University of BRISTOL

Best use of conjugate vaccines for the prevention of bacterial meningitis and septicaemia.

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SAGE working group

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Optimising the use of conjugate vaccines to prevent disease caused by *Haemophilus influenzae* type b, *Neisseria meningitidis* and *Streptococcus pneumoniae*

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Context

- Safe, effective conjugate vaccines exist offering protection against
  - *Haemophilus influenzae* type b
  - *Neisseria meningitidis*
  - *Streptococcus pneumoniae*
- Efforts to expand access to existing and new vaccines
  - Meningitis Vaccine Project
  - PneumoADIP
  - Hib Initiative
- 'Optimal' schedules have not been defined for these vaccines
- Lessons can be learned from experience with vaccines so far
- Inform research agenda by identifying knowledge gaps

Some key questions

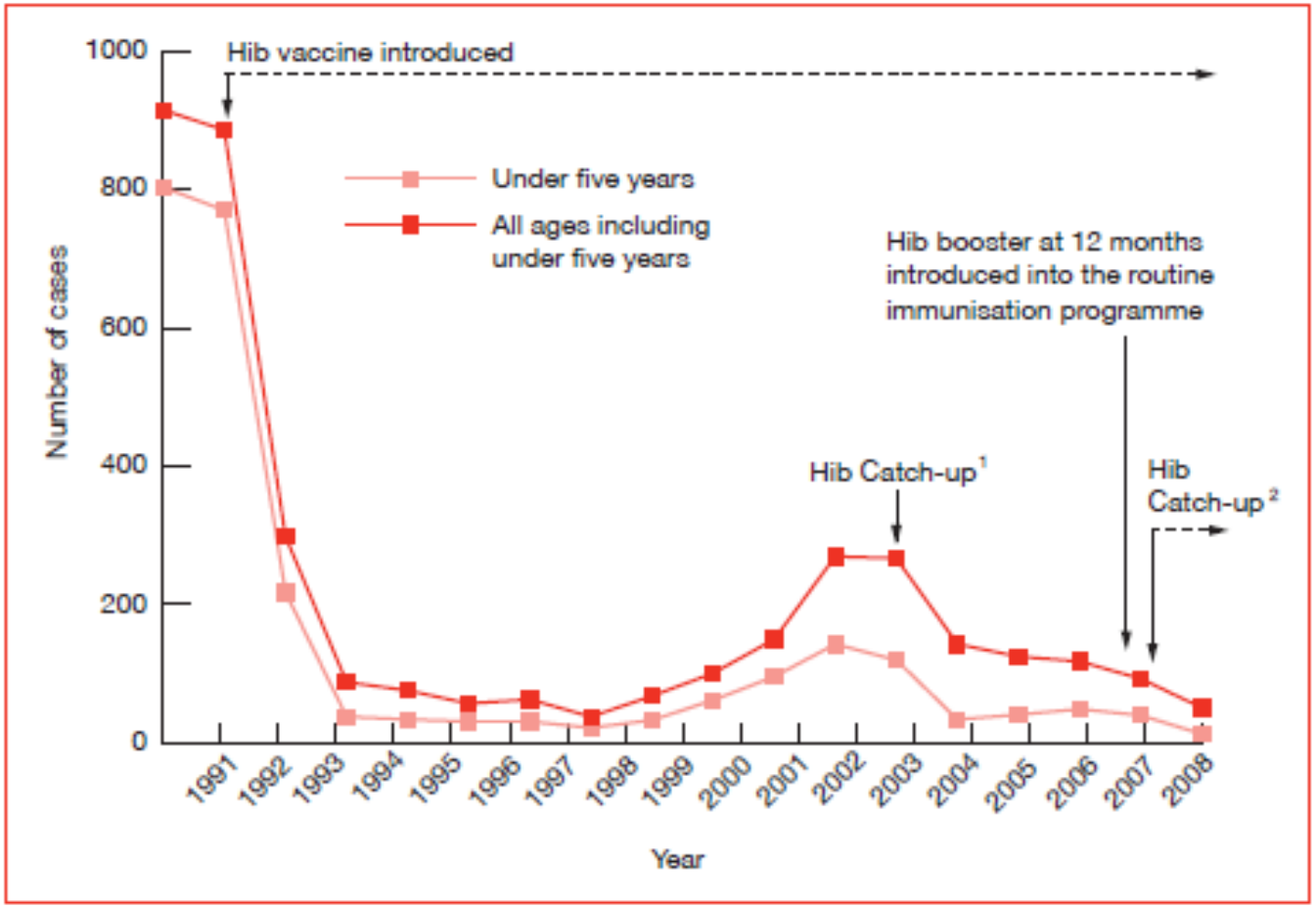
- Vaccine schedules
  - Doses required for primary immunisation?
  - Timing & age at primary immunisation?
  - Booster needed?
  - 1 dose in second year of life sufficient?
  - Duration of protection?
- Herd immunity
  - Coverage required?
  - Age groups to target?
- Impact of catch-up campaigns
- Safety
- Interactions with vaccines given in combination/ concomitantly
- Serogroup/ type replacement
- Programmatic feasibility
- Cost-effectiveness

What is an optimal schedule?

- Primary outcome in clinical trials = direct protection
  - Efficacy
  - Immunogenicity
- But effect of conjugate vaccines on carriage can lead to substantial indirect effects
- Consider population impact not just individual protection

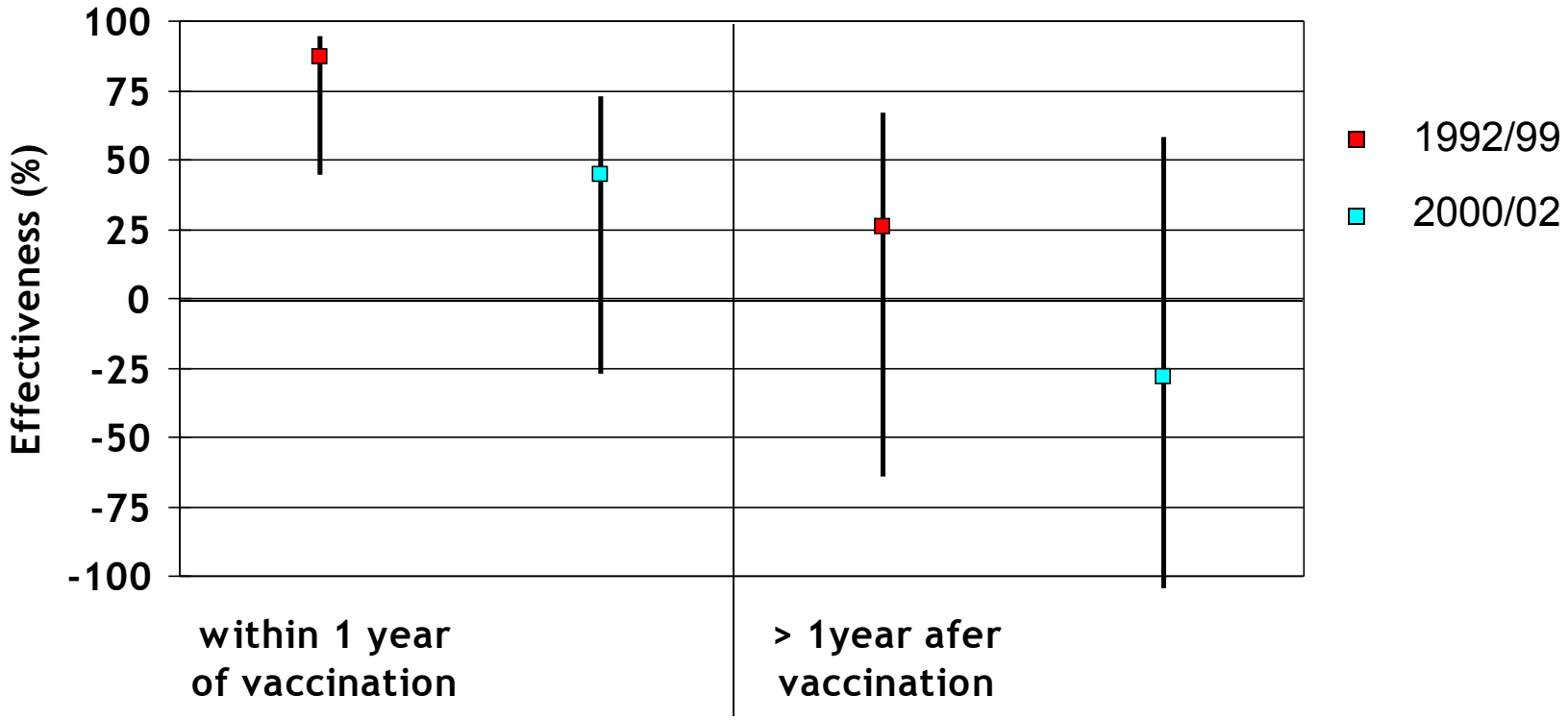
Haemophilus influenzae type b

England and Wales 1991 - 2008



Hib vaccine effectiveness UK children born 1992/99 and 2000/02

Ramsay *et al*. JID 2003; 188: 481-85

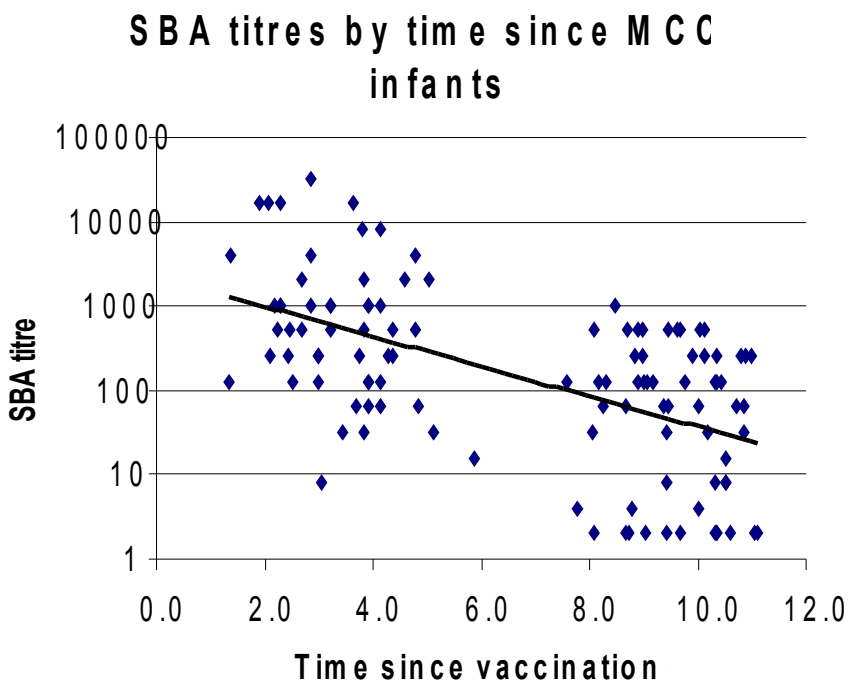


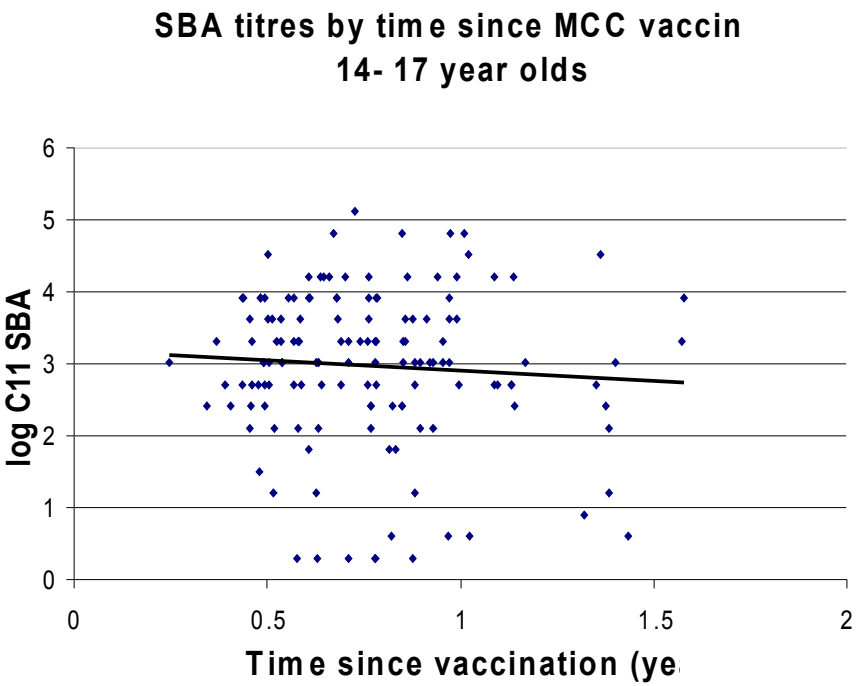
MCC vaccine effectiveness to June 2009 (England only)

HPA unpublished data (Campbell et al, paper submitted)

Cohort	Doses	% Vaccine effectiveness (95% CI) [1]			
		Overall	Time since scheduled vaccination.[2,3]		Difference between ≤ and >1 year since MCC vaccine
			Within 1 year	More than 1 year	
Routine: 2,3,4months	3	90 (77,95)	**97** (91,99)	**68** (-63, 90)	**P<0.01**
5 to 11 months	2	86 (54,96)	91 (-8, 100)	84 (31,97)	P=0.63
1 to 2 years	1	83 (60, 93)	89 (64,98)	71 (-40,93)	P=0.23
3 to 18 years	1	97 (90, 99)	96 (92,99)	93 (87,96)	P=0.13

MenC SBA antibody persistence by age (HPA unpublished)

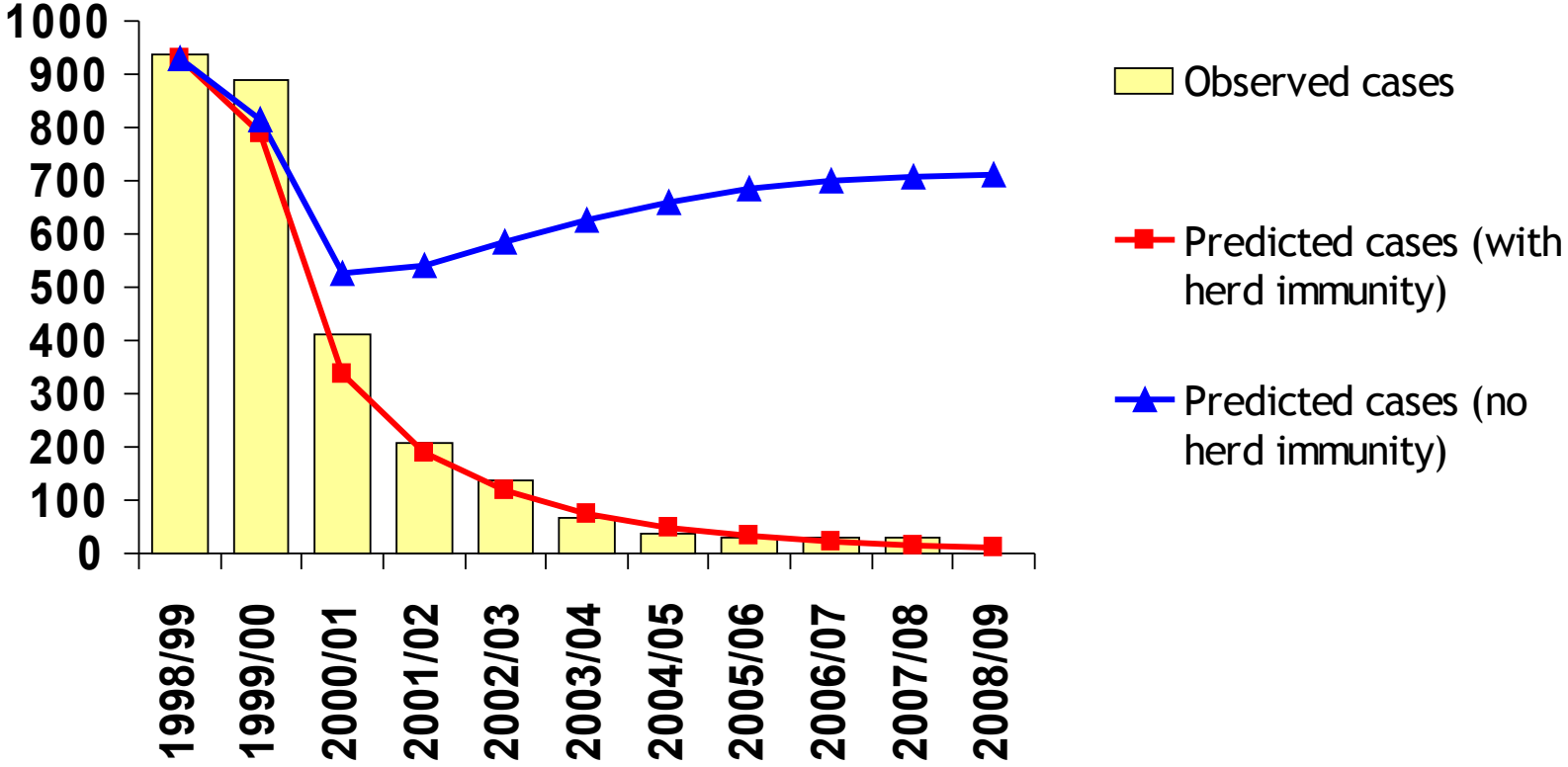




Slide courtesy of Ray Borrow/ Liz Miller

Herd immunity from MCC vaccine

Observed cases of serogroup C disease in England & Wales compared to model predictions



Lessons from UK "accelerated" schedule

- Effectiveness and antibodies wane rapidly after infant immunisation
  - But both persist longer after a single dose in older groups
  - Vaccine failures have evidence of memory
- Effect on carriage crucial
  - Waning of Hib VE masked initially ➔ important to measure direct and indirect effects separately
  - Cases of MenC remain low due to persisting herd effects
  - Catch-ups included age groups with high transmission

Current UK immunisation schedule

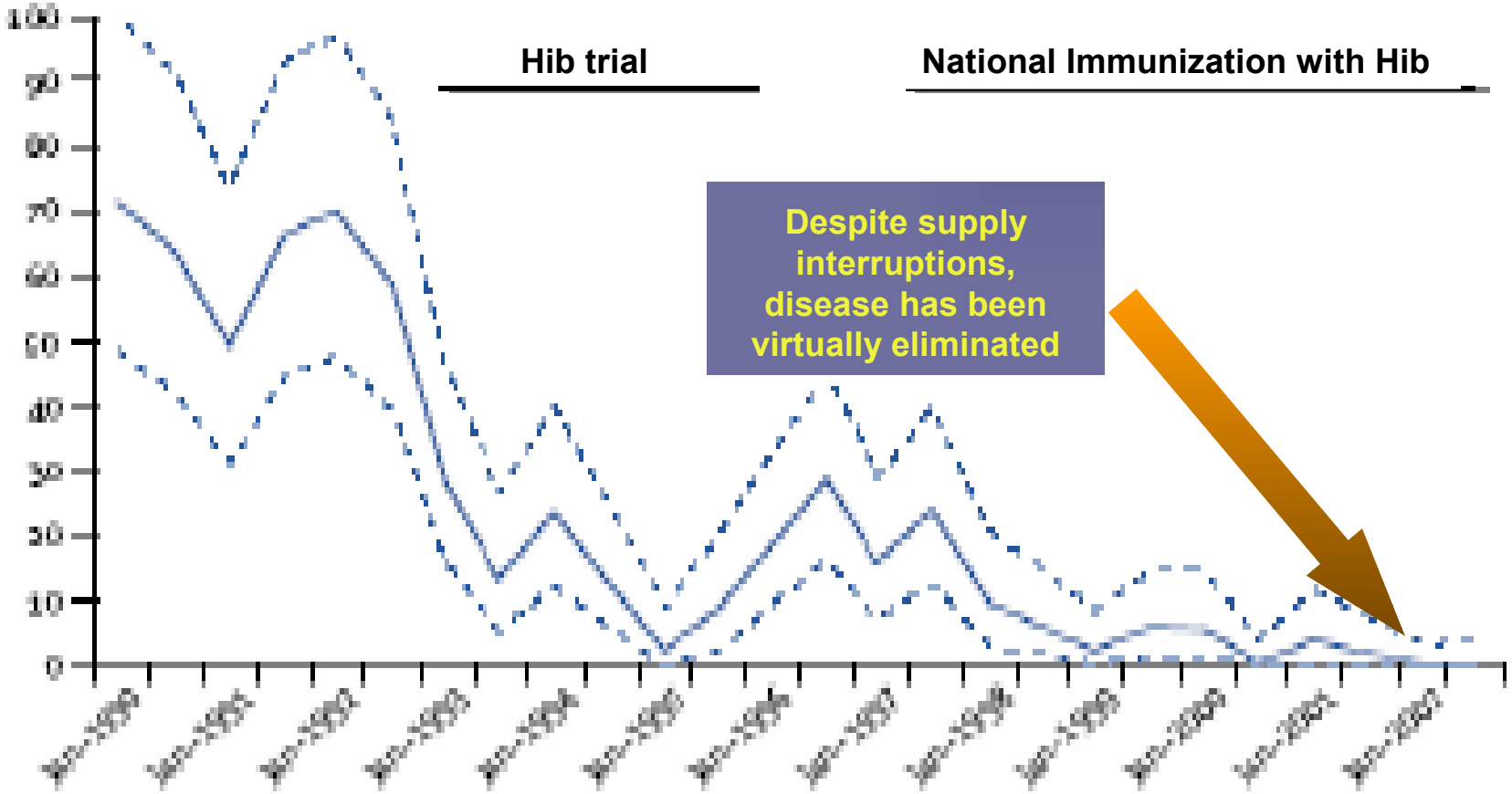
Age (months)	Vaccine
2	DTaP/ IPV/ Hib +PCV7
3	DTaP/ IPV/ Hib +MenC
4	DTaP/ IPV/ Hib +MenC + PCV7
12	Hib/ MenC
13	MMR + PCV7

Implications of UK experience

- EPI schedule 6,10, 14 weeks
- Conjugate vaccines increasingly included
- Caveats
  - Different vaccine formulations behave in different ways e.g tetanus *vs* CRM conjugate, aP combinations
  - Differences between antigens, e.g. MenA vs MenC, serotype 6B
  - Same vaccine can have different effect in different populations e.g. PCV7

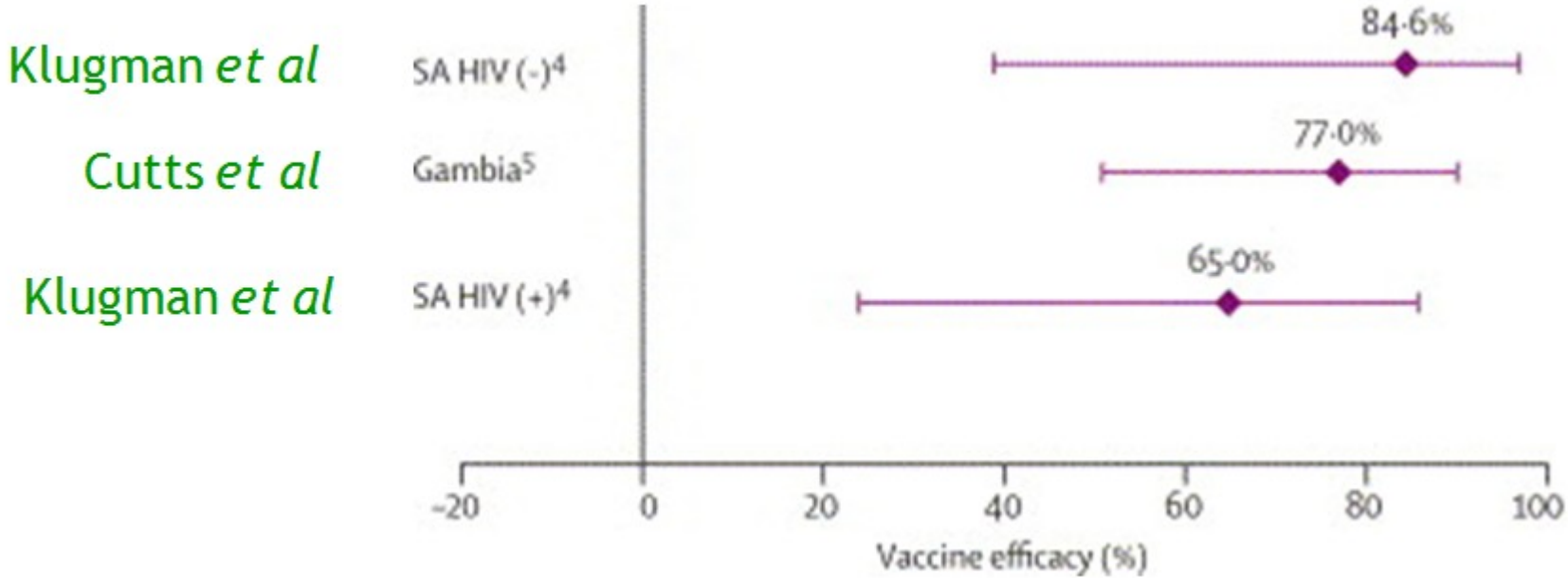
The Gambia Hib vaccine program resulted in virtual disease elimination

Incidence of Hib Meningitis/ 100,000 (children <5 years) in the Western Region of the Gambia



Slide from www.hibaction.org

RCTs of pneumococcal conjugate vaccine in Africa: Efficacy against vaccine-type invasive disease



** Gambia trial reported 16% (95% CI: 3-28%) reduction in mortality

Timeliness of vaccination

Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data

Andrew Clark, Colin Sanderson

Lancet 2009; 373: 1543–49

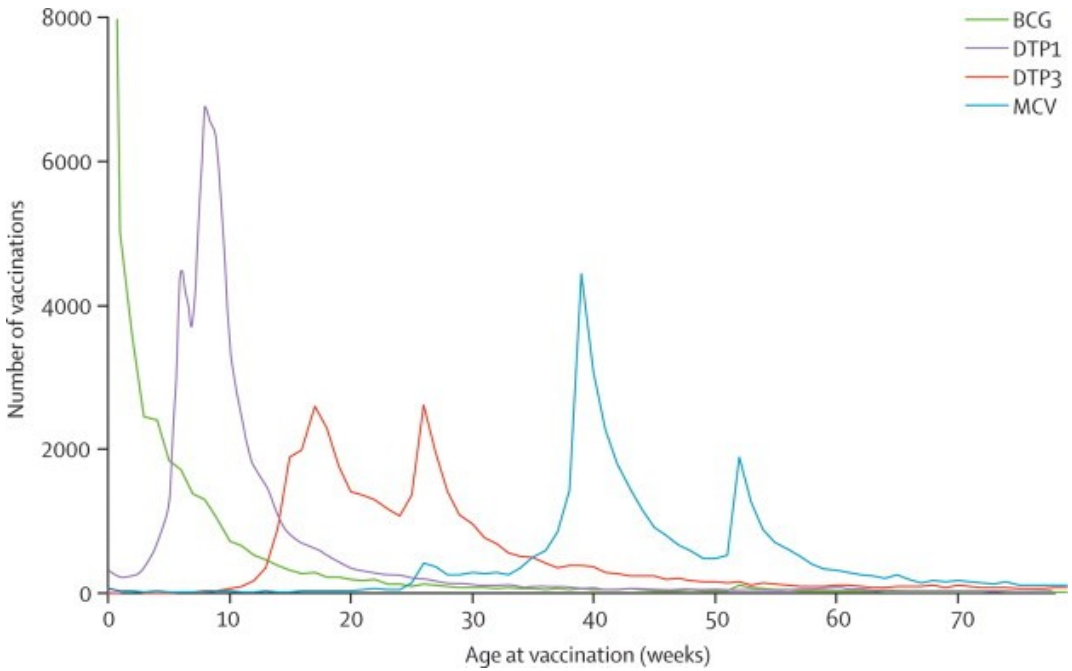


Figure 2. Age distributions for administration of BCG, DTP1, DTP3, and MCV1 vaccines, based on card dates only in children aged 18–35·9 months
BCG=bacille Calmette-Guérin. DTP=diphtheria, tetanus, and pertussis. MCV=measles-containing vaccine.

Alternatives

- 2+1
  - Later dose to extend protection
- Fewer doses
  - 2 doses e.g. 6, 14 weeks
  - 1 dose later e.g. 9 months
- Catch-up campaigns
- MVP approach
  - Target 1-29 year olds in mass campaigns
  - Routine: e.g. 14w + 9m

Conclusions

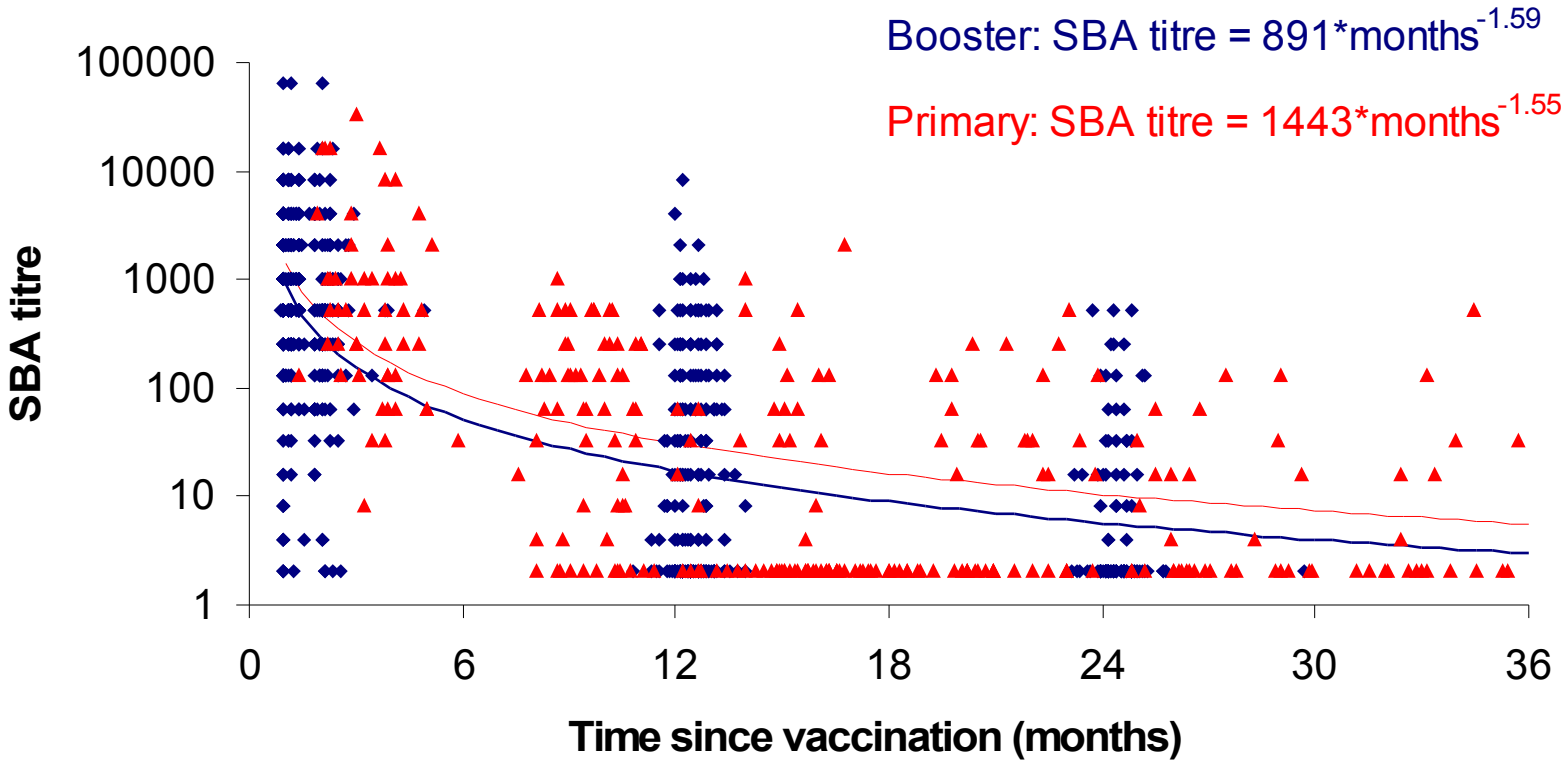
- 2,3,4 month schedule not optimal in UK
- Use of conjugate vaccines constrained by current EPI schedule
  - Best use *vs* any use
  - Alternative approaches are possible within current frameworks
- Need to consider direct and indirect effects
  - Modelling can help
  - Indirect effects can also be negative (replacement, reduction in natural boosting)
  - Further research e.g. into duration of protection

Acknowledgements

- Health Protection Agency
  - Liz Miller, Mary Ramsay
- SAGE subgroup on conjugate vaccines

MenC SBA titres by time since primary vaccination and time since booster

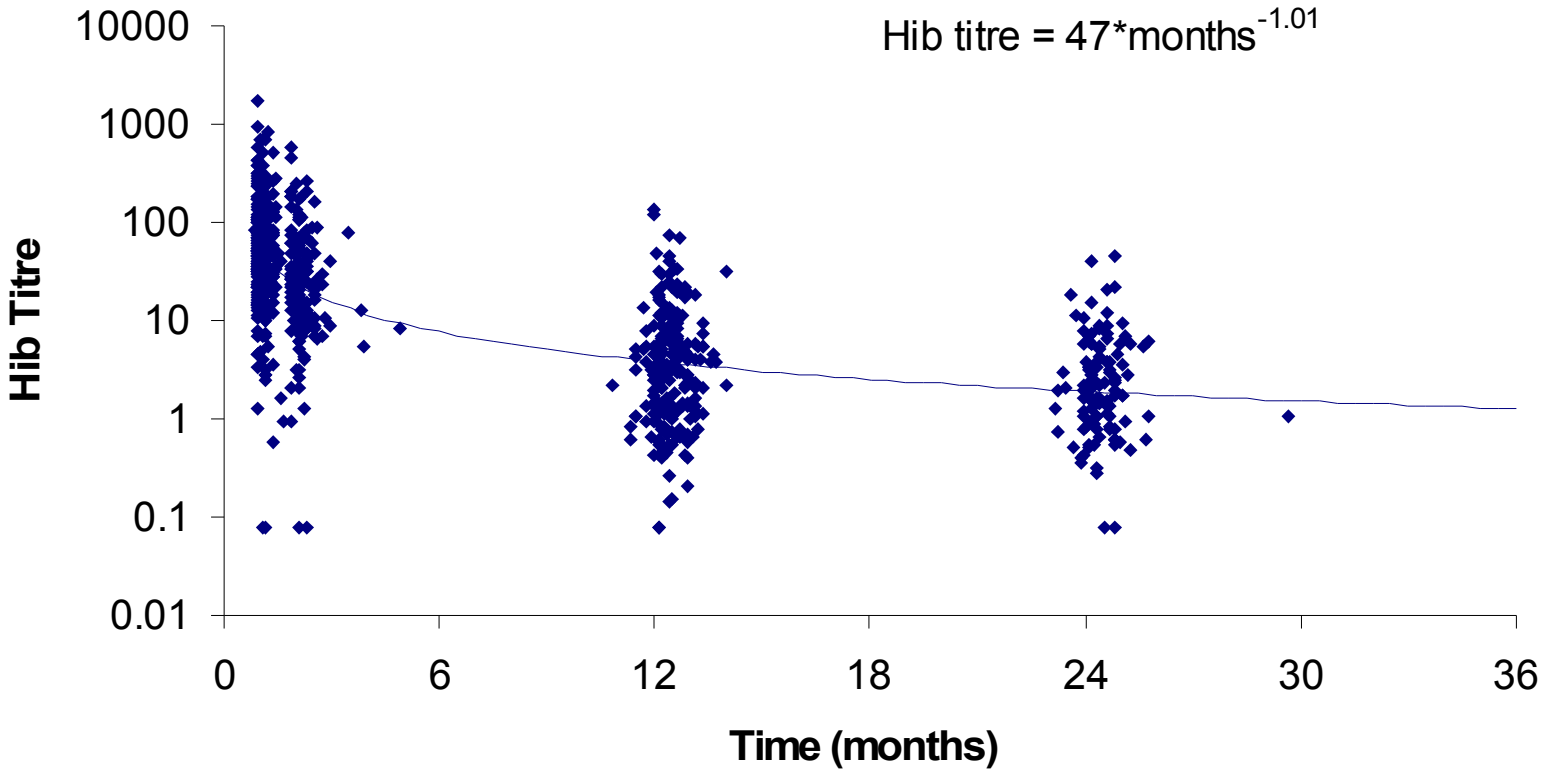
HPA unpublished data (Borrow et al, paper submitted)



Overall the decay pattern post booster is very similar to that after the primary schedule, slopes -1.59 vs. -1.55 (This is the change in logSBA per log10 unit of time).

Hib concentrations (?g/mL) by time since Menitorix booster

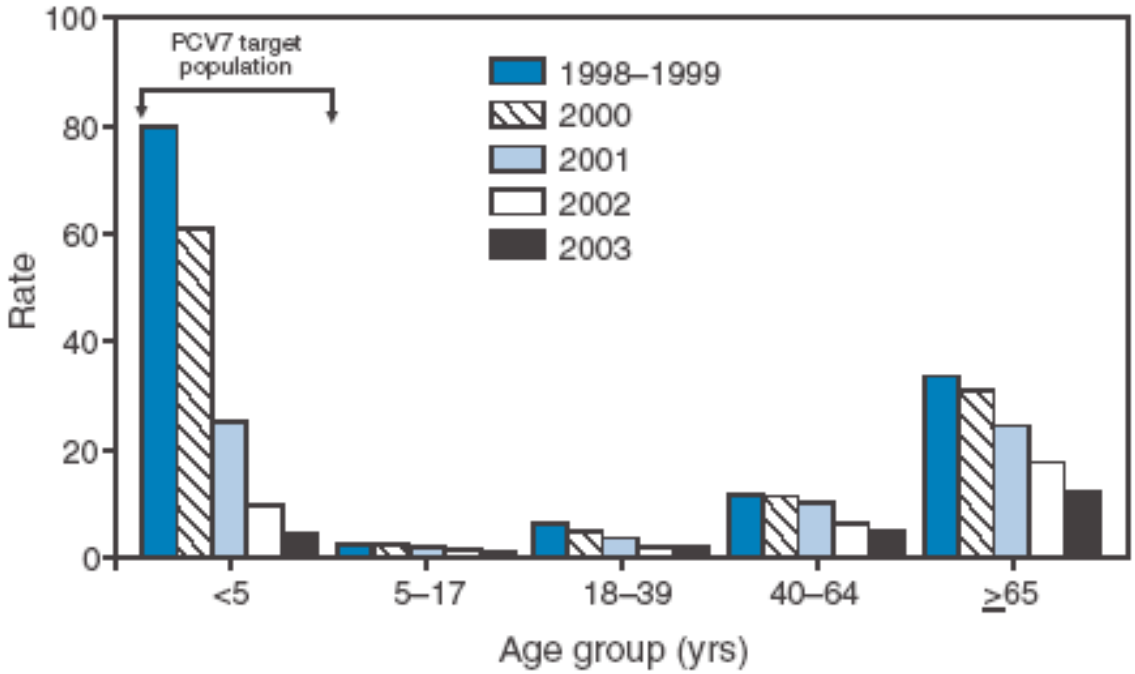
HPA unpublished data (Borrow et al, paper submitted)



The log-Hib vs. log-time model shows a slower rate of decline and similar to that reported in the earlier Hib-boost study (-1.01 compared to -1.08) Southern et al 2007.

Impact of PNC-7 vaccination in USA

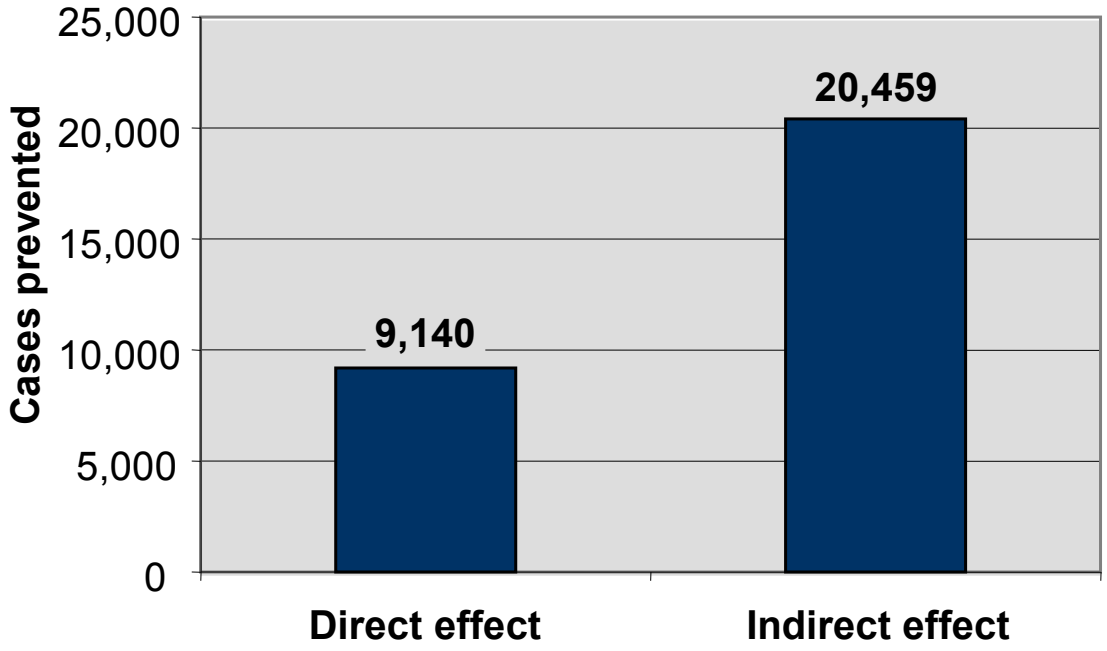
FIGURE 1. Rate* of vaccine-type (VT) invasive pneumococcal disease (IPD) before and after introduction of pneumococcal conjugate vaccine (PCV7), by age group and year — Active Bacterial Core surveillance, United States, 1998–2003



* Per 100,000 population.
† For each age group, the decrease in VT IPD rate for 2003 compared with the 1998–1999 baseline is statistically significant ($p<0.05$).

Source: MMWR weekly, 2005 / 54(36);893-897

Twice as many cases of IPD have been prevented as a result of PCV's indirect effect



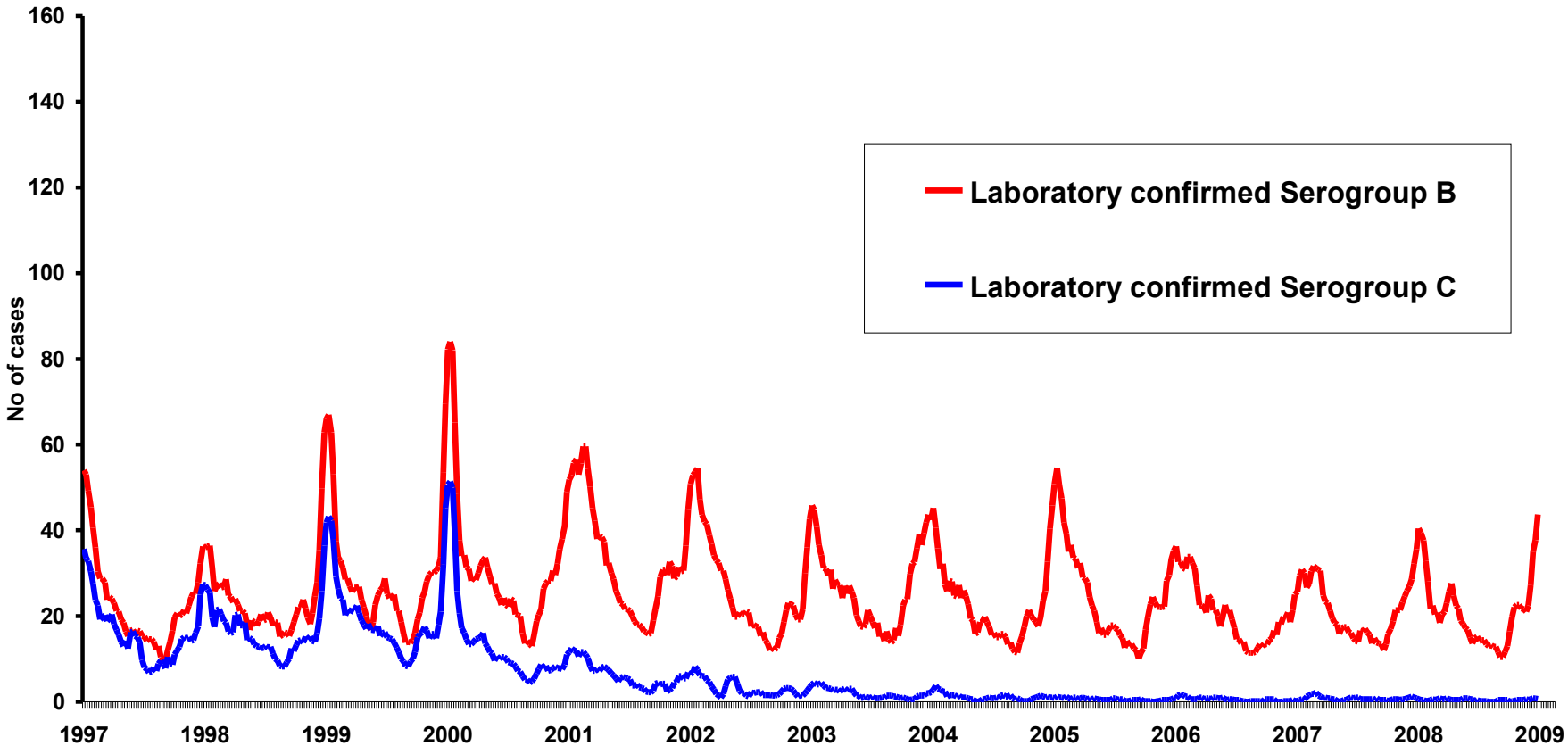
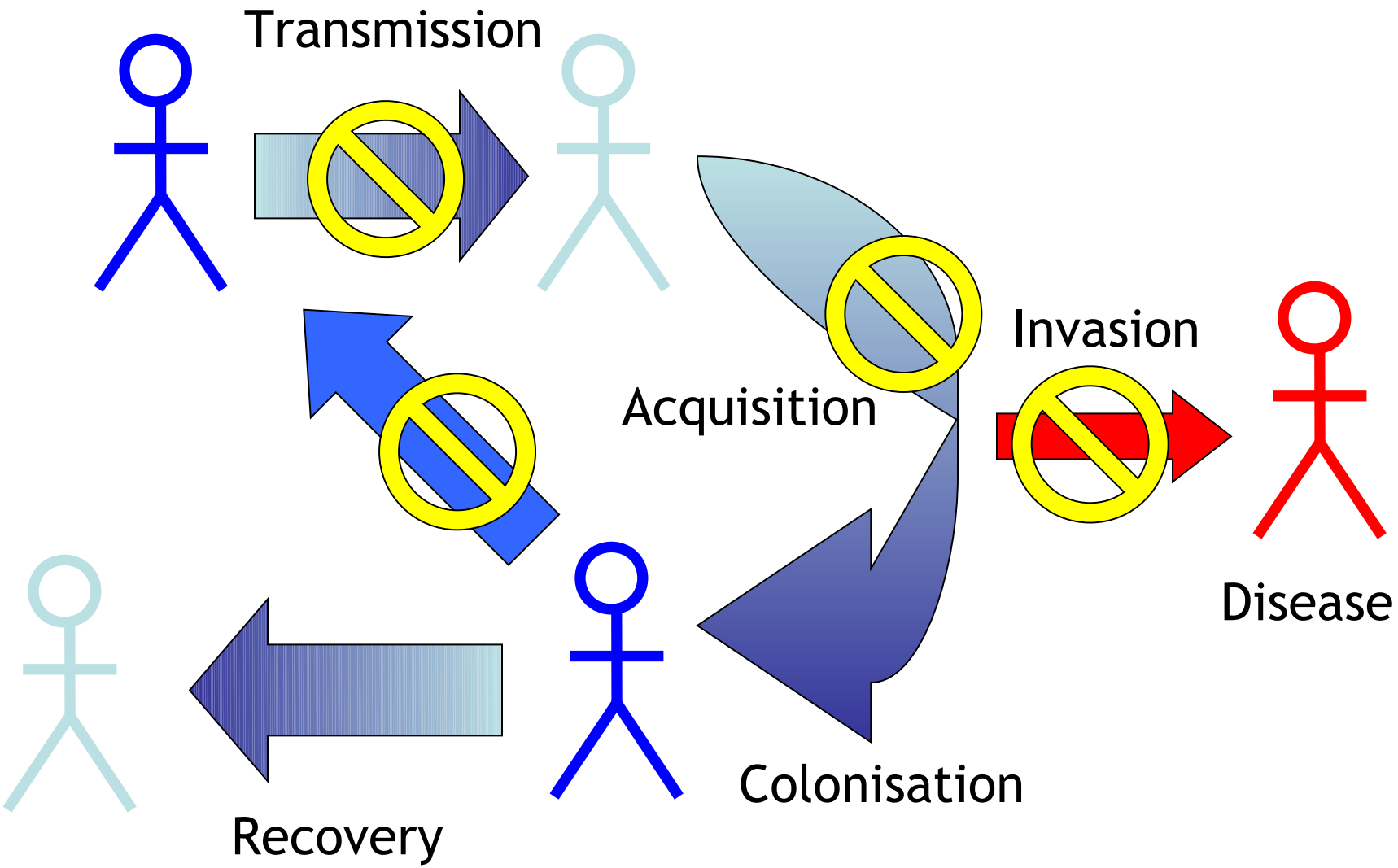
Estimated annual cases of vaccine-type IPD prevented in the US, 2003

CDC. MMWR 2005; 54: 893-7.

Slide from www.preventpneumo.org

Laboratory Confirmed Cases of Meningococcal Disease, England & Wales. Five Weekly Moving Averages: 1997 to 2009

Source: HPA Meningococcal Reference Unit, Manchester



Transmission cycle