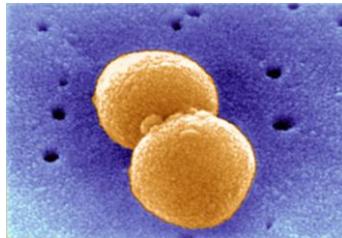




Public Health  
England

# Prevention of invasive pneumococcal disease in the UK and potential impact of 1+1 immunisation schedule



Nick Andrews, Shamez Ladhani Liz Miller, Yoon Choi

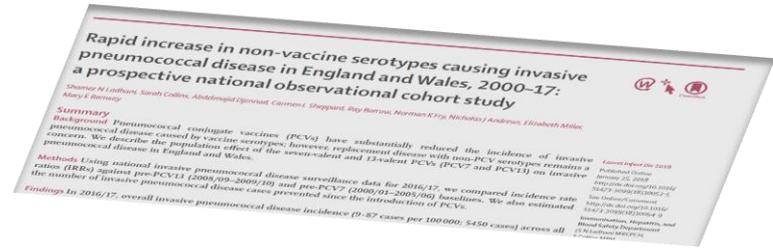
Public Health England

David Goldblatt

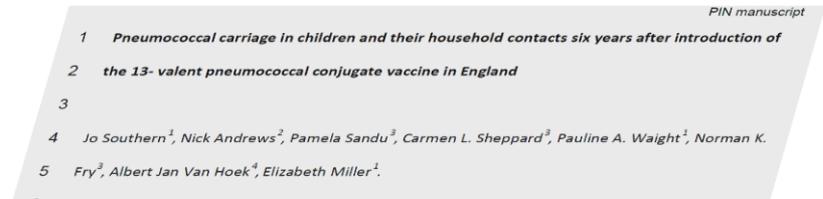
UCL Great Ormond Street Institute of Child Health

# Outline

- Invasive Pneumococcal Disease (IPD) epidemiology update (focus on <2,65+)



- Update of carriage and invasiveness

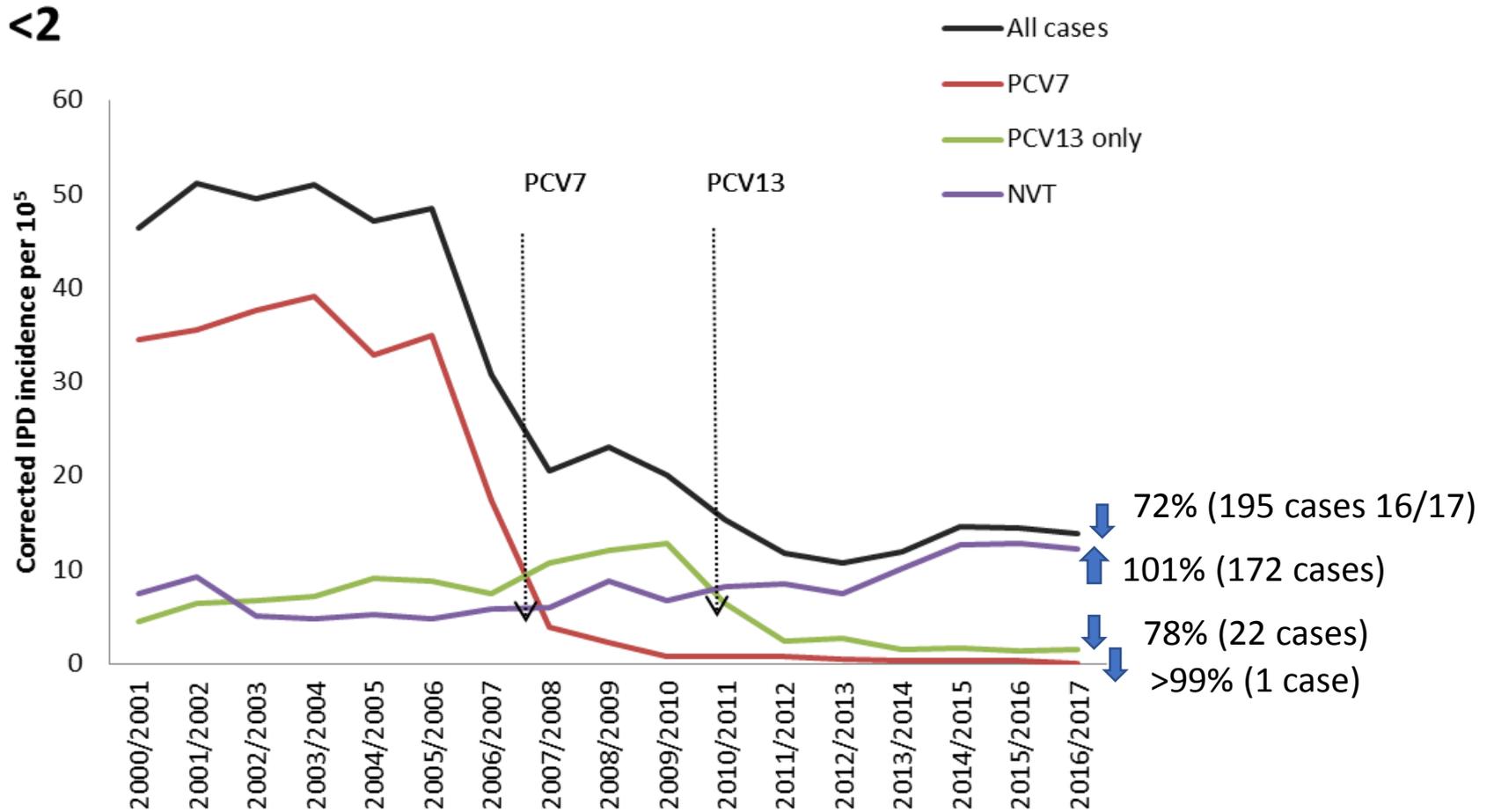


- Immunogenicity of 1+1 vs 2+1



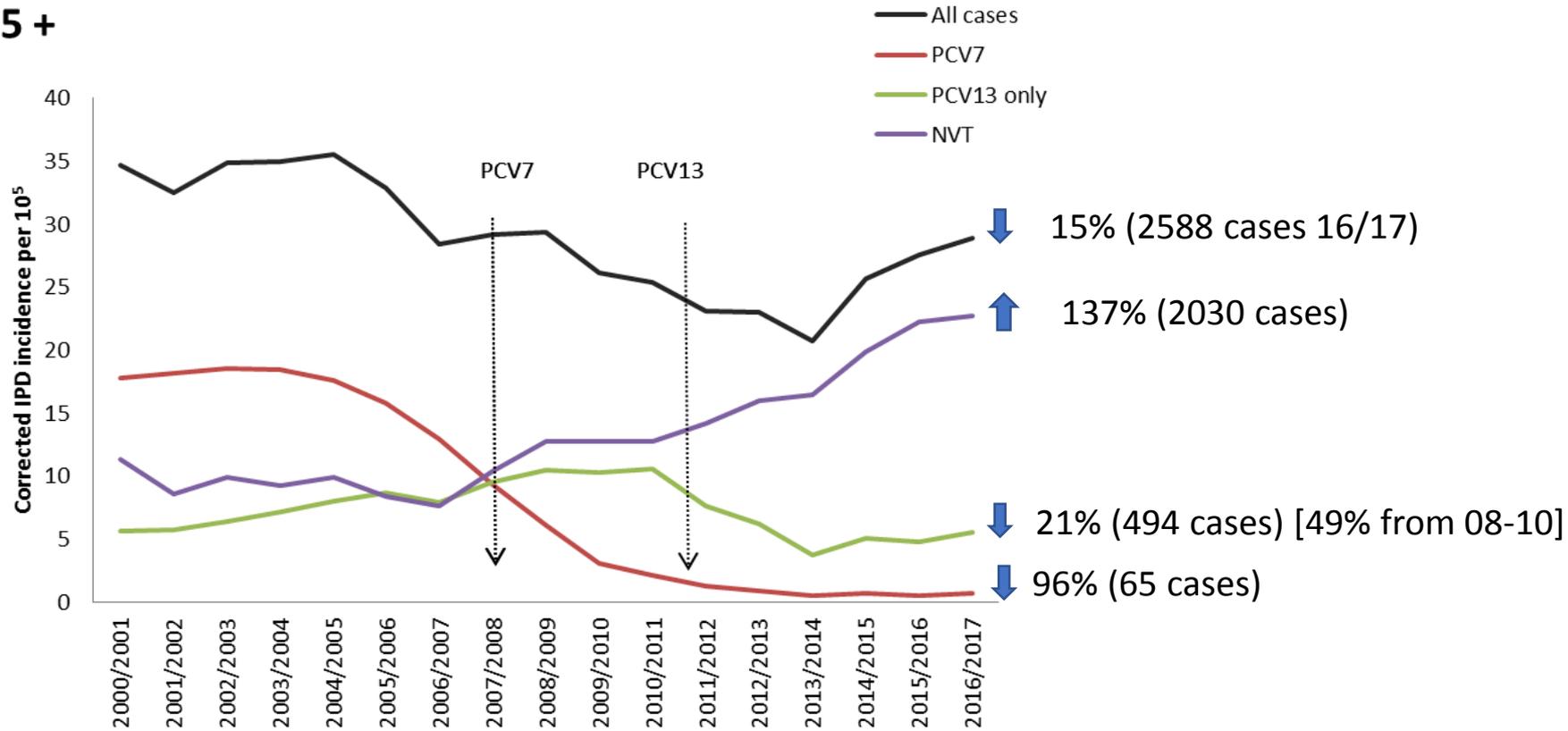
- Potential additional cases in infants (simple calculation)
- Mathematical modelling of a change to 1+1

# Incidence in <2 year-olds to 2016/17



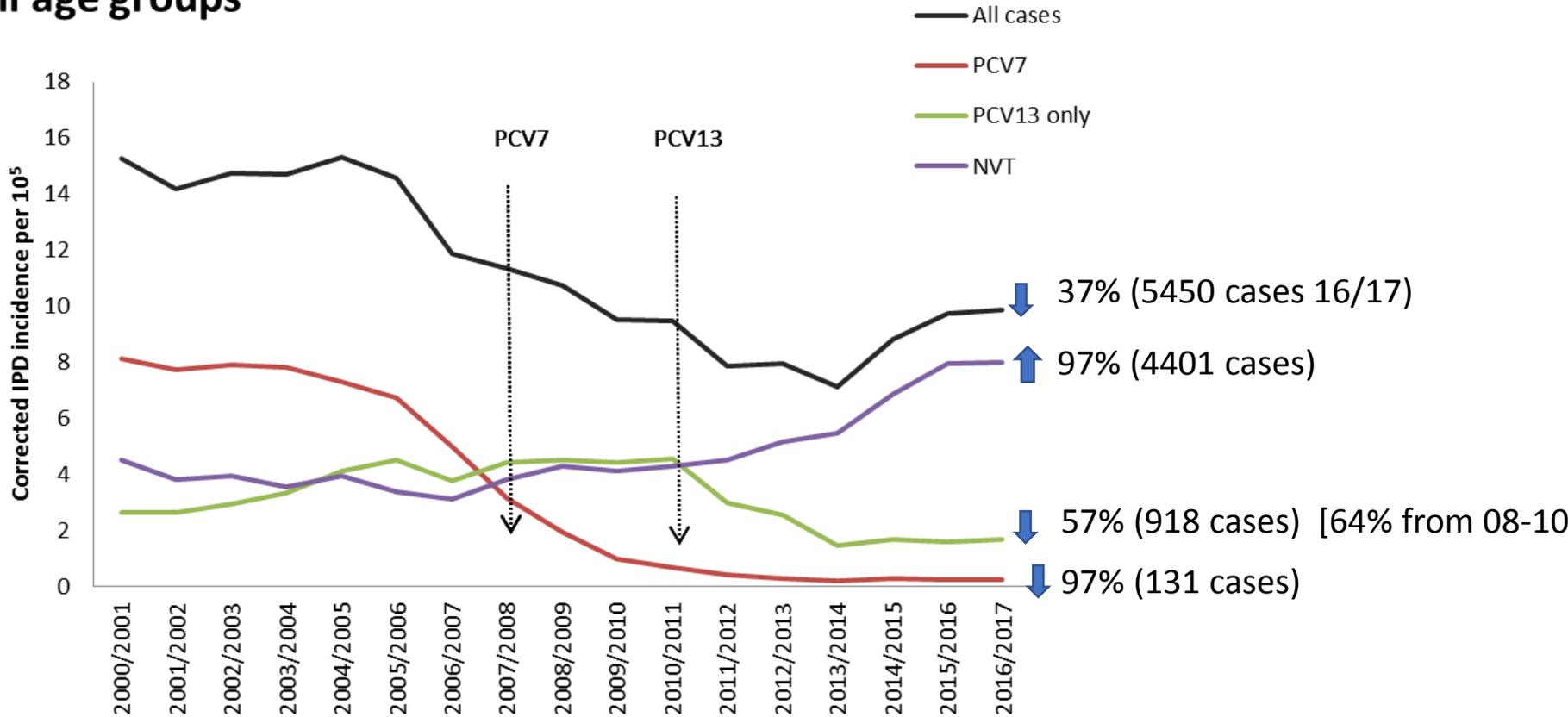
# Incidence in 65+ year-olds to 2016/17

65 +



# Adjusted annual IPD incidence

## All age groups



### Major replacing types

**8, 12F, 9N, 15A, 22F and 33F**

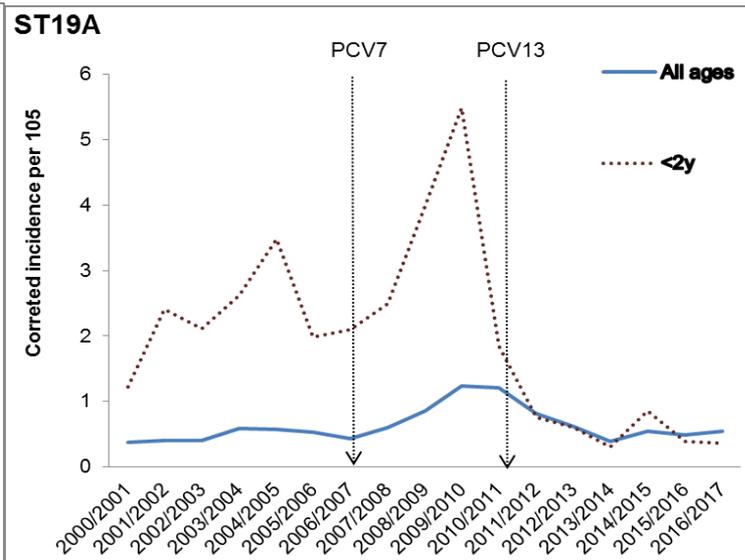
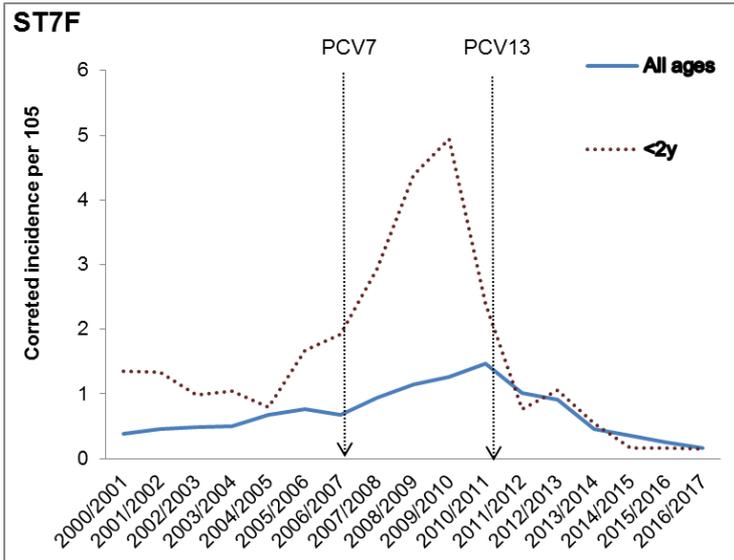
### PCV7 ST

**Very low – but some left(e.g. 19F)**

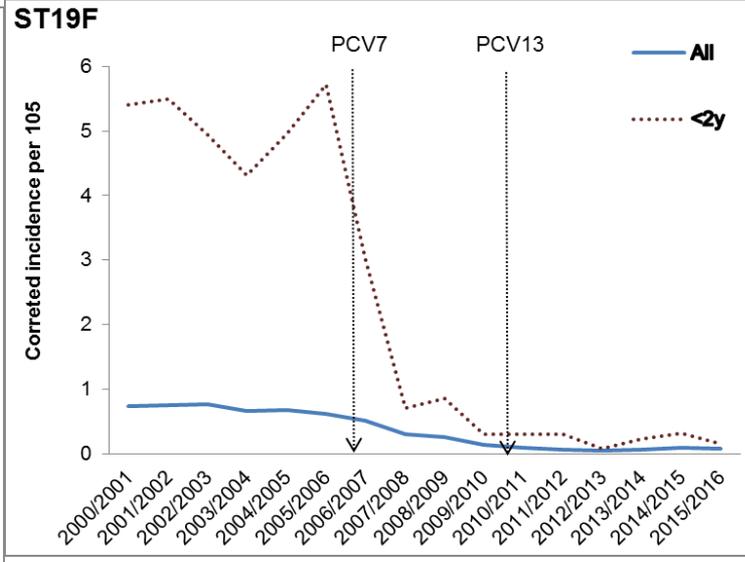
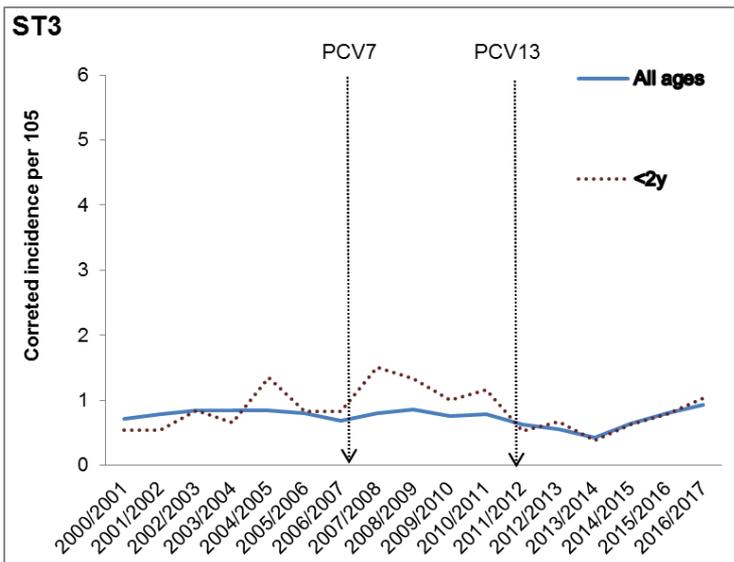
### PCV13 ST

**Some remains (ST3, 19A)**

# Vaccine Types of interest



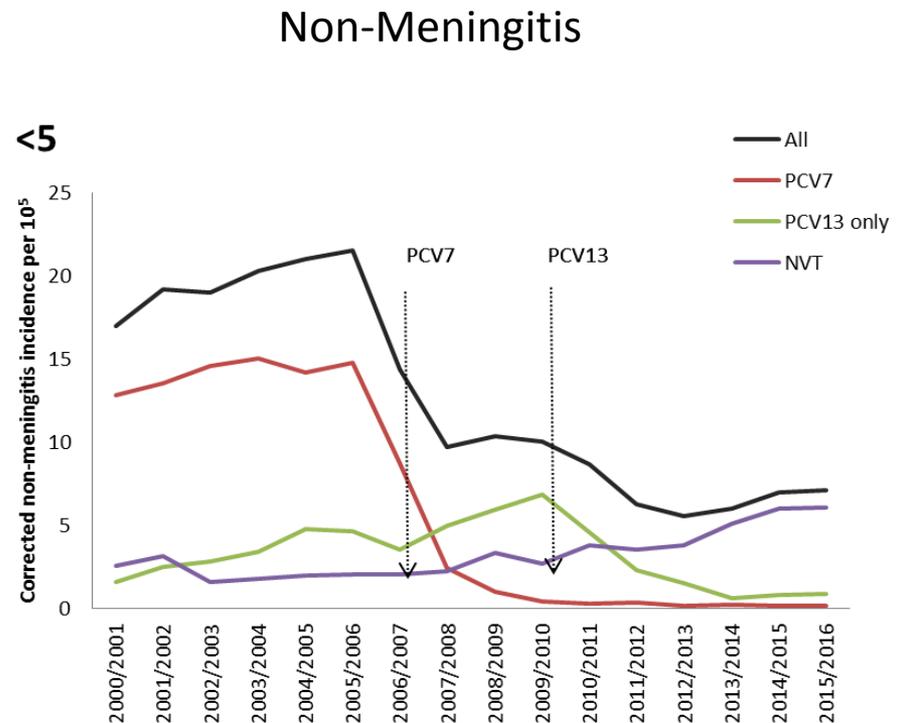
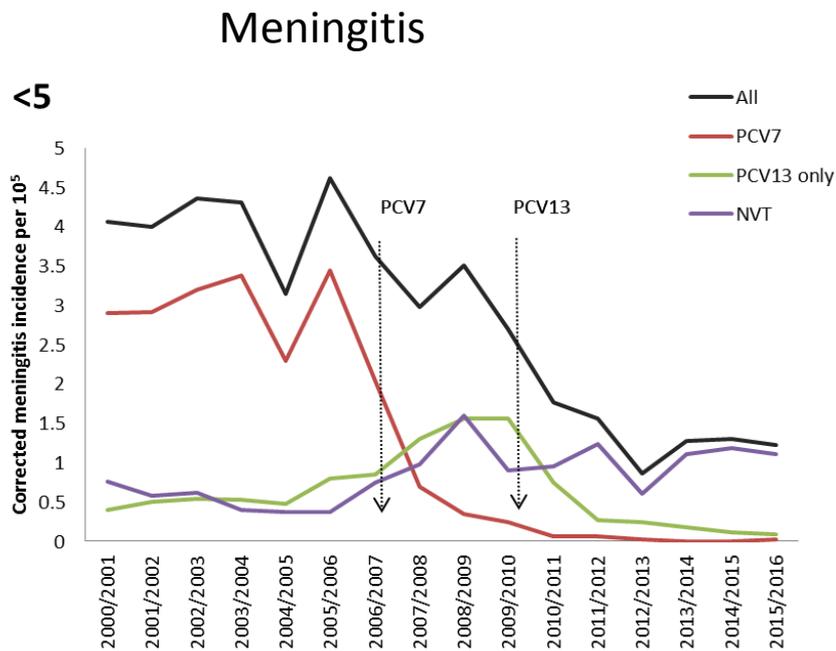
Still level so far in 2017/18



Also we have seen three 6C cases (vaccine related) in infants in 2016/17

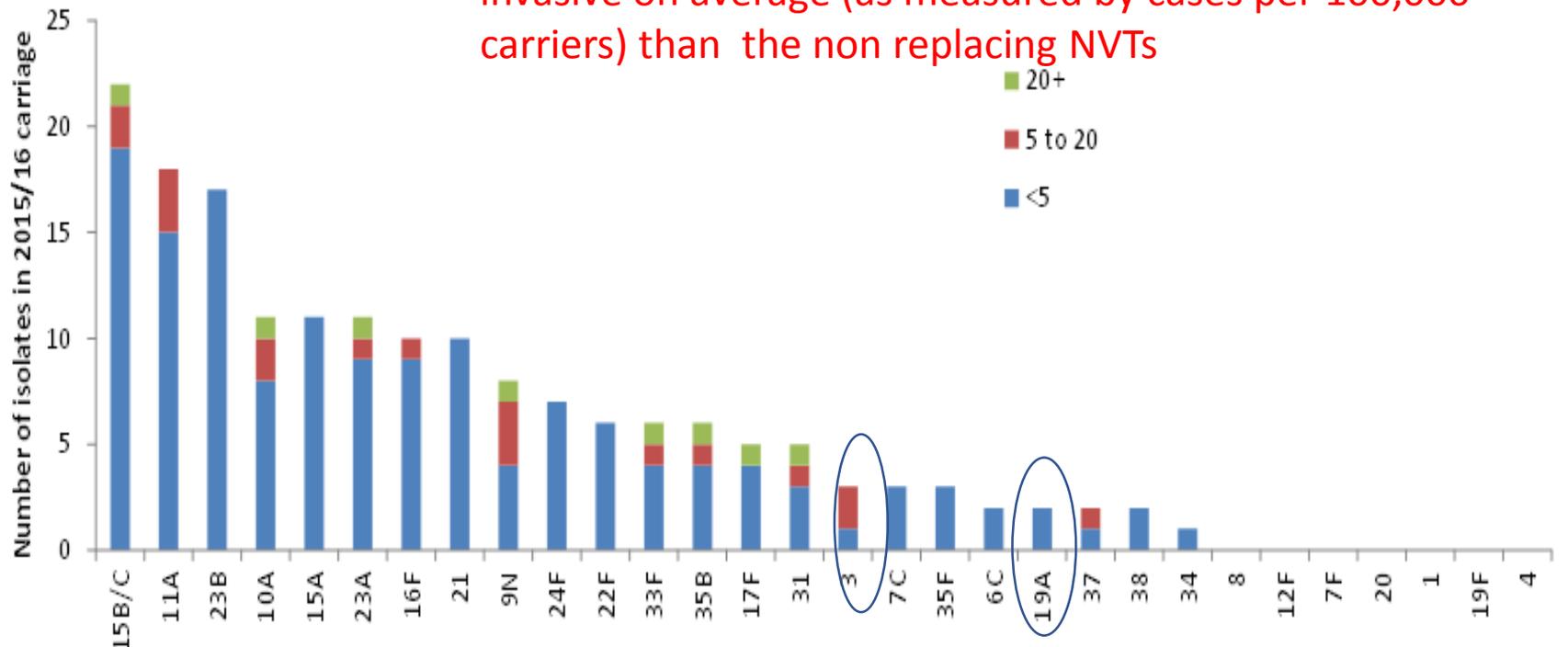
# Meningitis trends in under 5s.

- About 3-7% of IPD is meningitis (depending on serotype)
- Decreases have been greater for Meningitis than non-meningitis IPD.
- Why? - Replacing PCV13 serotypes have overall lower meningitis rates to PCV13 / non-replacing types.
- However one plus about VT 19A rate is the rate is low (3%)



# Carriage and invasiveness 2015/16 study

- Our forth carriage study from pre-PVC7 to now
- Carriage rates in <5 have remained at about 50% pre-post PCV.
- We did see ST 19A and ST4 carriage.
- The fact NVT IPD has gone up more than expected but overall carriage has stayed similar means the replacing NVTs are more invasive on average (as measured by cases per 100,000 carriers) than the non replacing NVTs



# Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1+1) compared with two primary doses and a booster (2+1) in UK infants: a multicentre, parallel group randomised controlled trial



Lancet Infectious Disease

*David Goldblatt\*, Jo Southern\*, Nick J Andrews, Polly Burbidge, Jo Partington, Lucy Roalfe, Marta Valente Pinto, Vasilli Thalasselis, Emma Plested, Hayley Richardson, Matthew D Snape, Elizabeth Miller*



## Funding

NIHR Policy Research Programme [Grant number 039/0031]

National Vaccine Evaluation Consortium

PI Liz Miller

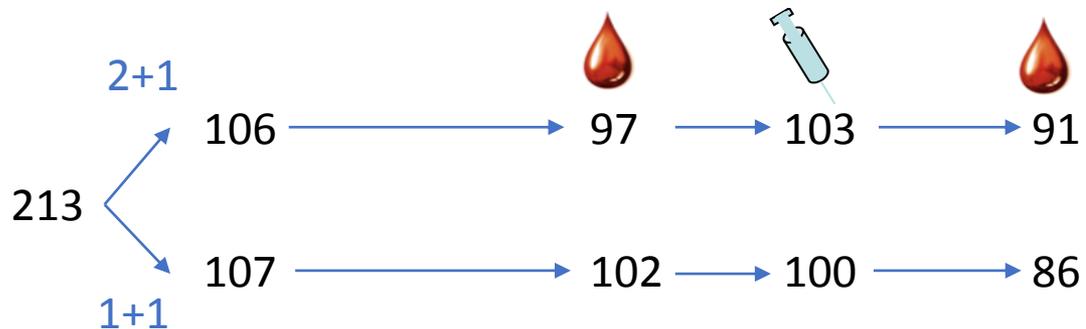
Bill and Melinda Gates Foundation [OPP1126431]:

PI David Goldblatt

BILL &  
MELINDA  
GATES  
*foundation*

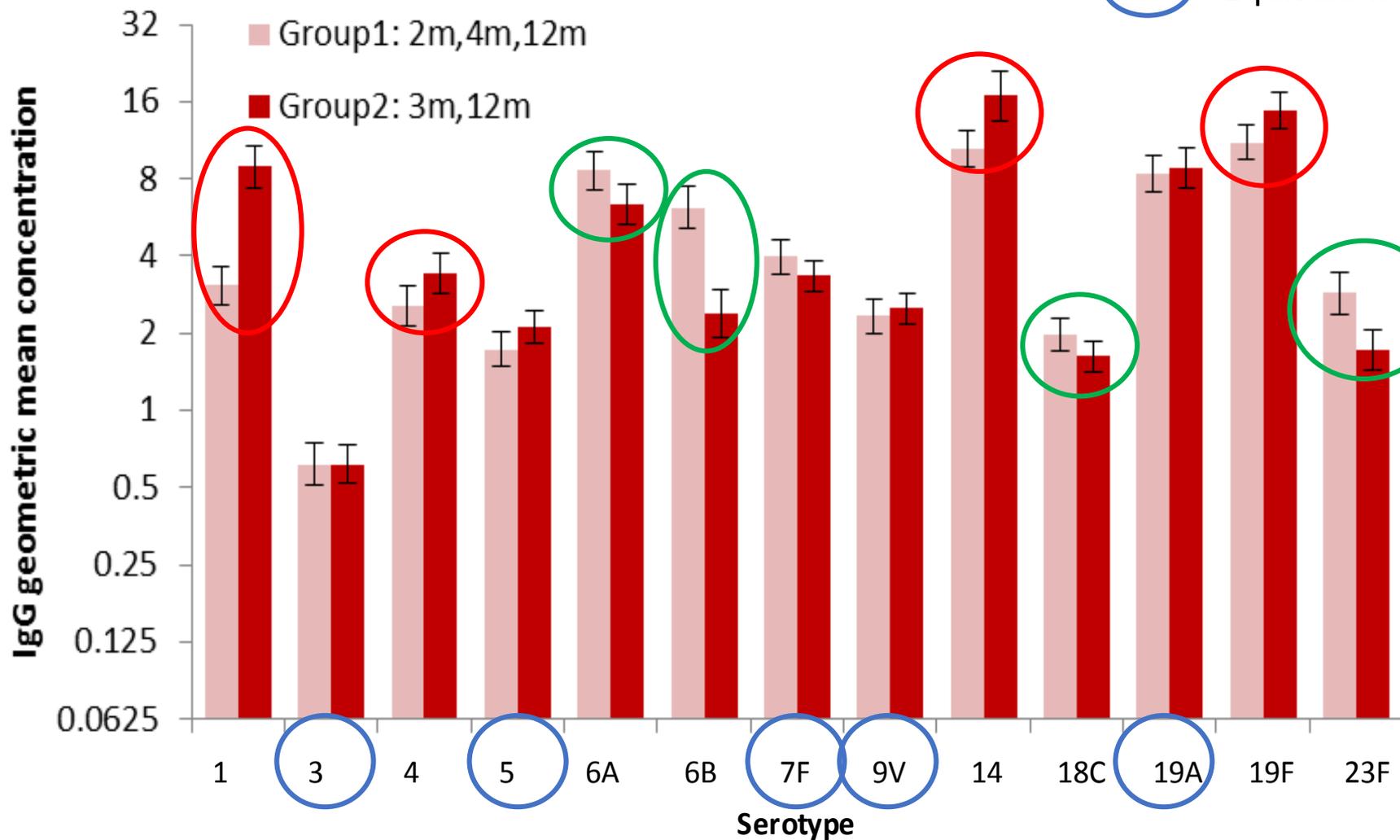
**Study Title: Assessment of post booster antibody responses in UK infants given a reduced priming schedule of meningococcal serogroup B and 13 valent pneumococcal conjugate vaccines**

Group	V1 2m	V2 3m	V3 4m	V4 5m	V5 12m	V6 13m	V7 18m
1  (n=100)  2+1	DTaP/IPV/ Hib  Men B <b>PCV13</b>  Rota	DTaP/IPV/ Hib    Rota	DTaP/IPV/ Hib  Men B <b>PCV13</b>  Rota			MenC/Hib  Men B <b>PCV13</b>	MMR

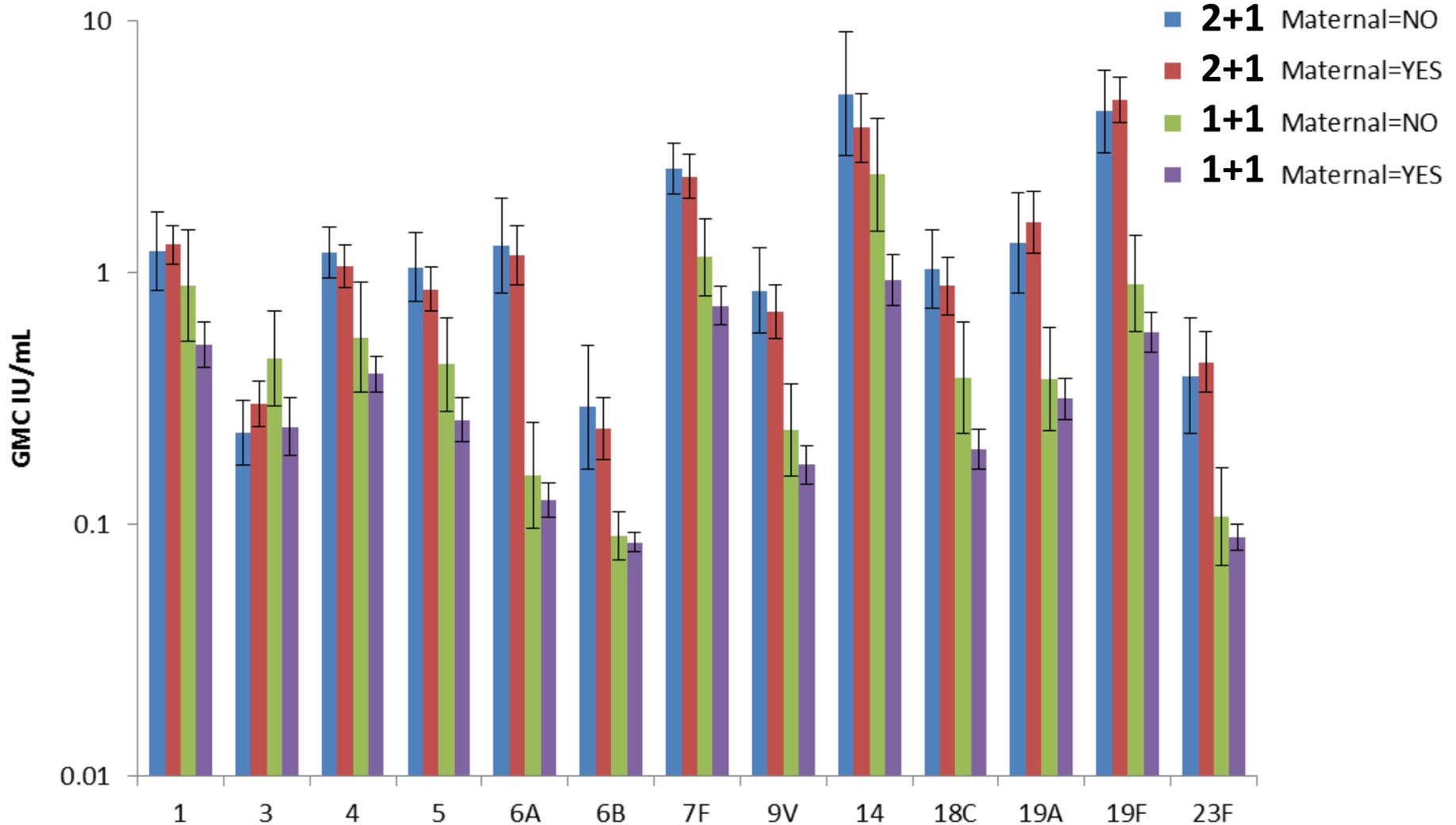


# IgG GMCs post booster

- 1+1 superior
- 2+1 superior
- Equivalent



# Post primary GMCs by maternal pertussis vaccination status and group: Impact on 1+1 only



# Relevant points so far....

- VT IPD had declined to low levels, but ST3 and 19A in particular persist, including in carriage. Although 7F and 19F are now rare and declining we have seen cases in the past year in infants.
- Recent replacing serotypes have a relatively high invasiveness (case:carrier ratio) but lower meningitis rate.
- Post booster antibody responses to 1+1 and 2+1 are similar.
- But after a single dose levels are lower than two doses, more-so if mother had Pertussis vaccine.

# Vaccine effectiveness in infants

**Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study**

*Nick J Andrews, Pauline A Waight, Polly Burbidge, Emma Pearce, Lucy Roofe, Marta Zancoli, Mary Slack, Shona Wilson, Elizabeth Miles, David Goldblatt*



1dose 2.5<13m VE 38% (95% CI -218-89)

Miller et al Vaccine 2011

	Age range (months)	Cases vaccinated: unvaccinated	Controls vaccinated: unvaccinated	Adjusted vaccine effectiveness* (95% CI)
<b>PCV13 serotypes not in PCV7 (plus 6C)† (1, 3, 6A, 6C, 7F, and 19A)</b>				
At least one dose	2.5 to <56	105:155	330:80	73% (57 to 83)
At least two-doses before age 12 months or one dose on or after age 12 months	4 to <56	76:146	280:76	73% (55 to 84)
One dose (before age 12 months)	2.5 to <13	28:43	48:24	60% (12 to 82)
Two-doses (before age 12 months)	4 to <13	23:34	118:20	80% (43 to 93)
One dose (on or after age 12 months)	13 to <56	28:112	65:56	73% (50 to 85)
2 + 1 dosing schedule	13 to <56	13:112	71:56	79% (25 to 94)
<b>PCV7 serotypes‡ (4, 6B, 9V, 14, 18C, 19F, and 23F)</b>				
At least one dose	2.5 to <56	18:4	248:8	83% (35 to 96)
At least two-doses before age 12 months or one dose on or after age 12 months	4 to <56	10:2	205:5	90% (34 to 98)

Andrews NJ et al. Lancet Infect Dis 2014;14:839-46

## KEY POINTS

- 1 dose: 60%
- 2 doses 80%

Varies by Serotype

- ST3 – none
- 19A lower
- 6C some cross

Could maternal interference matter?

# Simple calculation of possible additional vaccine type cases in those aged 3m-14m by changing to 1+1

## METHOD

- WE BACK CALCULATE HOW MANY VACCINE TYPE CASES WE WOULD HAVE EXPECTED IN 2016/17 IF WE HAD NOT USED THE VACCINE THAT YEAR – THEN WE SEE HOW MANY WE WOULD EXPECT TO GET WITH 1+1.
  - this needs...
  - VT (and related) cases numbers in 2016/17 (5 cases, three 19A, one 19F and one 6C)
  - Estimated vaccine effectiveness of 2 and 1 doses for these serotypes ( 19A and 6C this 70%(2dose) 40% (1dose), 19F (90%, 50%)
  - Coverage data by age (rapid rise to 93% after doses given)
- WE THEN ASSUME...
  - VE is low against ST3 so not included in the calculation
  - The 2016-17 VT rate will continue (so no continued decline)
  - Vaccine effectiveness post booster is the same for 1+1, 2+1
  - Herd effects not considered – just focus on infants.

# Results

Expected additional VT cases (per year) aged 3m-14m

**7 cases** (three 19A, three 19F, one 6C)

## NOTES

- Trends indicate 19F is continuing to decline so probably not realistic to think we would see this number in the future.
- 19A persistence is an issue, although it does have a lower meningitis rate.

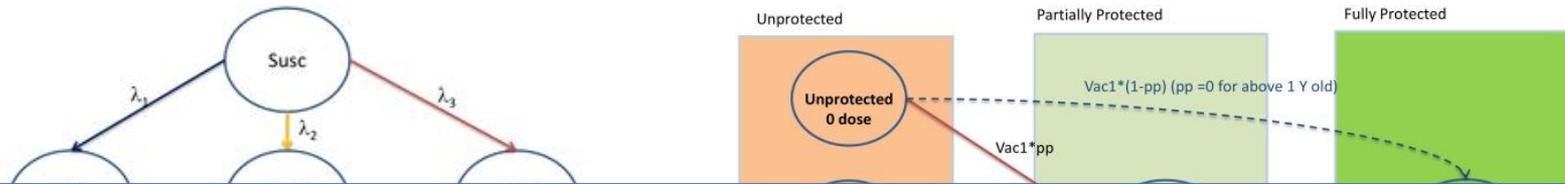
# Mathematical modelling of the change

- PHE Dynamic Model already used for projections of the impact of PCV7 / 13.
- Re-fitted and parameterised to better describe recent changes (i.e. bigger increase in NVTs and no Vaccine effectiveness for ST3).
- Unlike simple method it incorporates herd effects and effects in other ages.
- Allows for the fact increases in vaccine types are offset by a drop in non-vaccine types (as serotypes compete).

# Key assumptions

- 2+1 and 1+1 equivalent post booster, including waning (Recent unpublished work on vaccine effectiveness by age for 0+1 vs 2+1 doses suggests similar waning).
- ST 6C and ST 3 included as NVT
- ST 1 excluded (as in previous models) as it is an “epidemic strain – hard to model”. But ST 1 now rare.
- Competition between serotypes in three groupings: NVT, PCV7 and PCV13(minus ST1, 3 and PCV7 types)

# Model structure



OPEN ACCESS Freely available online



## Mathematical Modelling Long-Term Effects of Replacing Pevnar7 with Pevnar13 on Invasive Pneumococcal Diseases in England and Wales

Yoon Hong Choi<sup>1\*</sup>, Mark Jit<sup>1,2</sup>, Stefan Flasche<sup>1,3</sup>, Nigel Gay<sup>4</sup>, Elizabeth Miller<sup>1</sup>

- Dose-specific vaccine protection model
- 4,800 “weekly” age cohorts (week = 7.6 days)
- Competition parameters determine replacement level
- Vaccine Efficacy against carriage determines herd protection

# Model results < 2 year olds – added cases switching to 1+1

- Redacted (work in progress)

# Model results age 65+ added cases switching to 1+1

- Redacted (work in progress)

# Why consider 1+1 in the UK?

- Vaccine type disease now rare
- Immunogenicity after the booster generally equivalent. We would expect VE of 1+1 and 2+1 to be the same post booster.
- Additional cases expected to be low – but we can keep monitoring.
- Makes room in the infant schedule as fewer doses
- Fewer adverse events as fewer doses
- Potential savings

# Joint Committee on Vaccination and Immunity

The Joint Comm  
UK health depart

21. The Committee agreed that the PCV programme in the UK had been highly successful, with dramatic decreases in PCV13 vaccine type disease across the population. High uptake in the UK combined with good vaccine effectiveness provided the opportunity to move to an alternate schedule. Given the success of the programme, both in those vaccinated, and the wider population through population level protection, the Committee agreed that a move to a 1+1 schedule was appropriate for the UK situation. The Committee therefore advised a revised schedule for PCV13 vaccine, with vaccination offered at 3m and 12m.
22. The Committee re-emphasized the need for continuing high quality surveillance to identify any change in case numbers.

# Summary

- Immunogenicity of a 1+1 schedule is equivalent to or superior to a 2+1 schedule for 9 of the 13 serotypes in PCV13
- In settings where vaccine type IPD is currently at very low levels and coverage of the booster is high, priming with a single dose of PCV13 may have little effect on rates of pneumococcal infection
- The JCVI's recommendation to the Minister to move to a 1+1 PCV schedule in the UK, should it be implemented, will give us an opportunity to evaluate the efficacy of a 1+1 schedule in a HIC
- Ongoing studies in LMICs of a 1+1 schedule will help us understand whether this approach is universally acceptable.

# ACKNOWLEDGEMENTS

- **Public Health England:** Liz Miller, Yoon Choi, Shamez Ladhani, Jo Southern, Albert Jan Van-Hoek, Mary Ramsay, Rashmi Malkani, Sarah Collins, Majid Djennad, David Litt, Norman Fry, Carmen Sheppard, Ray Borrow, Research nurses, and more...
- Clinical trial participants.
- David Goldblatt and lab staff , UCL Great Ormond Street Institute of Child Health
- Matthew Snape and the OVG for recruitment to the 1+1 trial