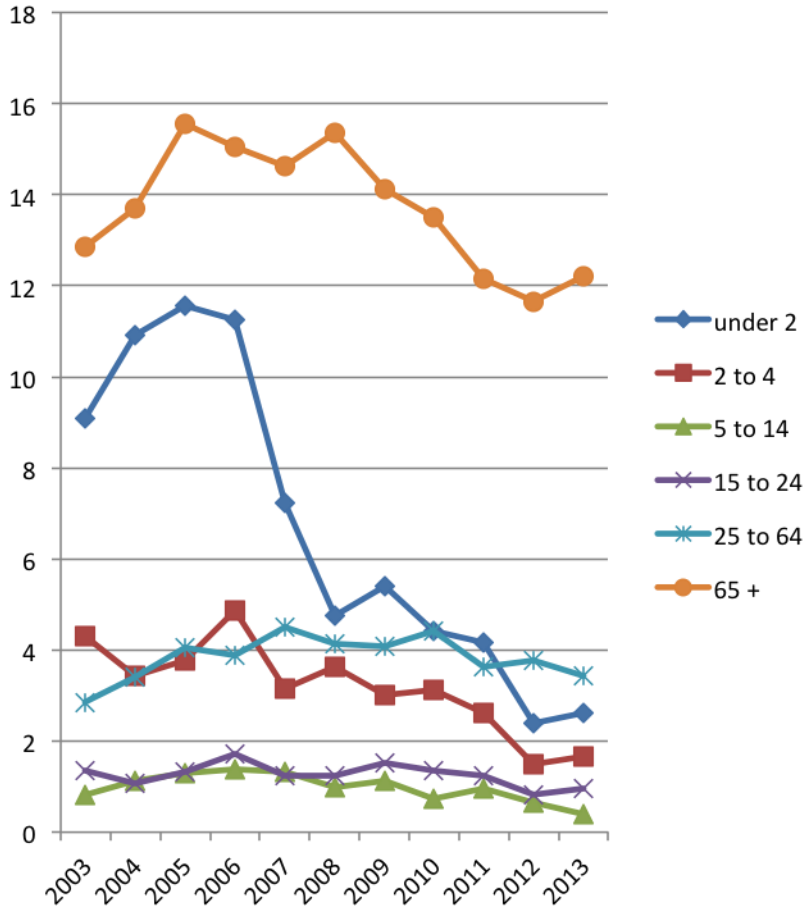
Impact of PCVs on Pneumonia

- Difficult to assess accurately
- Majority of invasive pneumococcal disease (80-90%) presents as pneumonia
- BUT only 10-20% pneumococcal pneumonia is bacteraemic
- Review hospital admissions for pneumonia using HES (Hospital Episode Statistics) data with ICD-10 code J13 (pneumococcal pneumonia)

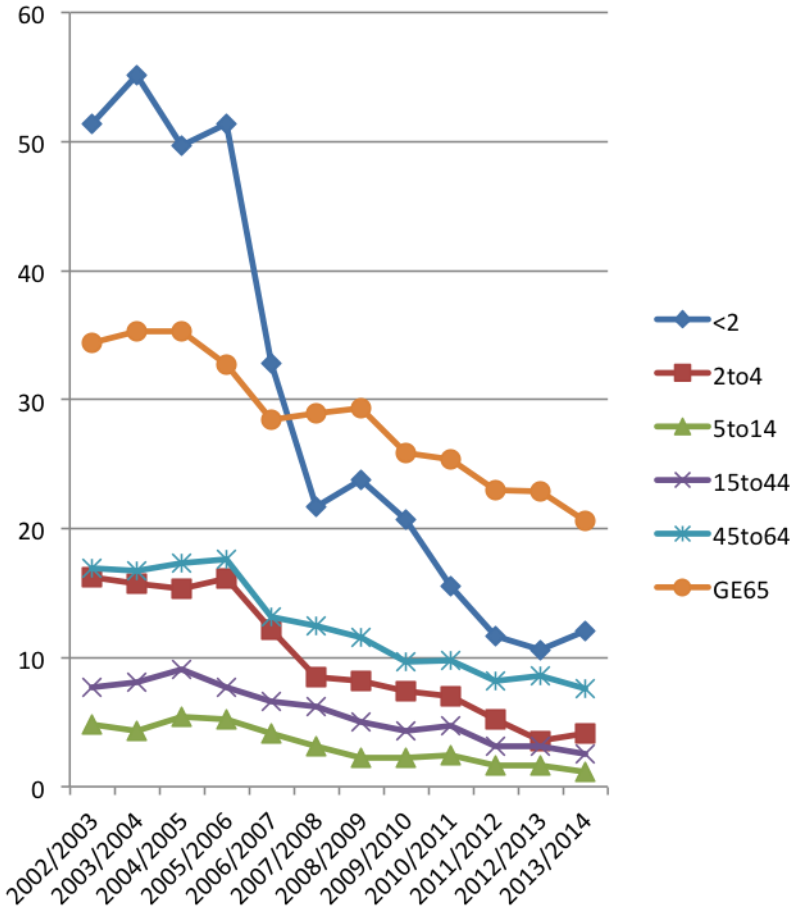
HES data England and Wales 2001-13
J13 = ICD-10 code for pneumococcal pneumonia

Annual incidence per 100,000 by age

J13



IPD



HES data England and Wales: J13 = ICD-10 code for pneumococcal pneumonia

Impact of PCVs on pneumonia

- Clear evidence of reduction in overall pneumococcal-specific pneumonia admissions (J13) similar to IPD changes
- Reduction in pneumococcal pneumonia admissions (J13) in low risk children < 5 years,

HES data England and Wales: J13 = ICD-10 code for pneumococcal pneumonia

Summary England and Wales

- PCV7 had a major impact on overall IPD (56% reduction) in young children despite serotype replacement
- Maximum impact of PCV7 on overall IPD within 4 years thereafter on-going reduction in VT IPD offset by increase in NVT
- Evidence of rapid herd protection effect with PCV13 (within 18 months) despite no catch up
- 2+1 accelerated schedule correct decision for UK

Summary England and Wales

- Significant reduction from PCV13 for all age IPD – 22% - within 3 years
- But steady increase in NVTs in > 45 year olds although still overall IPD reduction (14% for 65+ and 19% for 45-64 y olds)
- Decline in PCV7 serotypes continuing in 2012/13 , six years after introduction

Summary England and Wales

- IPD-incidence in <5 years in 2013/14 higher than in 2012/13
- Maximum population benefit in this age group may already have been achieved
- Broad range of serotypes caused non-PCV13 IPD in older children and adults
- PCV15 (includes 22F and 33F) may not cover emerging non- vaccine type IPD

Conclusions

- Laboratory-based surveillance is needed to accurately monitor serotype distribution
- Surveillance needs to be continued long term with high accuracy
  - in vaccinated and unvaccinated children
  - knowledge of vaccines received important
- Surveillance must cover the whole population
  - To detect unexpected results (eg. adults)
- Must be aware of natural fluctuations in serotype distribution

Conclusions

- Ideally surveillance should be carried out for several years BEFORE a vaccine is introduced
  - To establish a baseline
- Surveillance should be continued for many years AFTER a vaccine is introduced
  - To monitor vaccine impact
  - To monitor changes in serotype distribution

Acknowledgements

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•Public Health Laboratory, Manchester

•Ray Borrow, Elaine Stanford

•Infectious Diseases and Clinical Microbiology, University of Oxford, Derrick Crook, Catrin Moore (for reporting IPD cases serotyped by Oxford)