



World Health Organization

INITIATIVE FOR VACCINE RESEARCH (IVR)
WORKSHOP ON CORRELATES OF PROTECTION:
RELEVANT TO THE AFRICAN CONTEXT

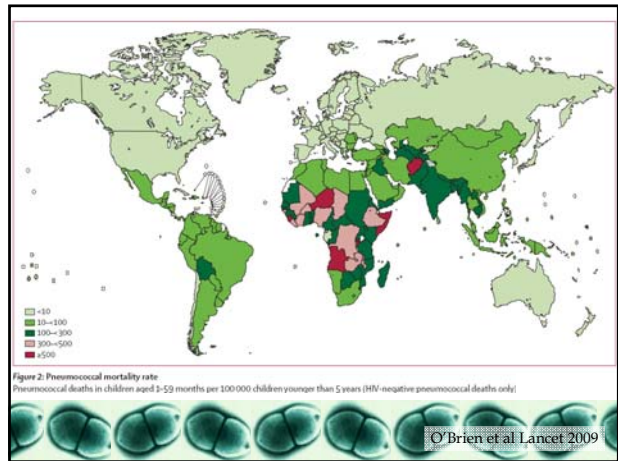
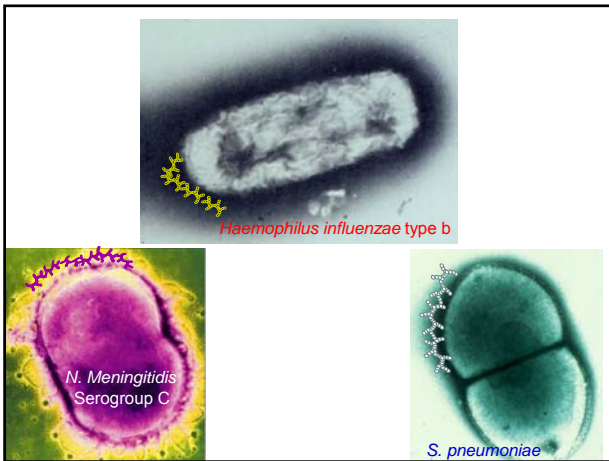
6 December 2009
Bamako, Mali

Immunological perspective on correlates for bacterial polysaccharide vaccines: responses, memory and assays

David Goldblatt
University College London, Institute of Child Health
London

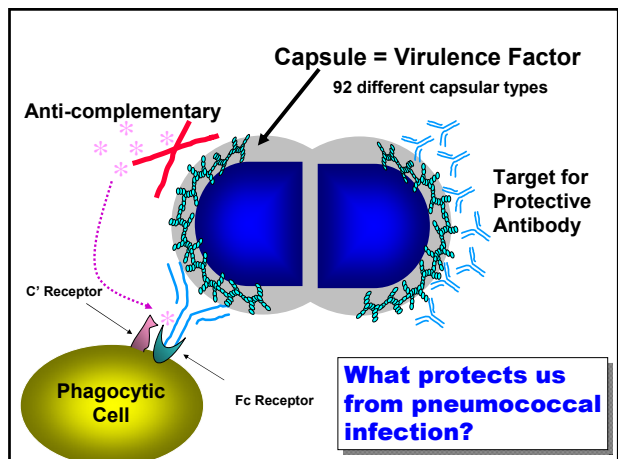
Talk Outline

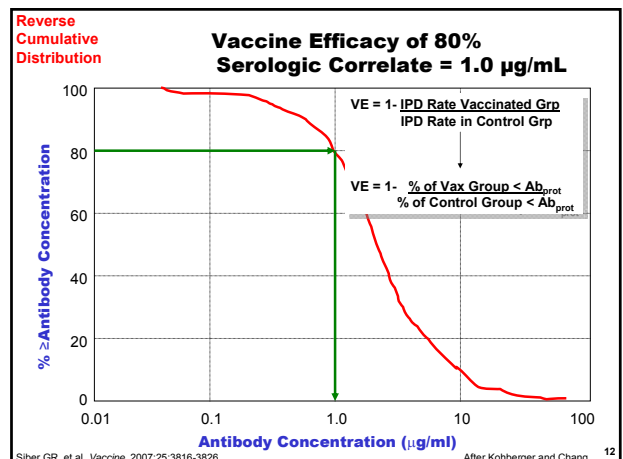
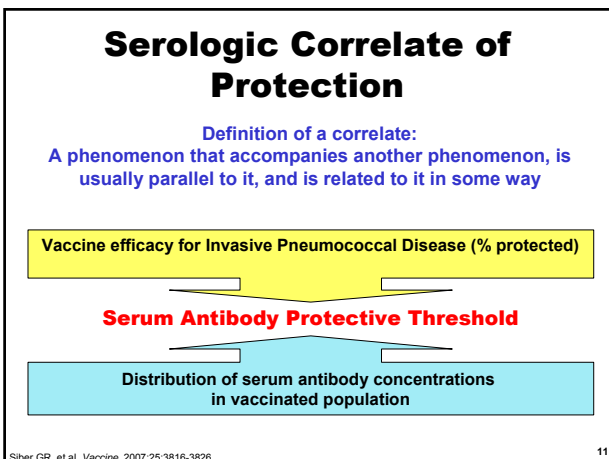
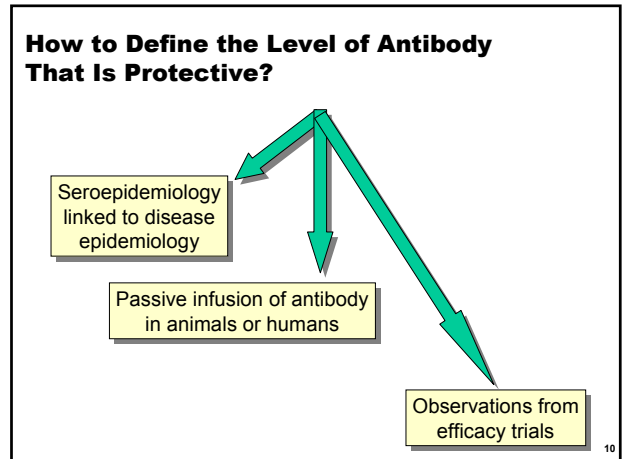
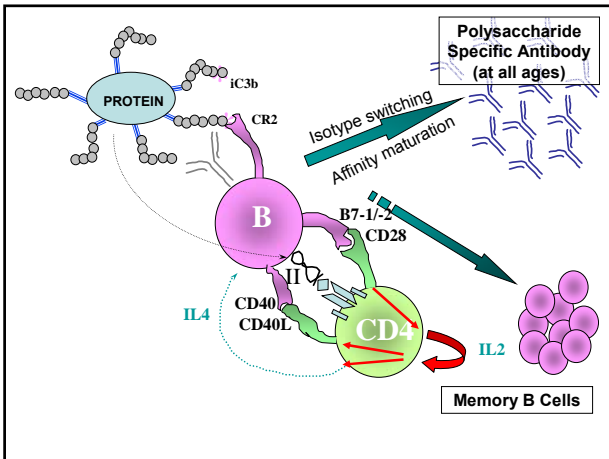
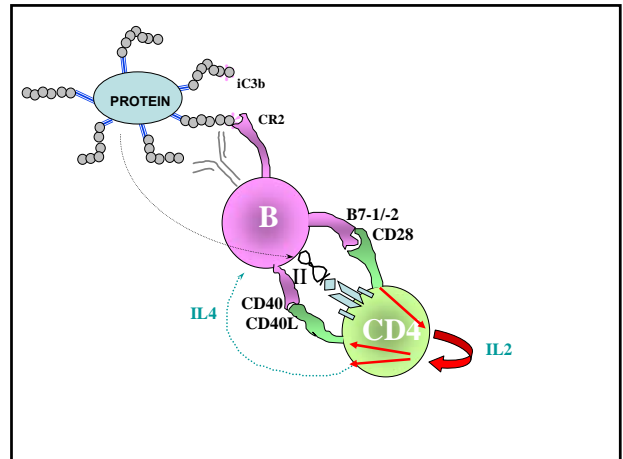
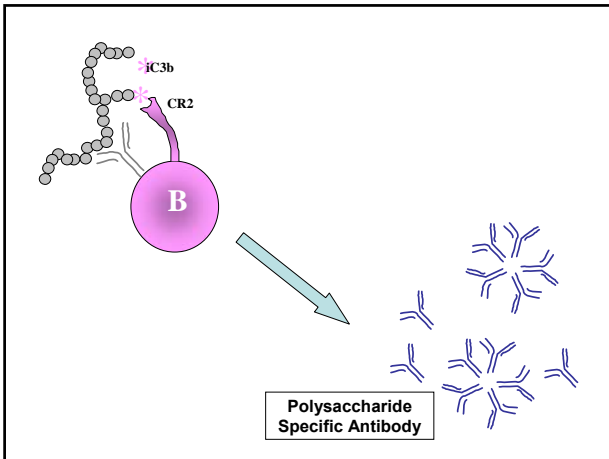
- Bacterial Capsular Polysaccharide Immunity
- Derivation of the Correlate of Protection for Pneumococcal Conjugates
- Are these correlates relevant in Africa?
- Can these correlates be used to predict the performance of the vaccine following introduction?
- Conclusions and further questions



Why do we need a correlate of protection for bacterial conjugate vaccines?

- Evaluation of licensed vaccines to inform local immunisation policy
- Licensing of the next generation of vaccines

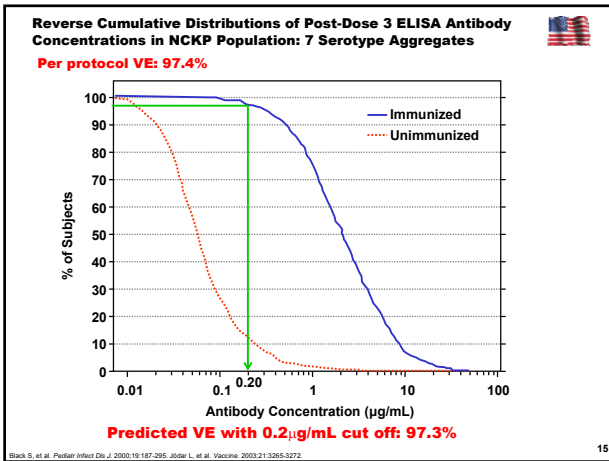
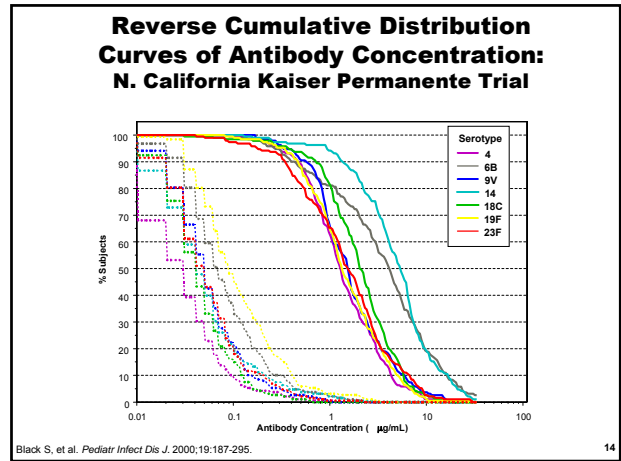




Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children

STEVEN BLACK, MD, HENRY SHINEFIELD, MD, BRUCE FREEMAN, MA, EDWIN LEWIS, MPH, PAULA RAY, MPH, JOHN R. HANSEN, BA, LAURA ELVIN, KATHY M ENSOR, RN, JILL HACKELL, MD, GEORGE SIBER, MD, FRANK MALINOSKI, MD, PHD, DACE MADORE, PHD, IH CHANG, PHD, ROBERT KOHBERGER, PHD, WENDY WATSON, MD, ROBERT AUSTRIAN, MD, KATEY EDWARDS, MD AND THE NORTHERN CALIFORNIA KAISER PERMANENTE VACCINE STUDY CENTER GROUP*

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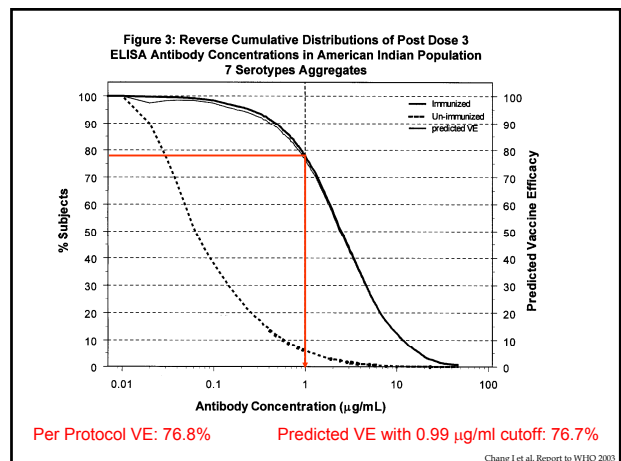



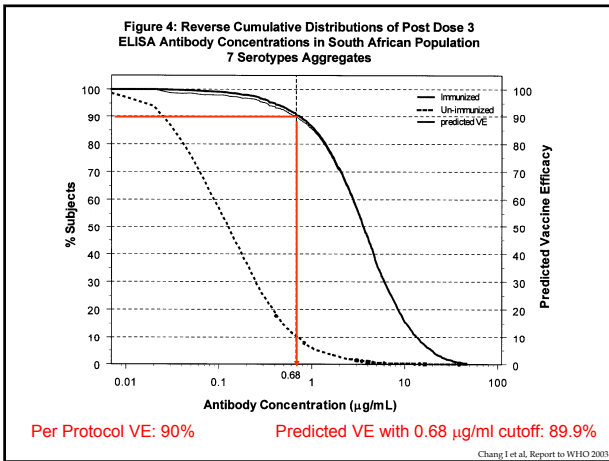
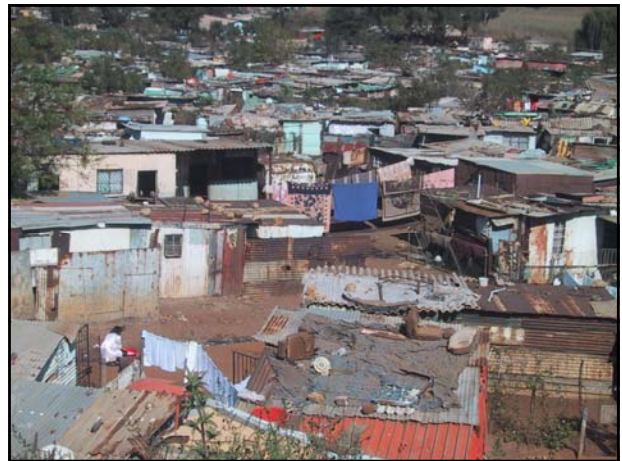
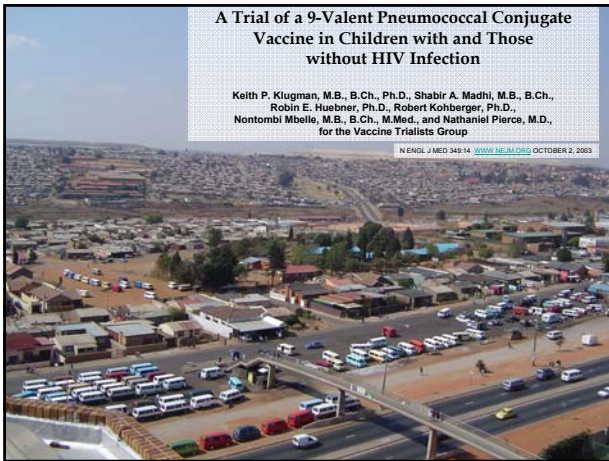
- ### Assumptions/Caveats
- Aggregate Efficacy
 - Aggregate Immunogenicity
 - Protection related to post primary IgG
 - Protective levels similar for different popⁿ
 - Protection is a step function

Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial

Katherine L O'Brien, Lawrence H Moulton, Raymond Reid, Robert Weatherholtz, Jane Oski, Laura Brown, Gaurav Kumar, Alan Parkinson, Diana Hu, Jill Hackell, Ih Chang, Robert Kohberger, George Siber, Mathuram Santosham

THE LANCET • Vol 362 • August 2, 2003



Protective Pneumococcal Antibody Concentrations - Protective Levels in 3 Controlled Trials -

Study:	Efficacy	Protective Level (µg/ml)	95% CI
NCKP	97.4%	0.20	(0.03, 0.67)
American Indian	76.8%	1.00	(0.25, > 50.00)
South Africa	90%	0.68	(0.03, 6.00)

Siber et al. Vaccine. 2007

Invasive Pneumococcal Disease

Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for young infants

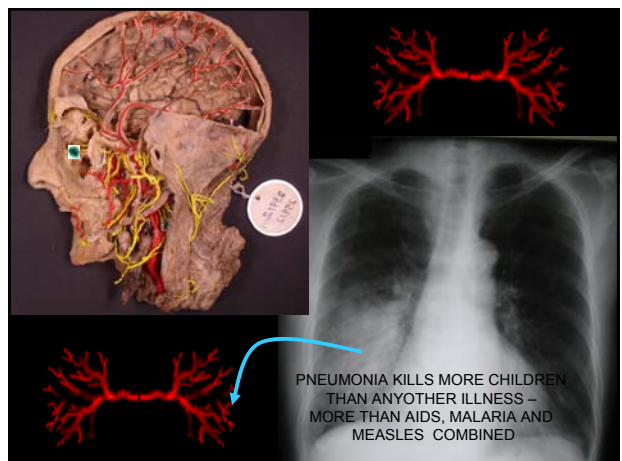
Luis Jódar^{a,1}, Jay Butler^b, George Carlone^c, Dagan^d, David Goldblatt^e, Helena Käyhty^f, Keith Klugman^g, Mikaytis^g, George Siber^h, Robert Kohberger^h, Ilan^g, Thomas Cherian^{a,4}

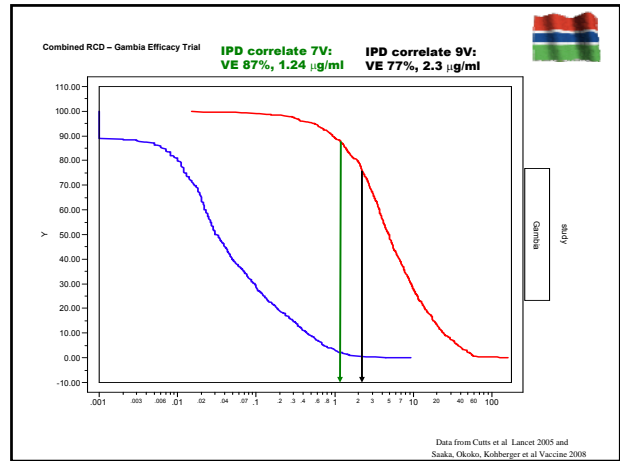
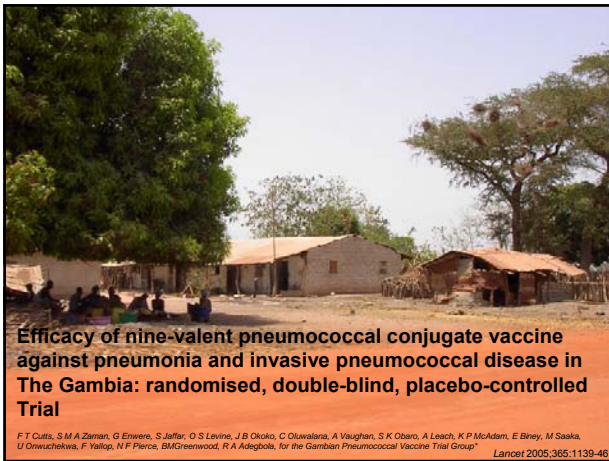
© World Health Organization: WHO Technical Report Series No. 927, 2005

Annex 2

Recommendations for the production and control of pneumococcal conjugate vaccines

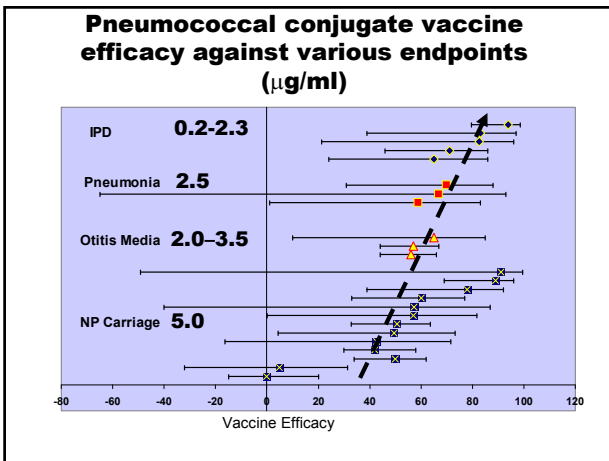
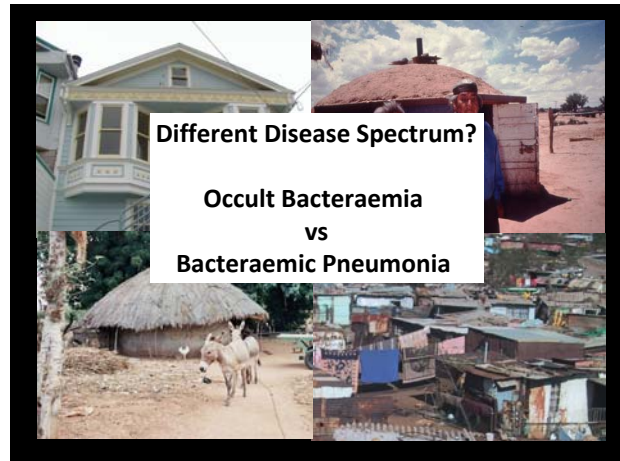
Non-inferiority at the serological correlate of protection 0.35µg/ml



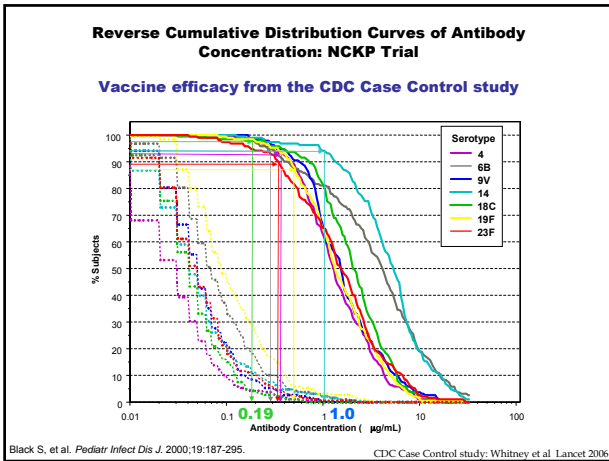


Protective Pneumococcal Antibody Concentrations - Protective Levels in 4 Controlled Trials -

Study:	Efficacy	Protective Level (µg/ml)	95% CI
NCKP	97.4%	0.20	(0.03, 0.67)
South Africa	90%	0.68	(0.03, 6.00)
American Indian	76.8%	1.00	(0.25, > 50.00)
Gambia (7V)	87%	1.24	(0.3-3.4)
Gambia (9V)	77%	2.3	(1.0, 5.0)



Can the consensus correlate (0.35) be used to predict vaccine efficacy?



ORIGINAL STUDIES

Immunogenicity of a Reduced Schedule of Pneumococcal Conjugate Vaccine in Healthy Infants and Correlates of Protection for Serotype 6B in the United Kingdom

David Goldblatt, MD, PhD, Jo Southern, MSc,† Lindsey Ashton, BSc,* Nick Andrews, MSc,† Sarah Woodgate, BSc,* Polly Burbidge, BSc,* Pauline Waugh, BSc,† and Elizabeth Miller, MD†*

**After 2 dose primary series
 Serotype 6B: 47% > 0.35µg/ml**

Pediatr Inf Dis J, 2010

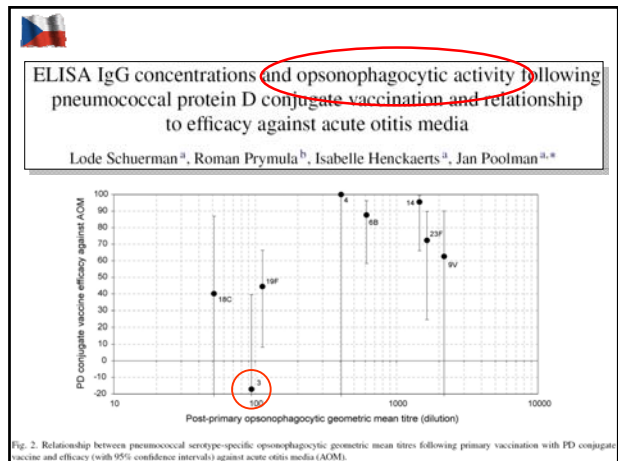
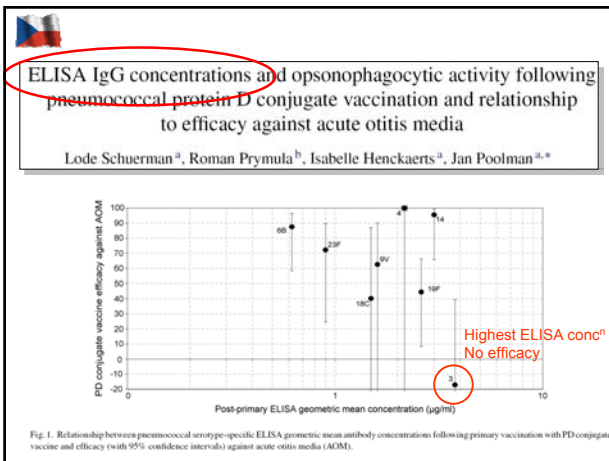
Cumulative weekly numbers of reports of IPD due to serotype 6B in children < 2 years of age England and Wales, Epidemiological year: July-June (2003-date)

Estimated 2 dose effectiveness in the UK for 6B: 67% (yet only 47%>0.35)

Data courtesy of Liz Miller, CfI, HPA

ELISA Value		OPA >1:8
<0.2	(n=32)	6/32 (19%)
0.2-0.35	(n=16)	11/16 (69%)
>0.35	(n=28)	23/28 (82%)

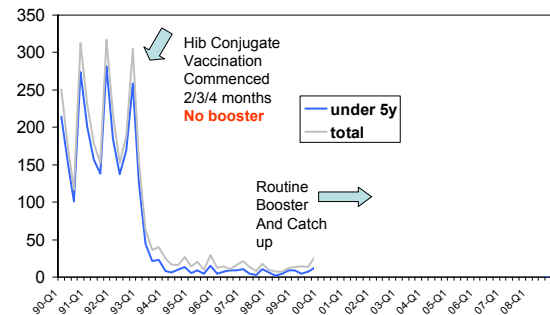
Goldblatt et al PIDJ 2010



Immune memory and long term protection?

- Elimination of carriage provides long term sustained reduction in the vulnerable population (Carriage as a correlate?- Gates Funded Grand Challenge "Pneumocar")
- What happens when carriage re-established?
- Can immune memory alone protect?

Cases of invasive Haemophilus influenzae type b (Hib), 1990-2008 by quarter, England and Wales



Source: Health Protection Agency (Mary Ramsay)

Summary and Conclusions

- Correlates for bacterial conjugates are required
- They are currently imperfect
- They are not the same for each serotype (pneumo)
- They are not the same for different populations for reasons that are likely to be multifactorial
- Concentrations after priming may not predict long term protection
- The role of the booster dose is not currently factored in when developing correlates (However: long term protection documented in South Africa without a booster!)
- Concentrations estimated by ELISA may not agree with functional antibody estimates
- Reduction in carriage may be a useful correlate
- Experience with different vaccines may not be directly applicable to each other even though all are capsular polysaccharide conjugates

Acknowledgements

- HPA UK: Liz Miller, Mary Ramsay
- Kate O'Brien
- Robert Kohberger