Reevaluating the use of correlates of protection:

Serological basis for use of meningococcal serogroup C conjugate vaccines in the UK:

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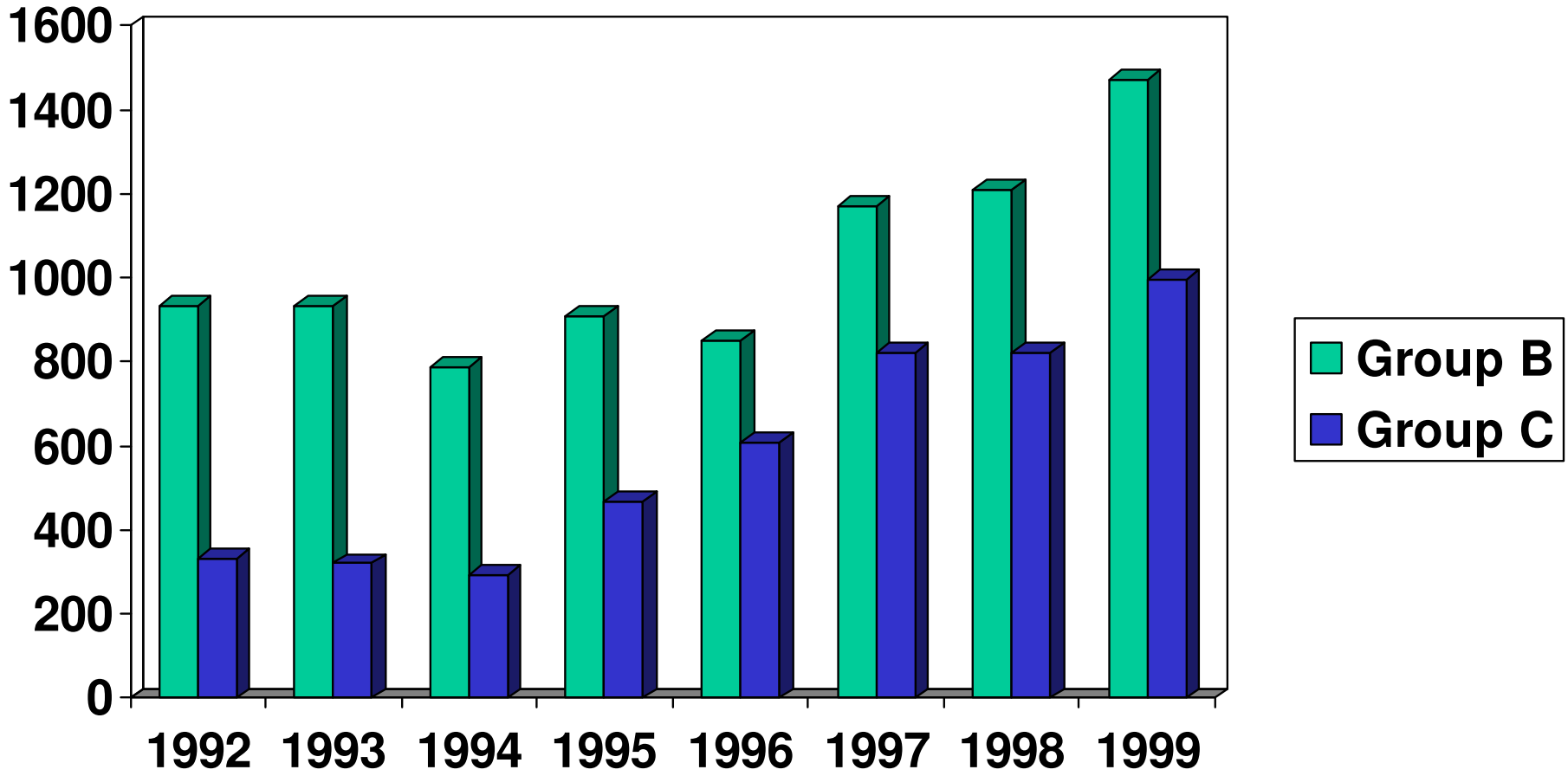
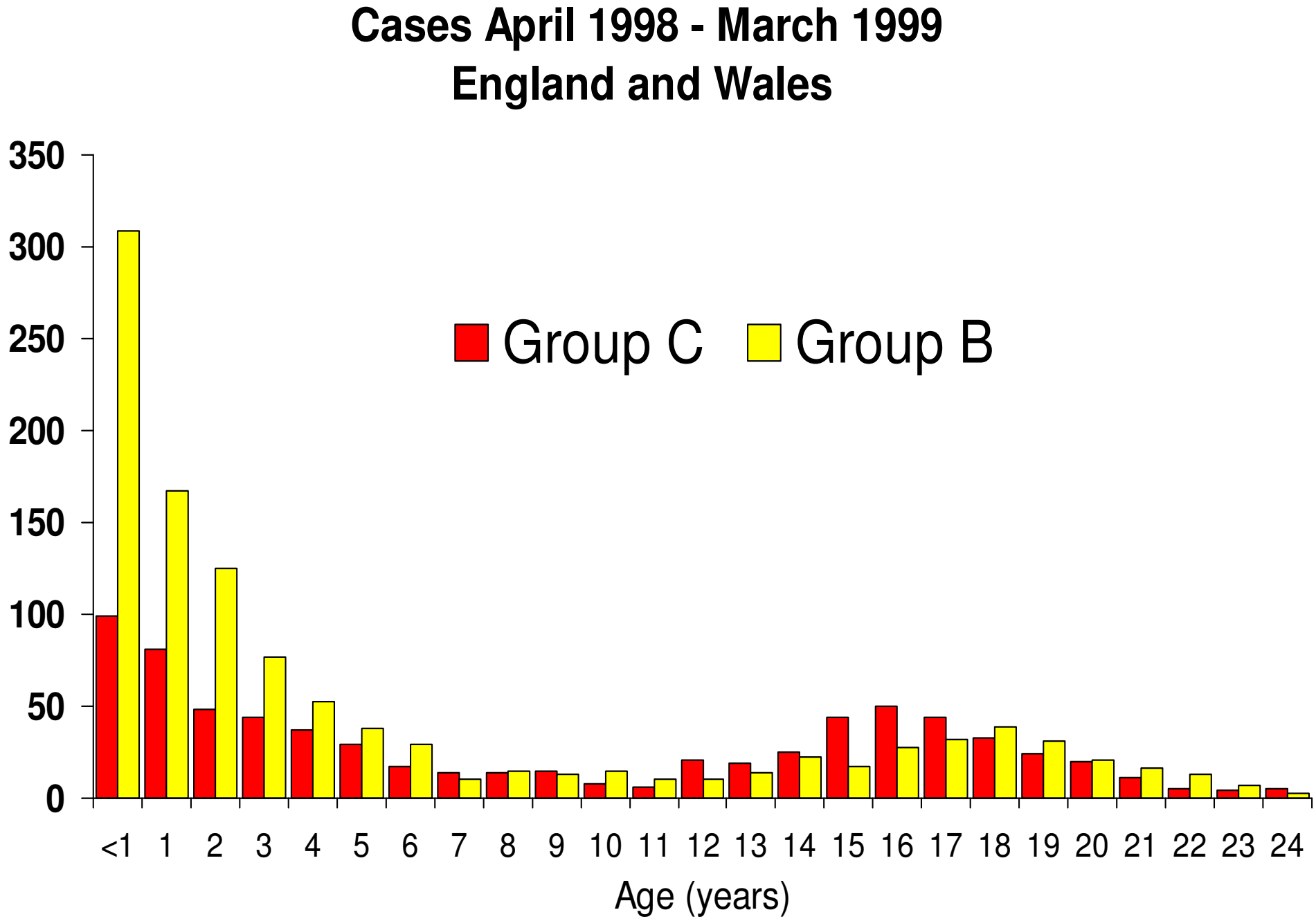
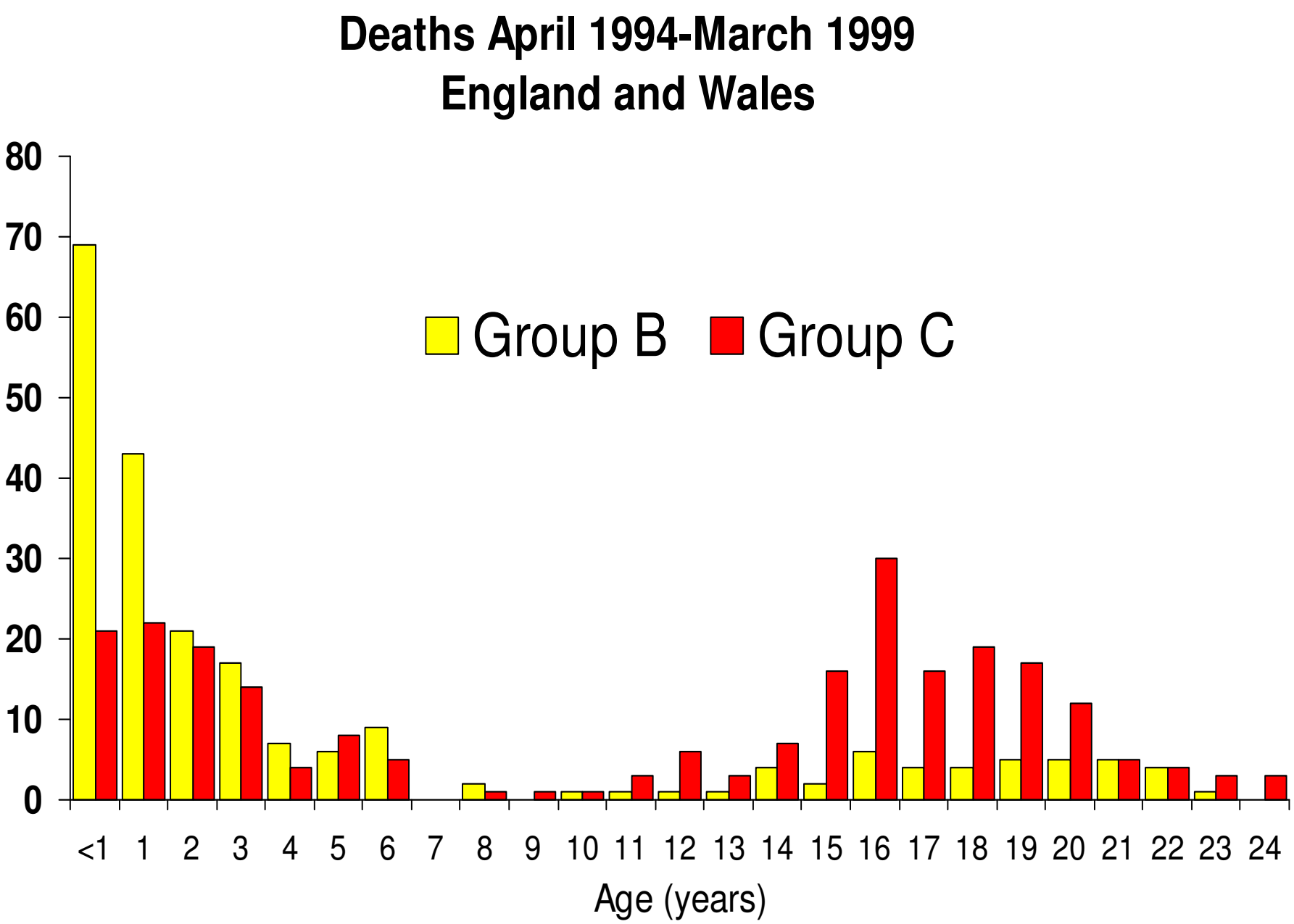
Outline

- Meningococcal group C disease in England/Wales and conjugate vaccines
- The need for a correlate
- The Goldschneider correlate
- A change to the assay
- Clinical trial results
- Post-licensure validation of the correlate

Annual cases of meningococcal groups B and C infection in England &Wales before group C conjugate vaccine introduction




Cases April 1998 - March 1999
England and Wales
350
300
250
200
150
100
50
0
Group C
Group B
<1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Age (years)


Deaths April 1994-March 1999
England and Wales
80
70
60
50
40
30
20
10
0
Group B
Group C
<1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Age (years)

Conjugate vaccines being developed in the late 1990s

- technology previously used in Hib conjugate vaccine
- polysaccharide antigen attached to a carrier protein e.g. tetanus toxoid, CRM_{197}
- T cell dependent response
  - immunological memory and prolonged protection
  - affinity maturation
  - good response in young infants
  - reduces carriage resulting in herd immunity

The need for a correlate (or surrogate)

- Incidence in under 5's is about 1 in 10,000 per year
- A placebo controlled trial to detect a 70% efficacy would need 600,000 children (an entire UK birth cohort) if followed for one year.
- A trial based on a correlate would need <50 individuals to detect the equivalent effect.
- We want to look at about three vaccines at different ages
- Without an accepted correlate vaccines would never have been developed.

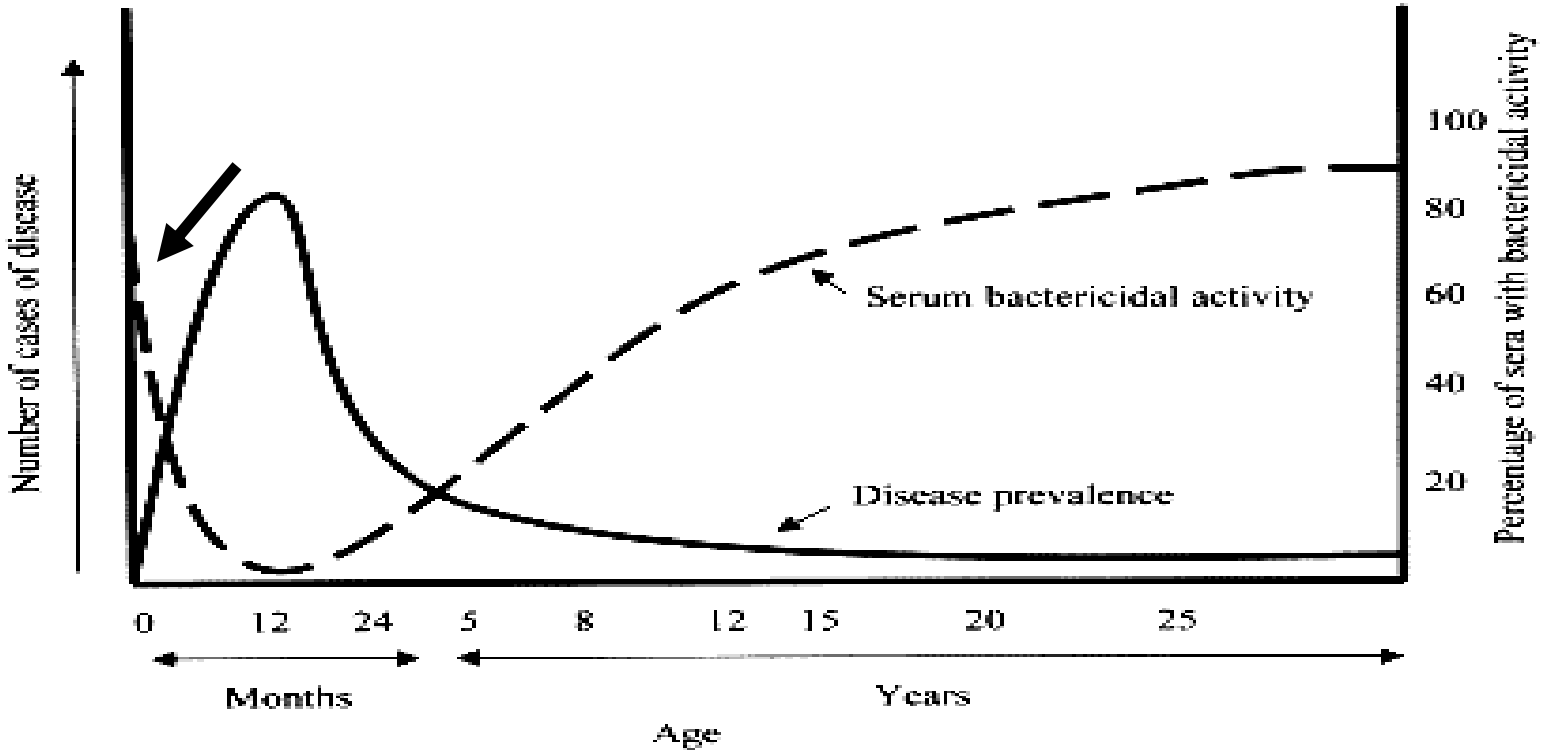
The Goldschneider* correlate

- Serum bactericidal assay (SBA) measuring functional antibodies against MenC strains.

- A cut-off of 1:4 (i.e. killing occurs at serum dilutions of 1:4 or more).

* **Goldschneider *et al.* J. Exp. Med. 1969;129,1327-48**

The age dependent prevalence of meningococcal disease in relation to population immunity measured by serum bactericidal activity from Goldschneider *et al*., 1969).



BASIS OF SEROLOGICAL CORRELATE OF PROTECTION FOR SEROGROUP C DISEASE

Studies in army recruits in USA by Goldschneider

Prior serum bactericidal antibody with human complement (hSBA) against C strain ≥ 1:4

- 8.7% of cases (2/23)

- 67.0% of non-cases (154/230)

Could be interpreted as an efficacy of 95%
odds of disease in those with pre-level ≥ 1:4 compared to <1:4=0.05

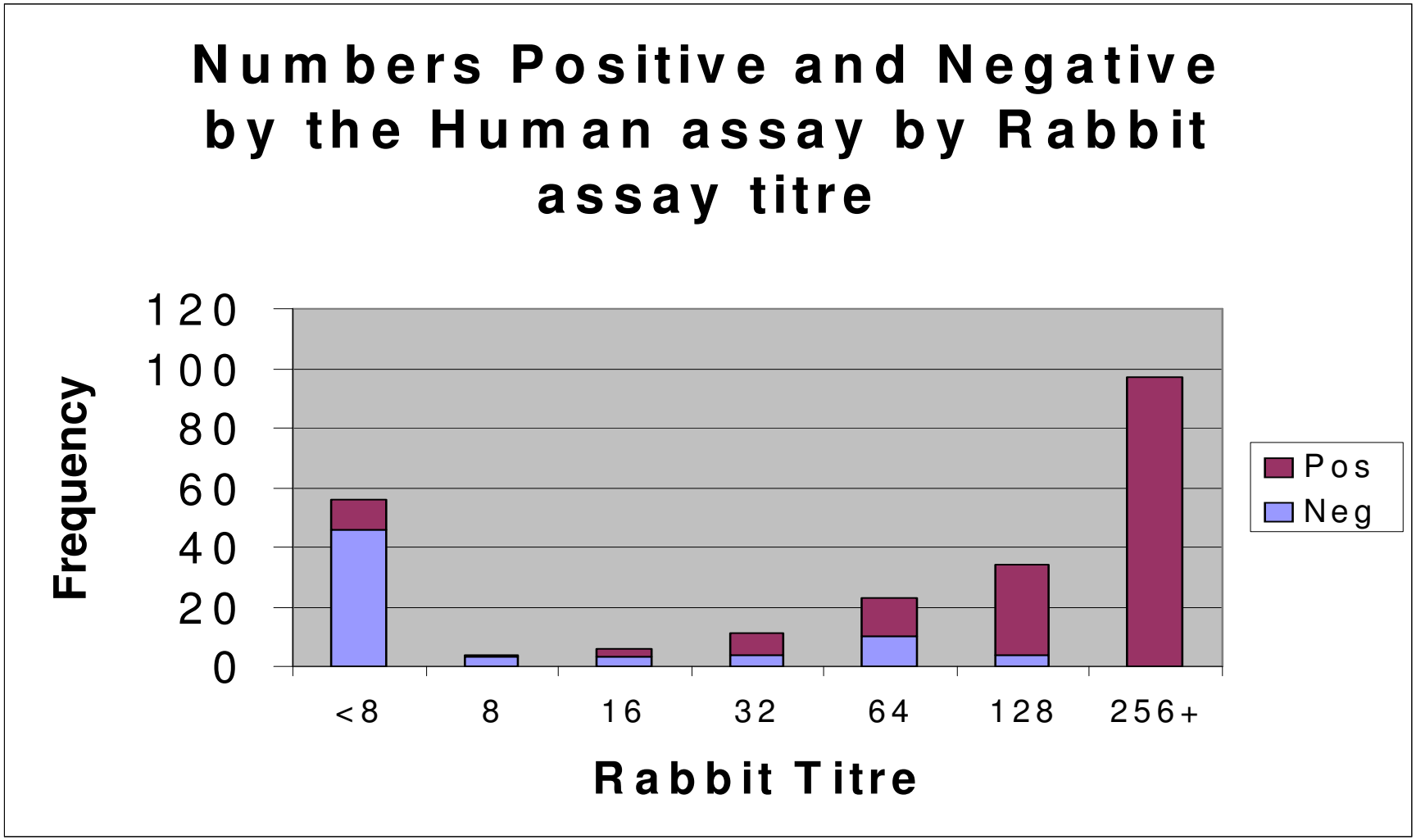
Note of caution

- Correlate is based on immunity attained through natural exposure.
- Vaccine induced immunity may give equivalent SBA levels but may not give protection as full as natural exposure even with equivalent SBA.
- Correlate based on study in adults – not children

A change in the assay

- The Goldschneider assay was based on dilution in human complement (hSBA).
- This source of complement is very hard to find in large quantities and standardise.
- The assay was therefore changed to use baby rabbit complement (rSBA) as recommended by WHO.
- But what about the correlate? Could we still use a cut-off of 1:4?

Study to compare hSBA and rSBA*



* Borrow et al 2001: serological basis for use of meningococcal serogroup C conjugate vaccines in the UK: reevaluation of correlates of protection

Comments

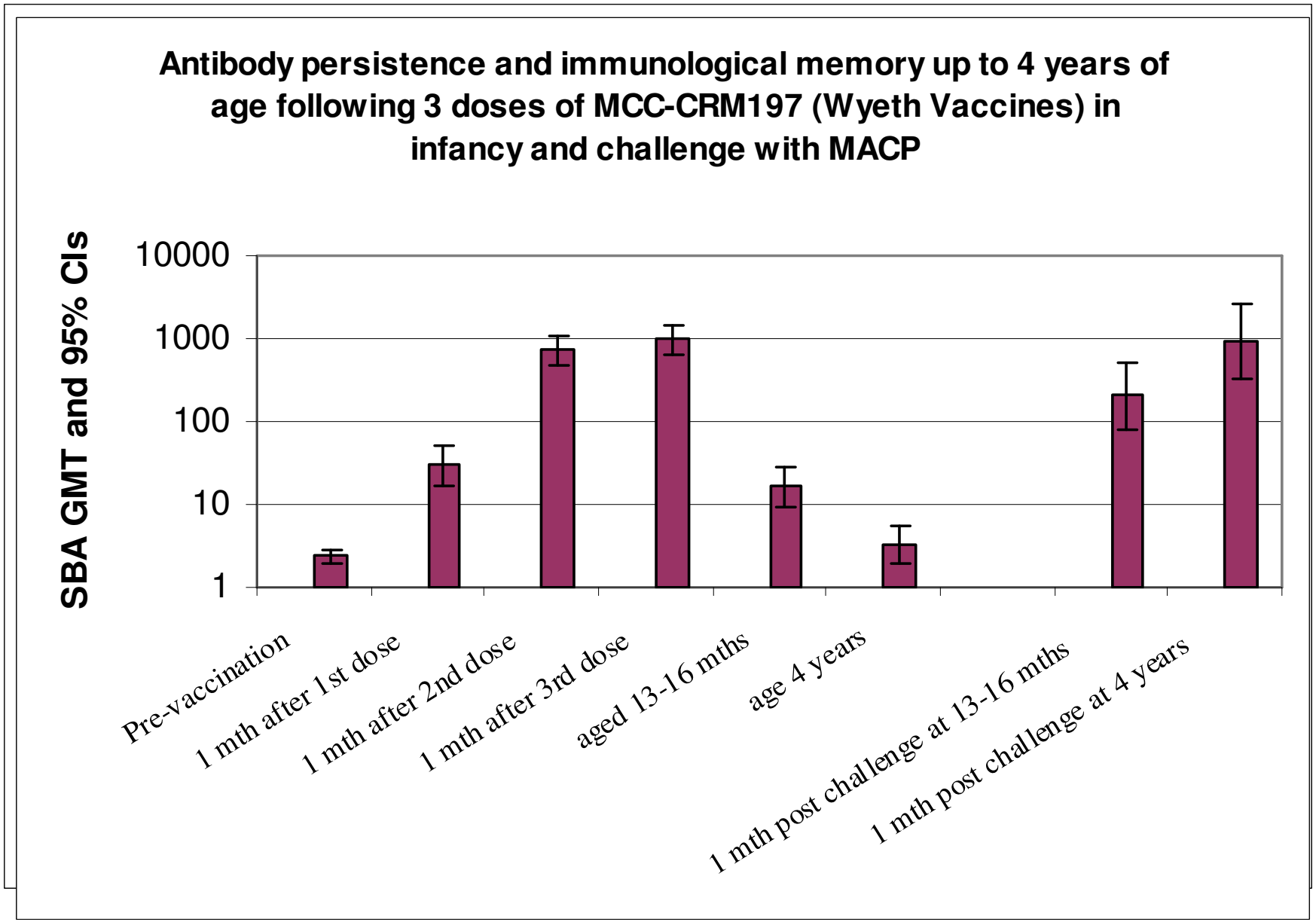
- Results of <1:8 were mainly negative and >=1:128 positive by hSBA
- Between 1:8 and 1:64 – less clear.
- Additional requirements in this range:
  - 4 fold rise pre to post vaccination
  - hSBA result (not generally available)
  - induction of memory

Assessment of immunological memory to MCC vaccines

- SBA response to plain polysaccharide boost greater than in unprimed individuals
- Increase in antibody avidity with time
- Long term protection (only from post licensure surveillance)

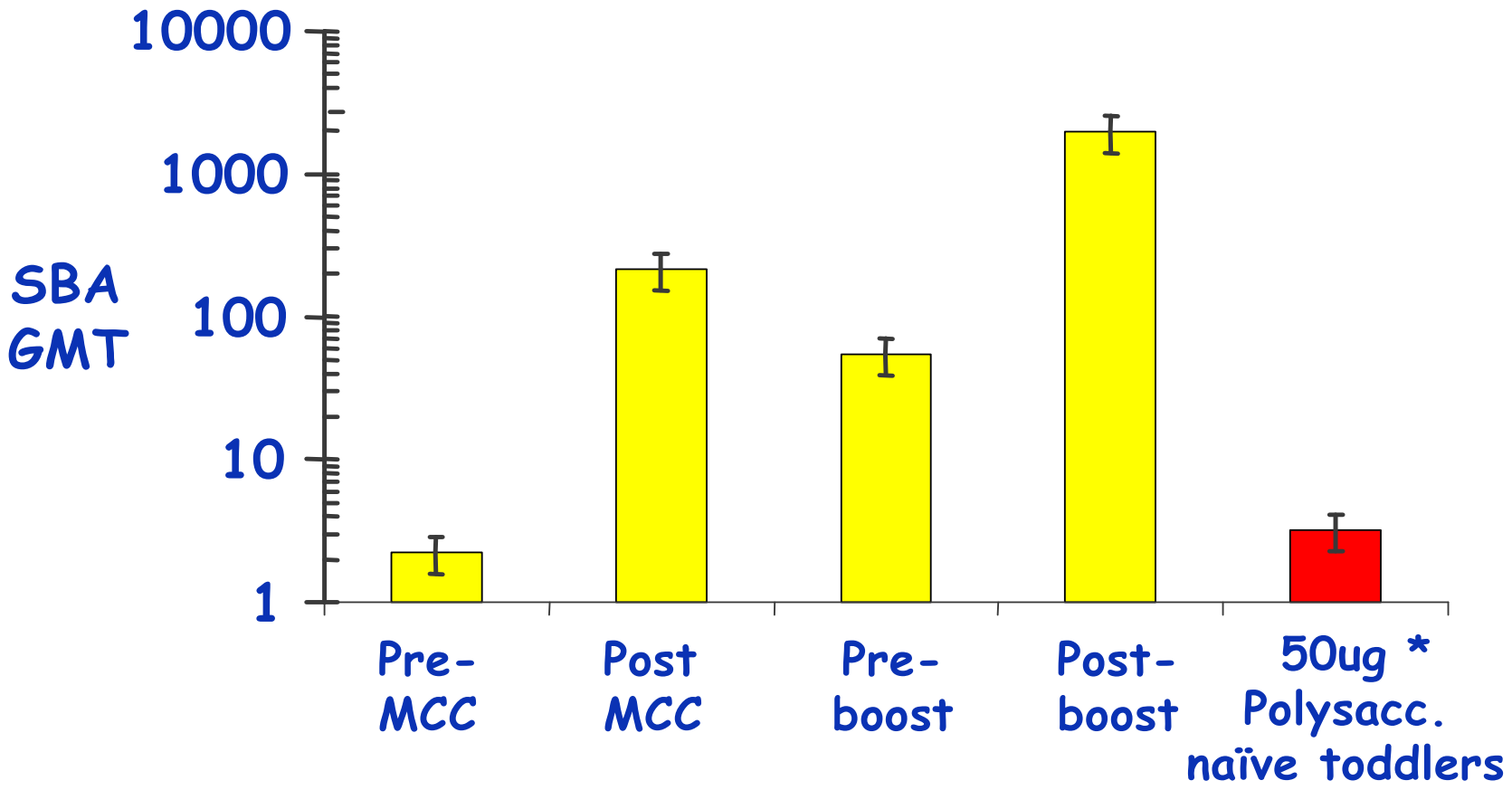
Clinical Trial Results

- 2900 children / young adults in various immunogenicity trials funded by the department of health.



Borrow et al. 2002 J. Infect. Dis. 186:1353-1357
Richmond et al. 1999 J. Infect. Dis. 179: 1569-1572

SBA responses to MCC vaccines & 10ug plain polysaccharide booster 6 months later in UK toddlers

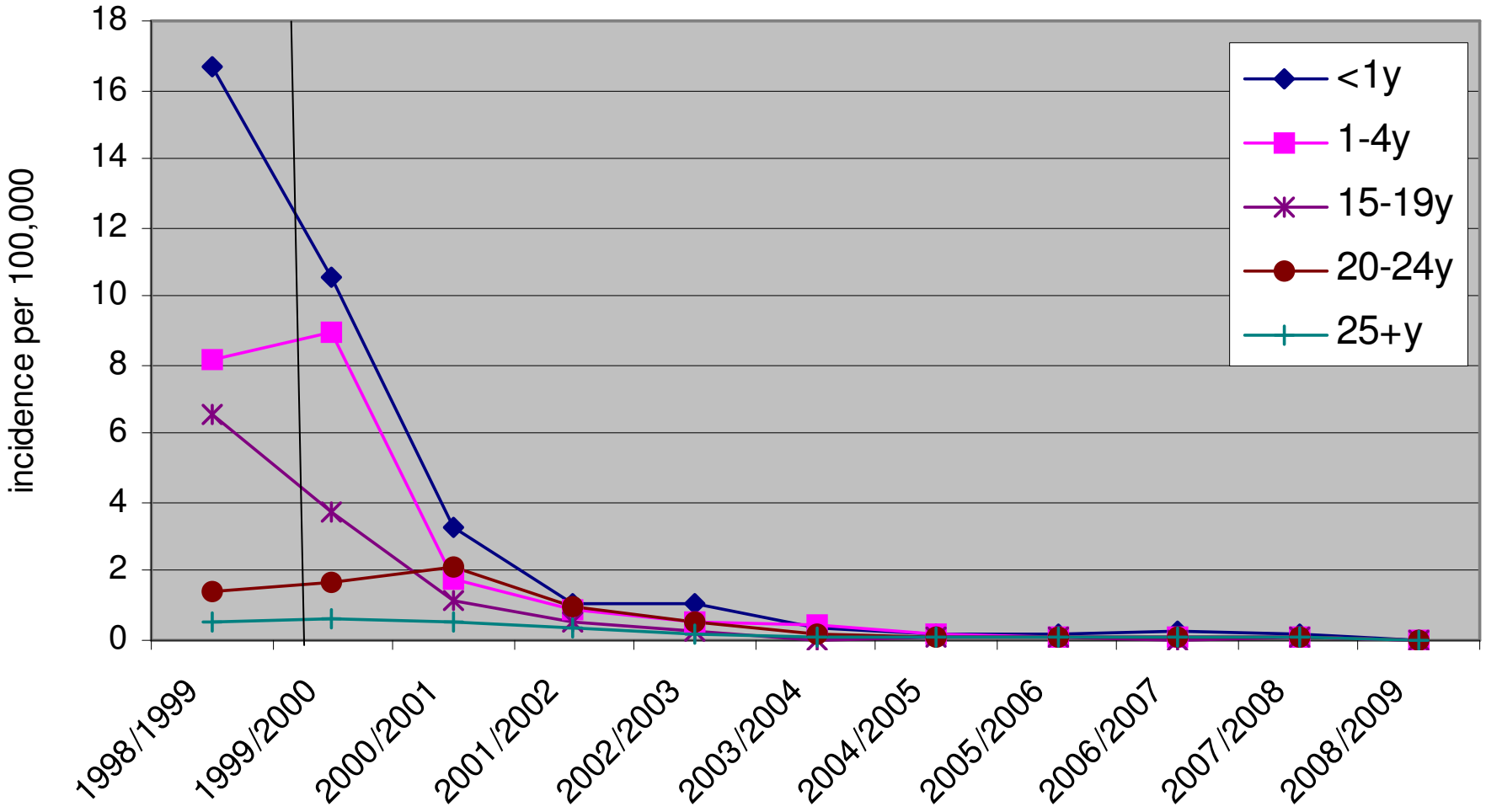


Comments from trials

- Post vaccination the proportion with titres >=1:128 was high for the primary schedule and older children. This waned rapidly, but avidity matured and responses to a polysaccharide challenge were good.
- For toddlers 40% had equivocal titres (8 to 64) post one dose, but these individuals had almost all shown 4 fold rises and also achieved levels >=128 on a challenge and had avidity maturation.

Vaccine licensed and introduced in late 1999 with catch-up to age 18.

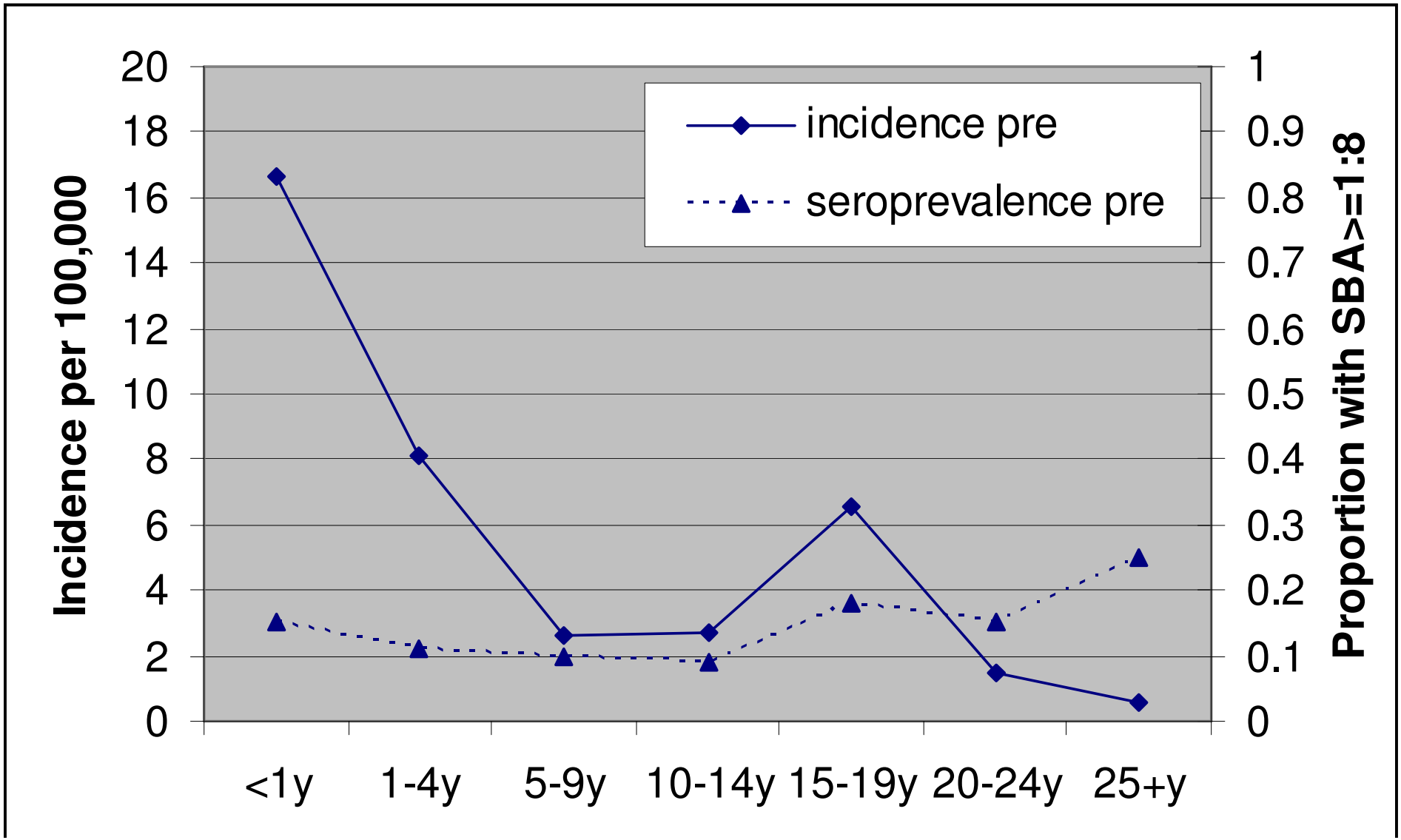
Meningococcal group C incidence in England and Wales 1998-2009 in selected ages



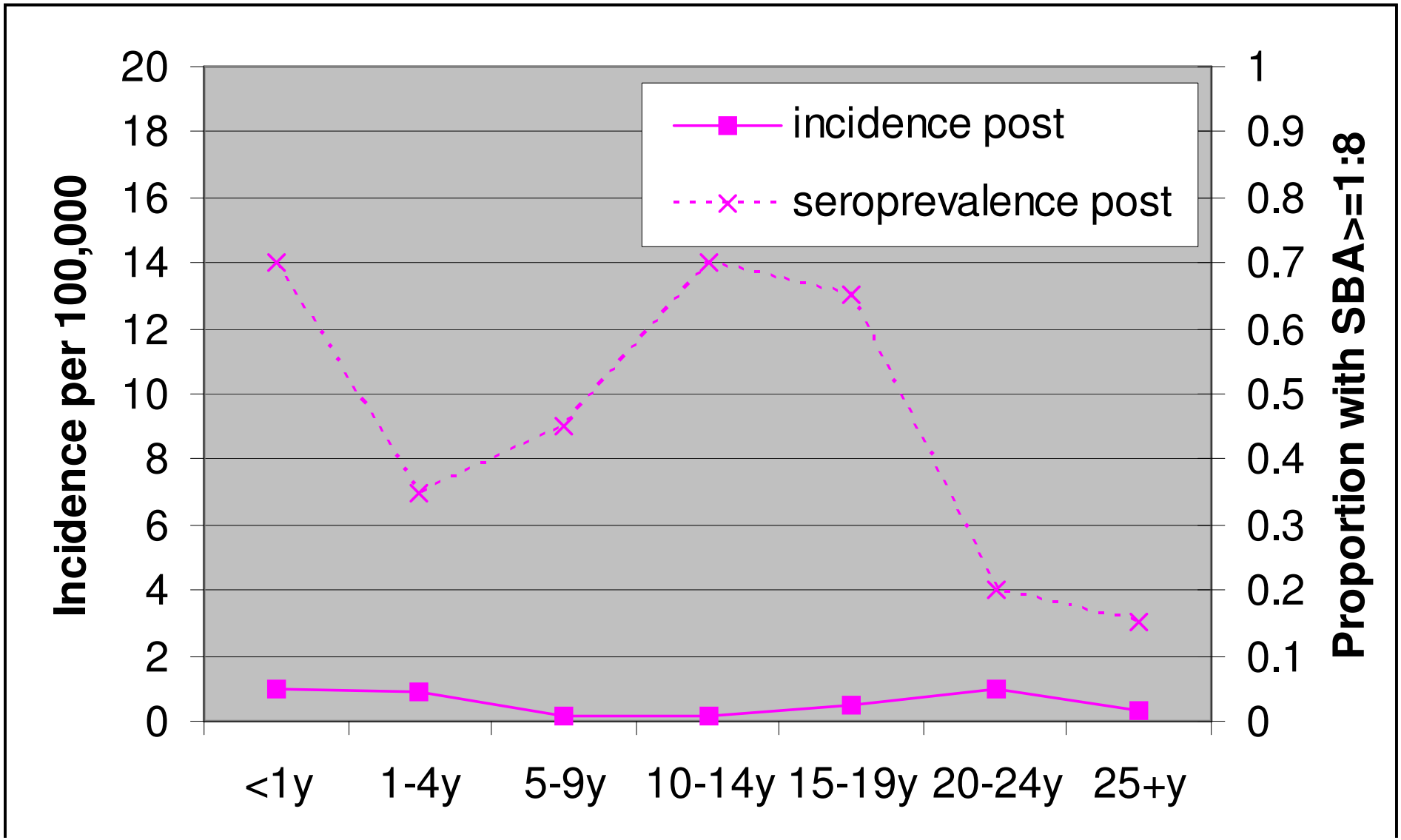
Post-licensure validation of a correlate (1)

- Look at population antibody levels pre and post vaccination compared to disease incidence pre and post vaccination. (Goldsneider curves)

Incidence and seroprevalence before vaccine introduction (1999)



Incidence and seroprevalence after vaccine introduction (1999)



Comment

- Overall SBA has increased and disease increased pre to post vaccination
- Not a classic Goldschneider curve prior to vaccine. E.g. the increase in 15-19 year olds reflects behaviour changes rather than increased susceptibility
- But we do see the pre to post vaccine effect of lower incidence correlating with higher proportions with SBA >= 1:8

Post-licensure validation of a correlate (2)

- Calculate observed vaccine effectiveness (screening method)*
- Calculate predicted effectiveness based on different assay cut-offs (comparison of post vaccination titres with titres in unvaccinated individuals).**
- Compare these

*Farrington CP. 1995. Estimation of vaccine effectiveness using the screening method. Int J Epidemiolo 1995; 22:742-746.

** Andrews N, Borrow R, Miller E. Validation of serological correlate of protection for meningococcal C conjugate vaccine using efficacy estimates from post-licensure surveillance in England. 2003. Clinical and Diagnostic Laboratory Immunology.10:780-786.

Calculating observed VE by the screening method

- VE = 1 – odds of vaccination in cases/odds of vaccination in the population

$$VE = 1 - \frac{PCV/(1-PCV)}{PPV/(1-PPV)}$$

PCV = proportion of cases vaccinated, PPV = proportion population vaccinated

Example - Observed VE within one year of vaccination of one year olds (toddlers)

- 4 vaccinated cases
- 11 unvaccinated cases
- PCV = 4/15 (0.27)
- PPV = 0.77
- VE = 1 - (0.27/0.73) / (0.77/0.23) = 89%
  (95% CI 64%-98%)

Predicted VE (all or nothing method)

vaccinated

90% chance titre >=1:8 1m post vaccination

unvaccinated

5% chance titre >=1:8 at same age (natural exposure)

EXPOSURE: if titre >= 1:8 then probability of being ill is 0 but if less than 1:8 it is d for both individuals. Also both individuals equally likely to be exposed

P(ill) = d*0.1

P(ill) = d*0.95

VE = 1 – d*0.1/d*0.95 = 1-0.1/0.95 = 0.89 or 89%

Herd immunity effect on the calculation

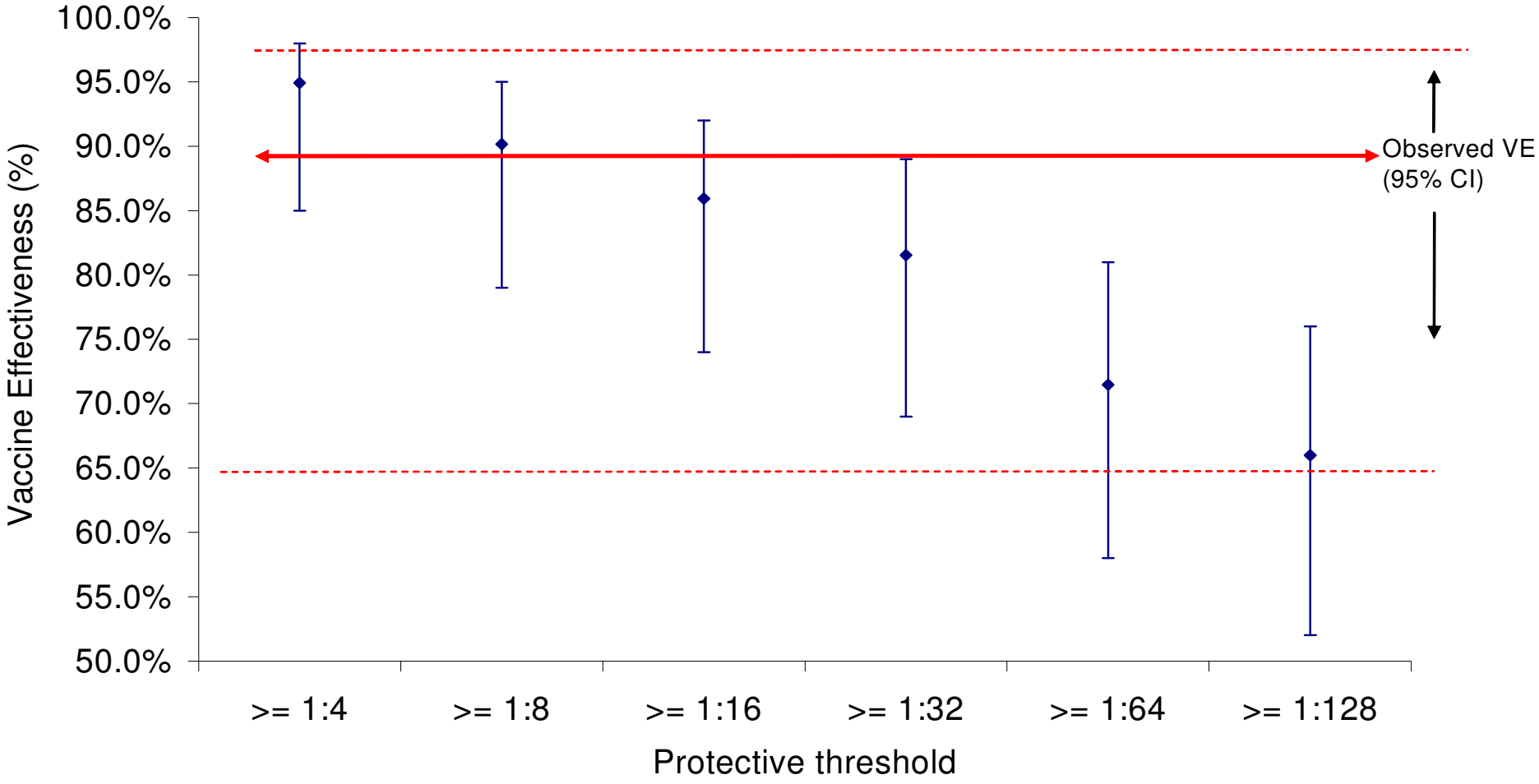
- Herd immunity means unvaccinated unlikely to be exposed.
- Therefore a few years after vaccine introduced there is a negligible chance of protective antibodies if unvaccinated.
- Formula simplifies to VE = proportion with titres >= 1:8.

Example of Predicted VE in toddlers

- 1m Post Vaccinated 6/70 (8.6%) had titres <1:8
- In unvaccinated infants of a similar age 233/267 (87.3%) had titres <1:8
- VE = 1 – 0.086/0.873 = 0.90 = 90% (95% CI 79-95)
- This calculation can be repeated using different titre cut-offs

Cut	**Predicted VE (95% CI)**
1:8	90 (79-95)
1:16	86 (74-92)
1:32	82 (69-89)
1:64	71 (58-81)
1:128	66 (52-76)

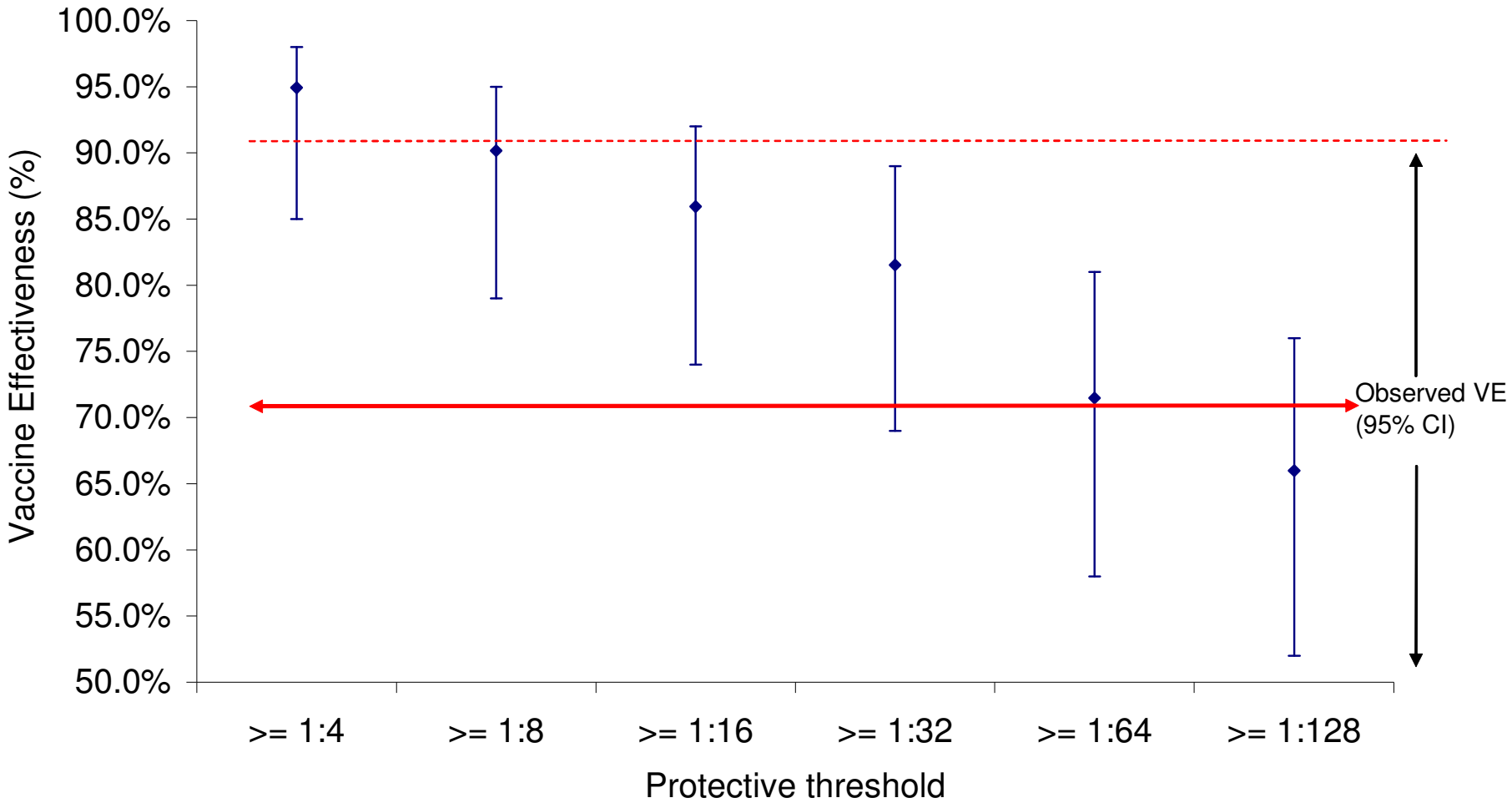
Comparison of Observed and Predicted VE for Toddlers (***using 1 month post vaccination titres*** to predict VE ***within first year after vaccination)***



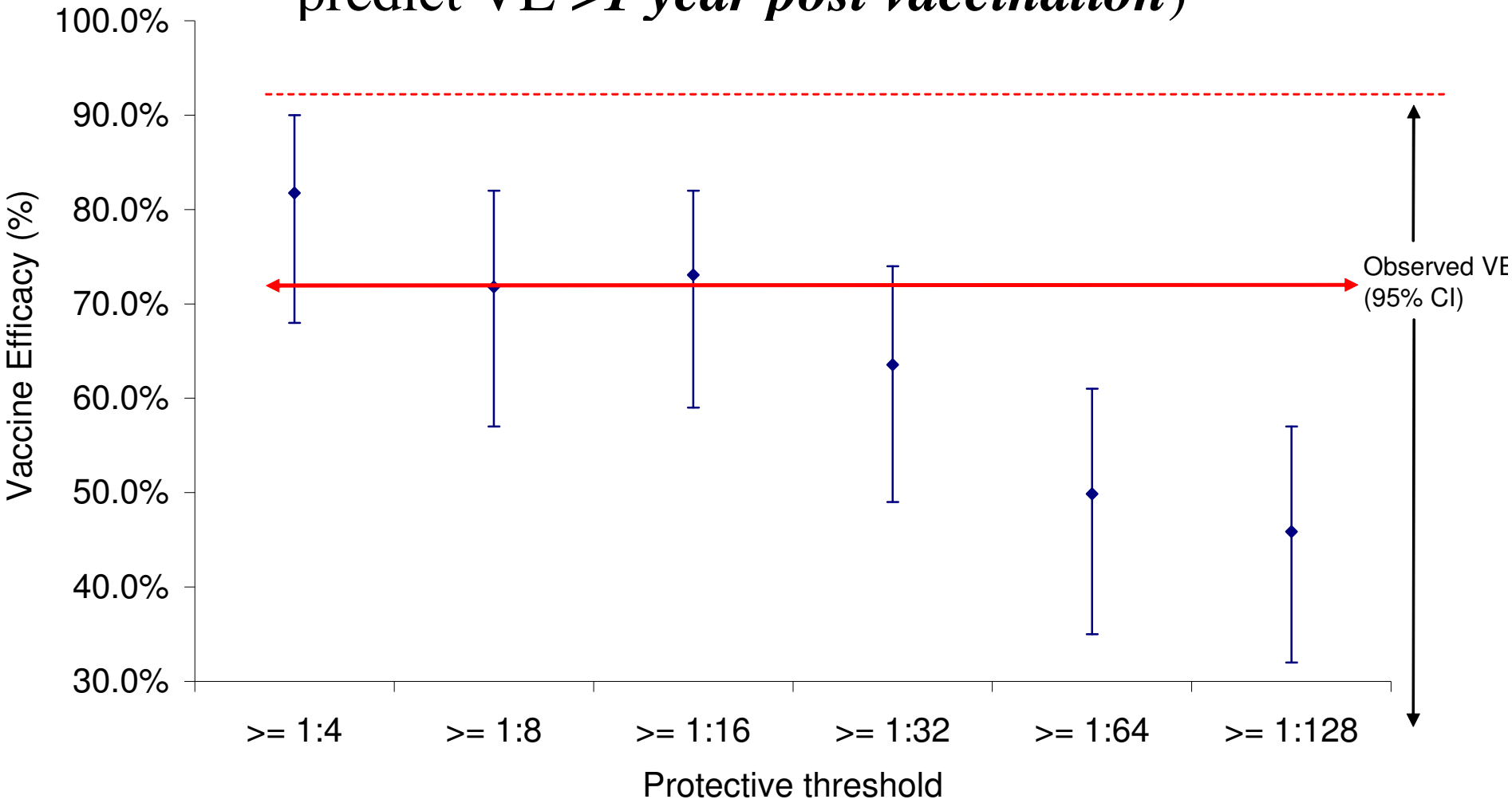
Assessing VE by time since vaccination

- Trials showed that SBA titres wane quite rapidly
- Does the initial SBA response predict VE or is it the circulating antibody that predicts VE – i.e. the current SBA level?
- We need to compared predicted VE based on 1 month titres and also based on titres at a later time point with VE in the longer term.

Comparison of Observed and Predicted VE for Toddlers (***using 1 month post vaccination titres*** to predict VE ***>1year post vaccination***)



Comparison of Observed and Predicted VE for Toddlers (***using 7 m post vaccination titres*** to predict VE ***>1 year post vaccination***)



Comment

- For toddlers the 1:8 cut-off based on 1 month post vaccination titres predicts short term VE well but not long term VE
- For longer term VE it seems a 1:8 cut-off works if you use 9m post vaccination titres

Comments

- There has been an observed decline in vaccine effectiveness by time since vaccination – most notably in infants.
- This decline is hard to quantify due to very low numbers of cases as a result of herd immunity.
- The decline is consistent with declines in SBA levels
- This suggests that that the immune memory studies may have incorrectly predicted protection when SBA had declined.
- Auckland et al (JID 2006) found that vaccine failures had significantly higher acute avidity indices and higher convalescent SBA levels than unvaccinated controls (i.e. memory response but too slow to prevent infection).
- A booster dose has been introduced for infants which we are evaluating

Comments

- Circulating antibody as measured as an SBA titre correlates with protection. A cut-off of about 1:8 most closely correlates with effectiveness. The 1:128 cut-off would appear too high.
- Comparison of observed and predicted VE is a useful method to validate a correlate of protection, although more precise VE estimates would be ideal.

Acknowledgements

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- **Institute of Child Health, London ; David Goldblatt**