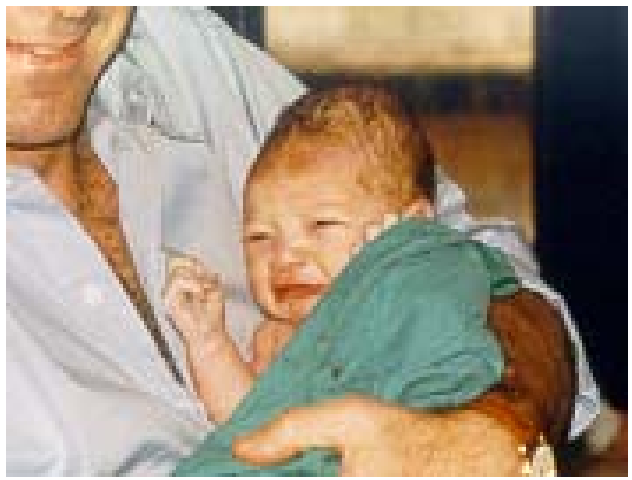
Session 4:
Immunogenicity and efficacy of polysaccharide and polysaccharide-protein conjugate vaccines in neonates

Pneumococcal Vaccine in the Newborn

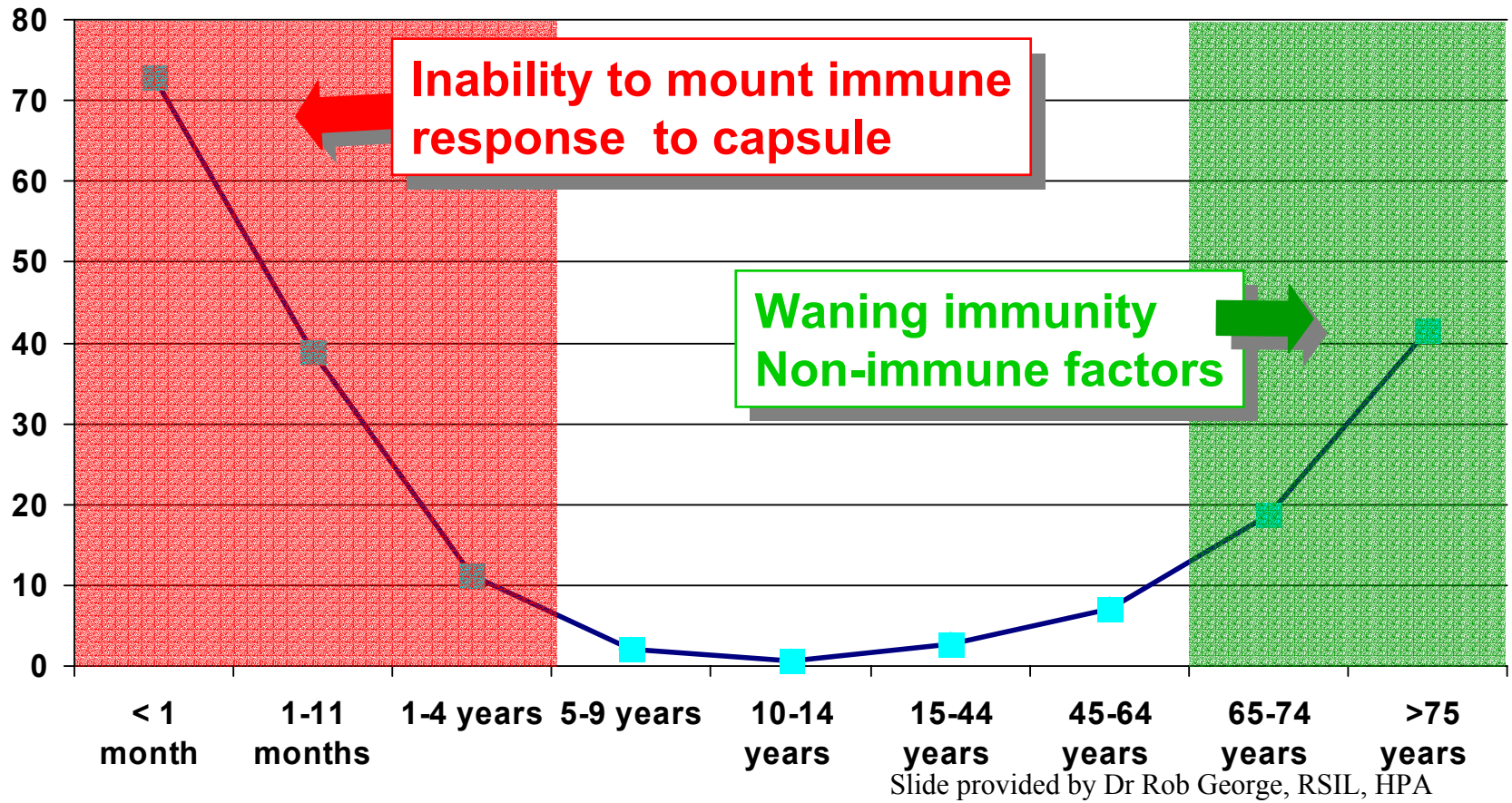
- Mathu Santosham: Burden of disease
- Dan Granoff: Utility of Hib conjugate vaccines in early life
- Alex Lucas: Molecular Mechanisms



Pneumococcal Vaccine in the Newborn

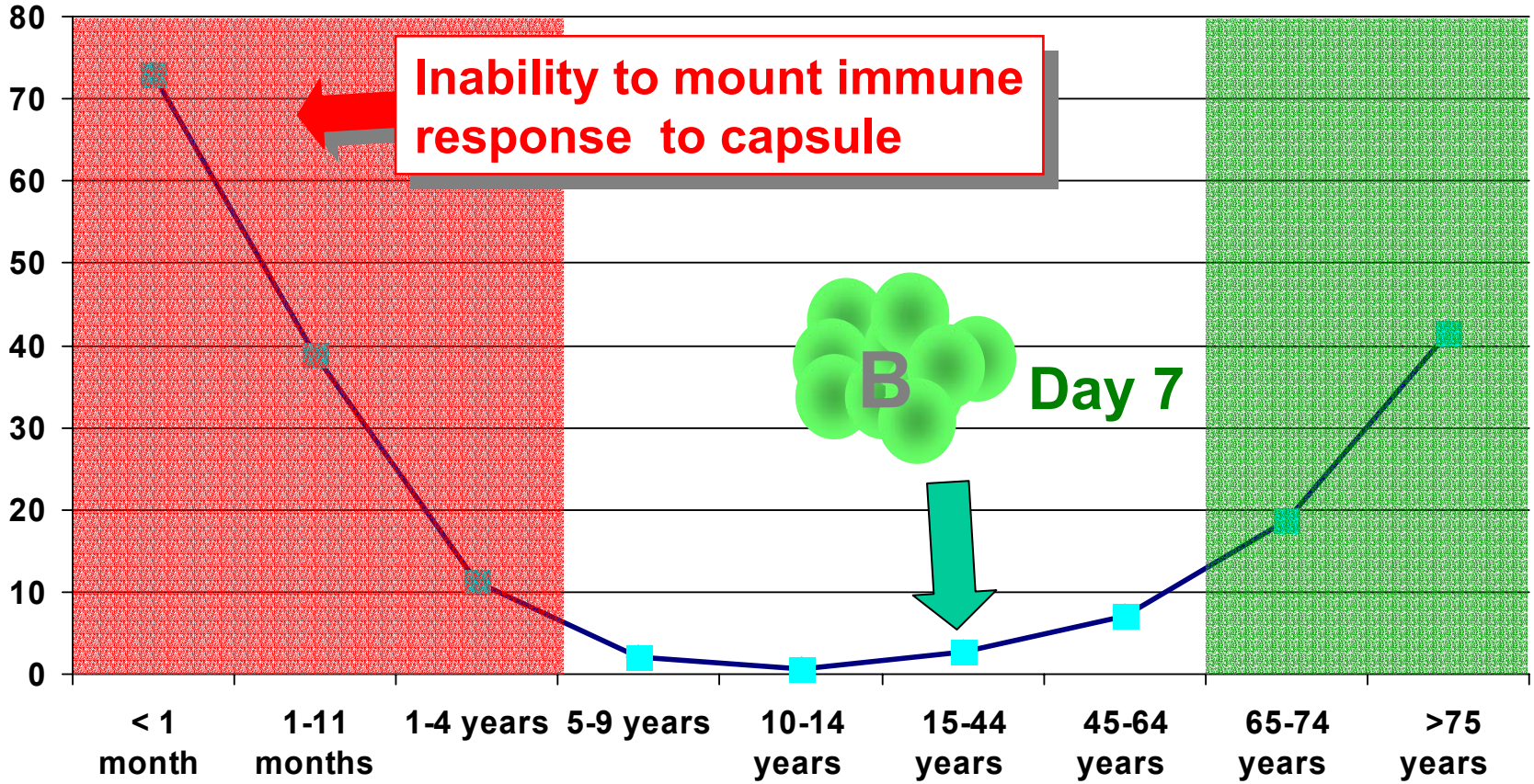
- The basis for natural immunity in adults
- Pneumococcal carriage in early life
- The case for neonatal vaccination
- Design of a study to evaluate pneumococcal conjugates at birth

Invasive Pneumococcal infection, England & Wales, Incidence per 100,000 by age group 2000



Slide provided by Dr Rob George, RSIL, HPA

Incidence per 100,000 by age group 2000 Invasive Pneumococcal infection, England & Wales



Slide provided by Dr Rob George, RSIL, HPA

Circulating pneumococcal specific B cells isolated 7 days after a

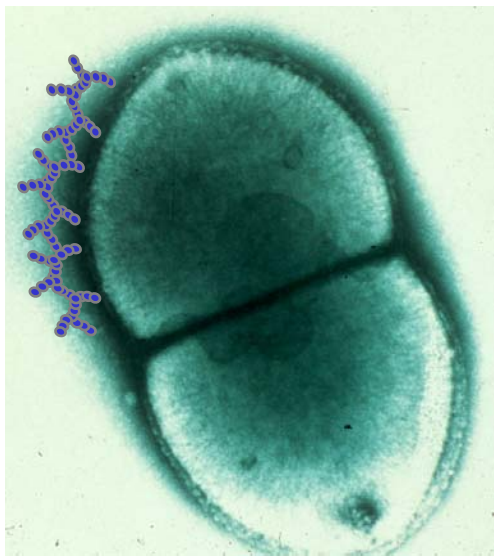
first pneumococcal conjugate

or

polysaccharide vaccines in adults were

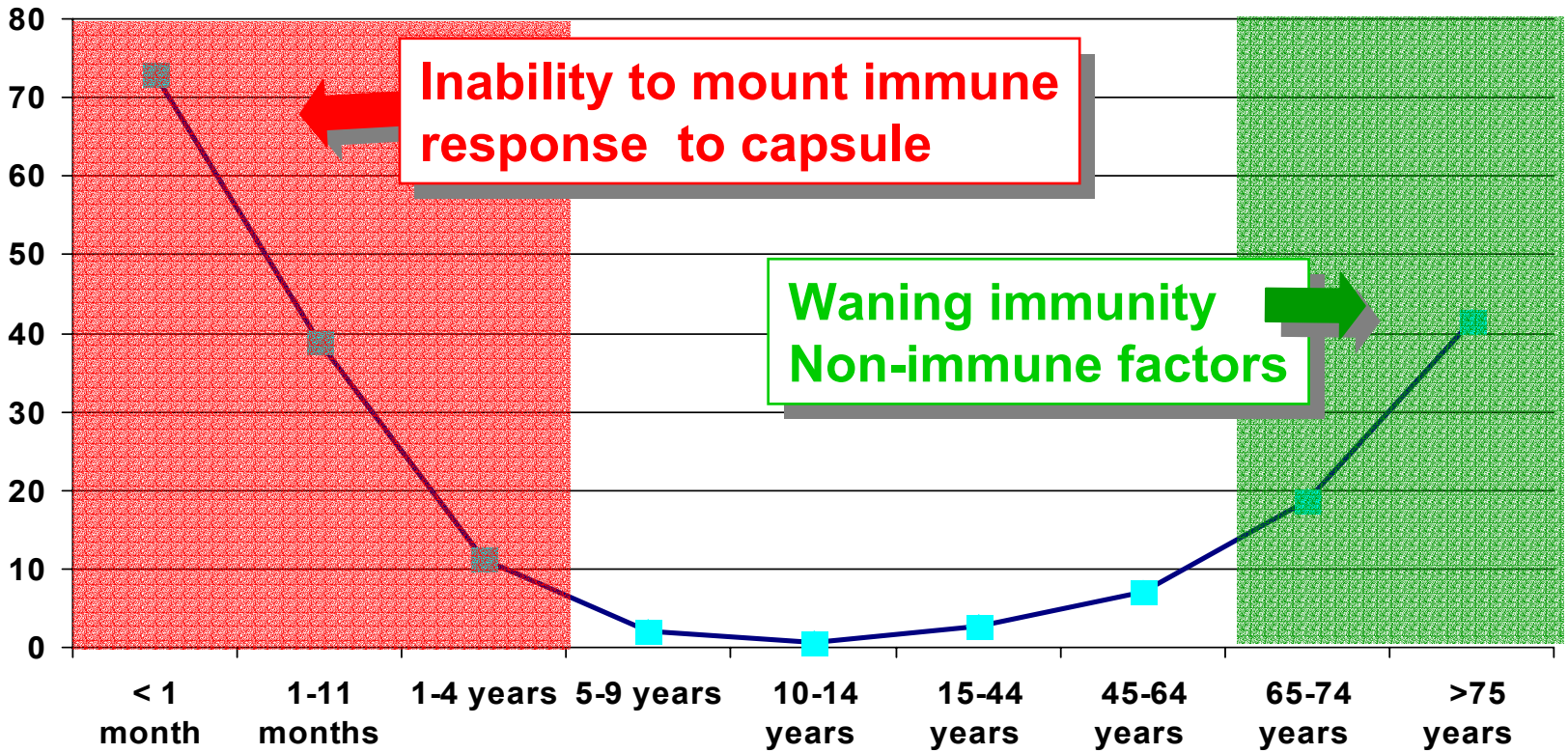
restimulated

memory B cells



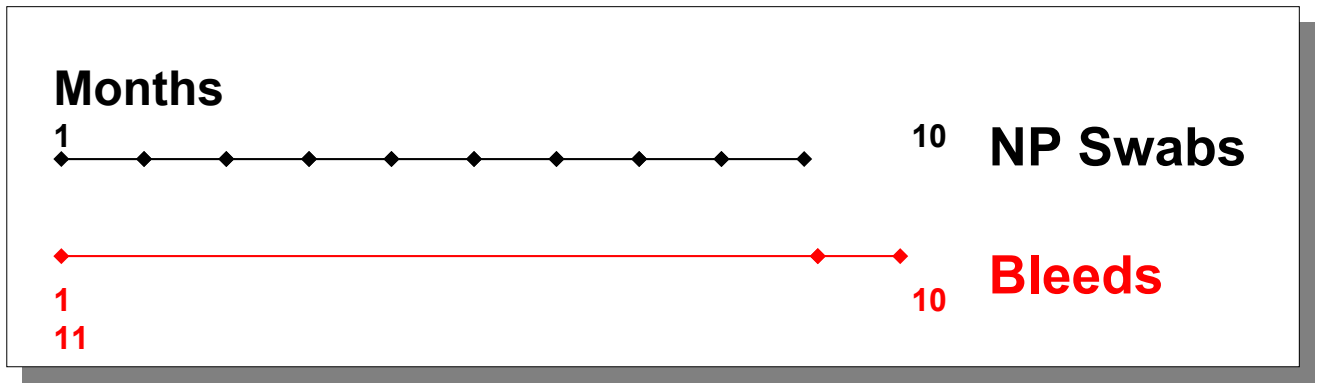
Baxendale et al *Eur J Immunol 2000*
Lucas et al *Inf & Immun 2001*
Janoff et al *ISPPD 2002*

Invasive Pneumococcal infection, England & Wales, Incidence per 100,000 by age group 2000



Slide provided by Dr Rob George, RSIL, HPA

Overall Study Design:

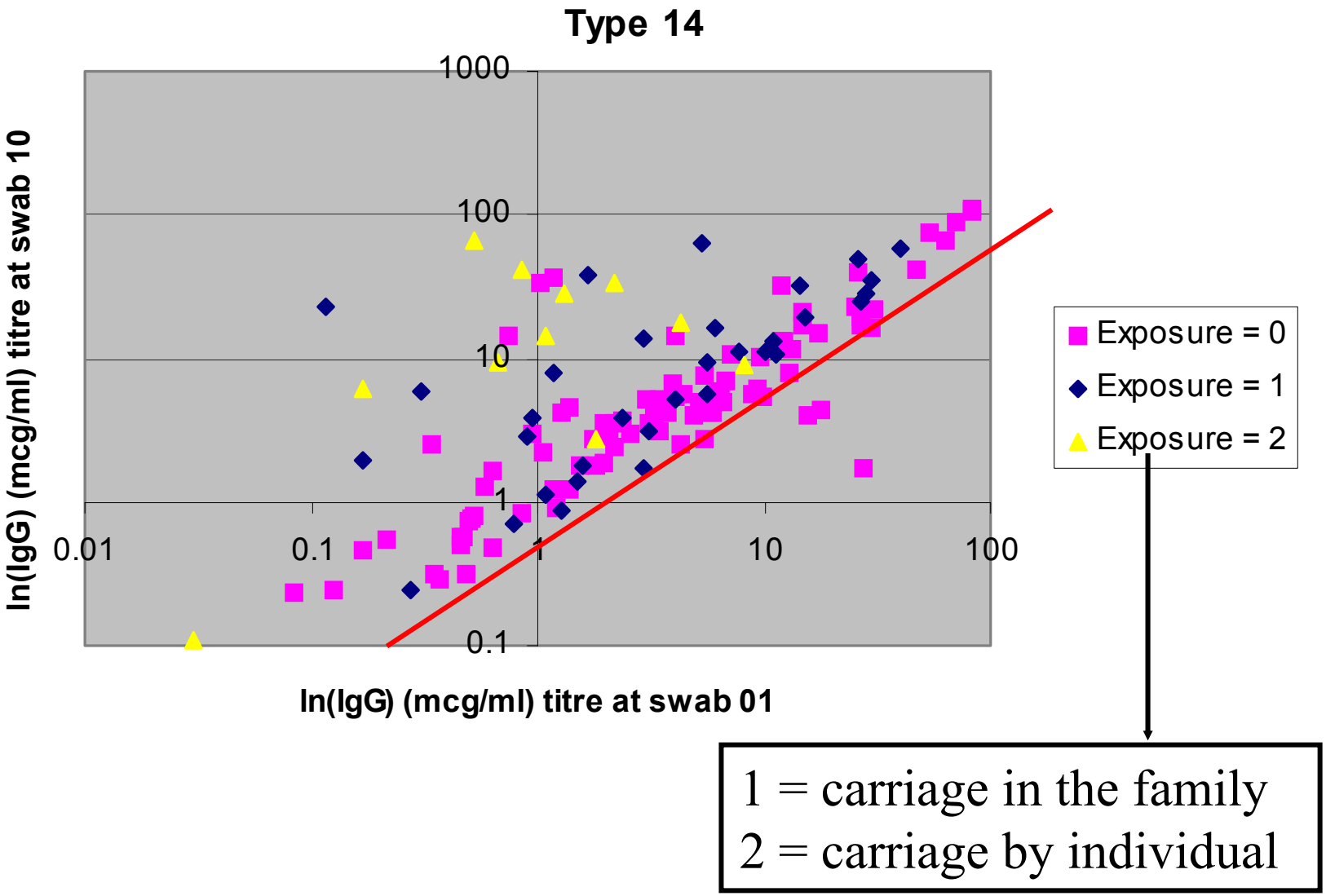


Results:

129 families recruited

Swabs: 3753 swabs taken
932 (25%) were positive

EC PNCEuro Collaboration
ICH/HPA/KTL
Unpublished


Type 14
1000
100
10
1
0.1
0.01
0.1
1
10
100
ln(IgG) (mcg/ml) titre at swab 10
ln(IgG) (mcg/ml) titre at swab 01
Exposure = 0
Exposure = 1
Exposure = 2
1 = carriage in the family
2 = carriage by individual

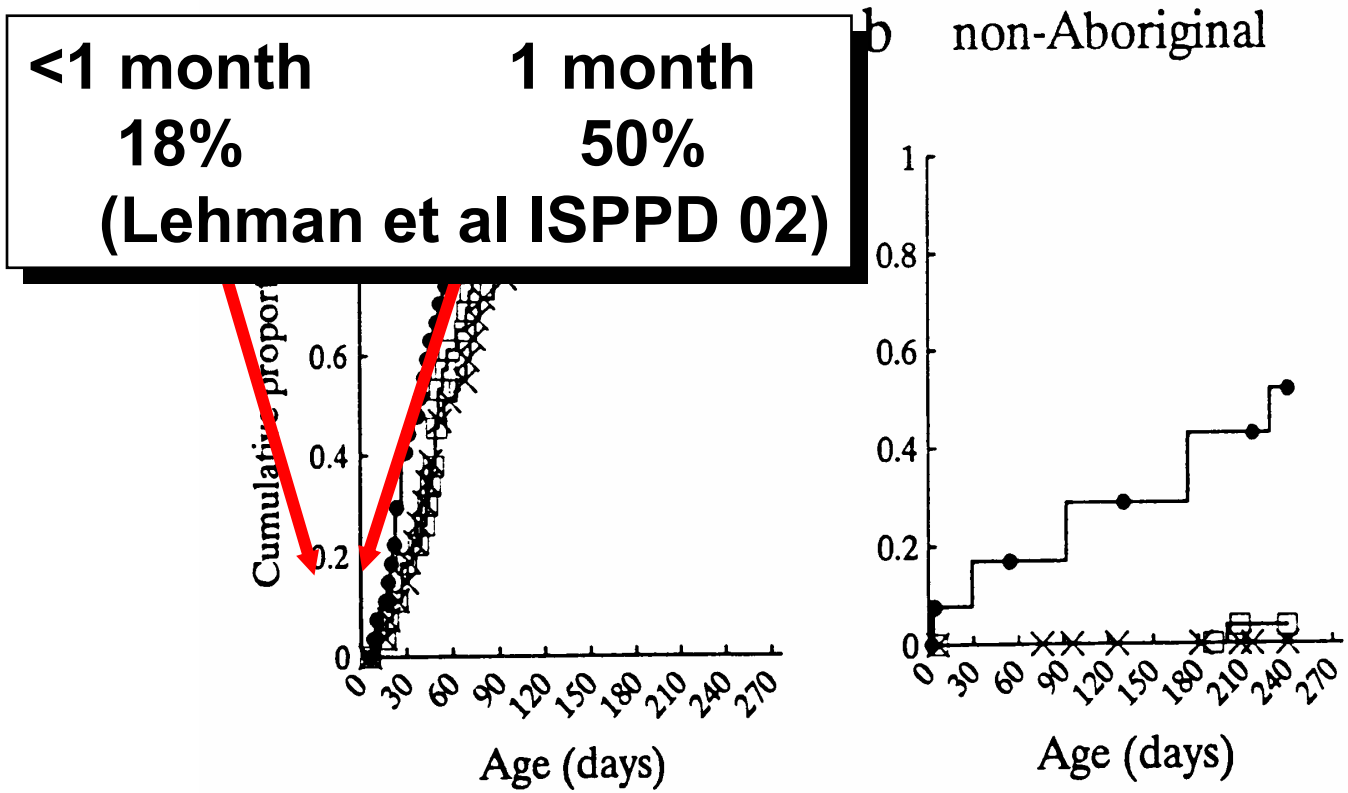
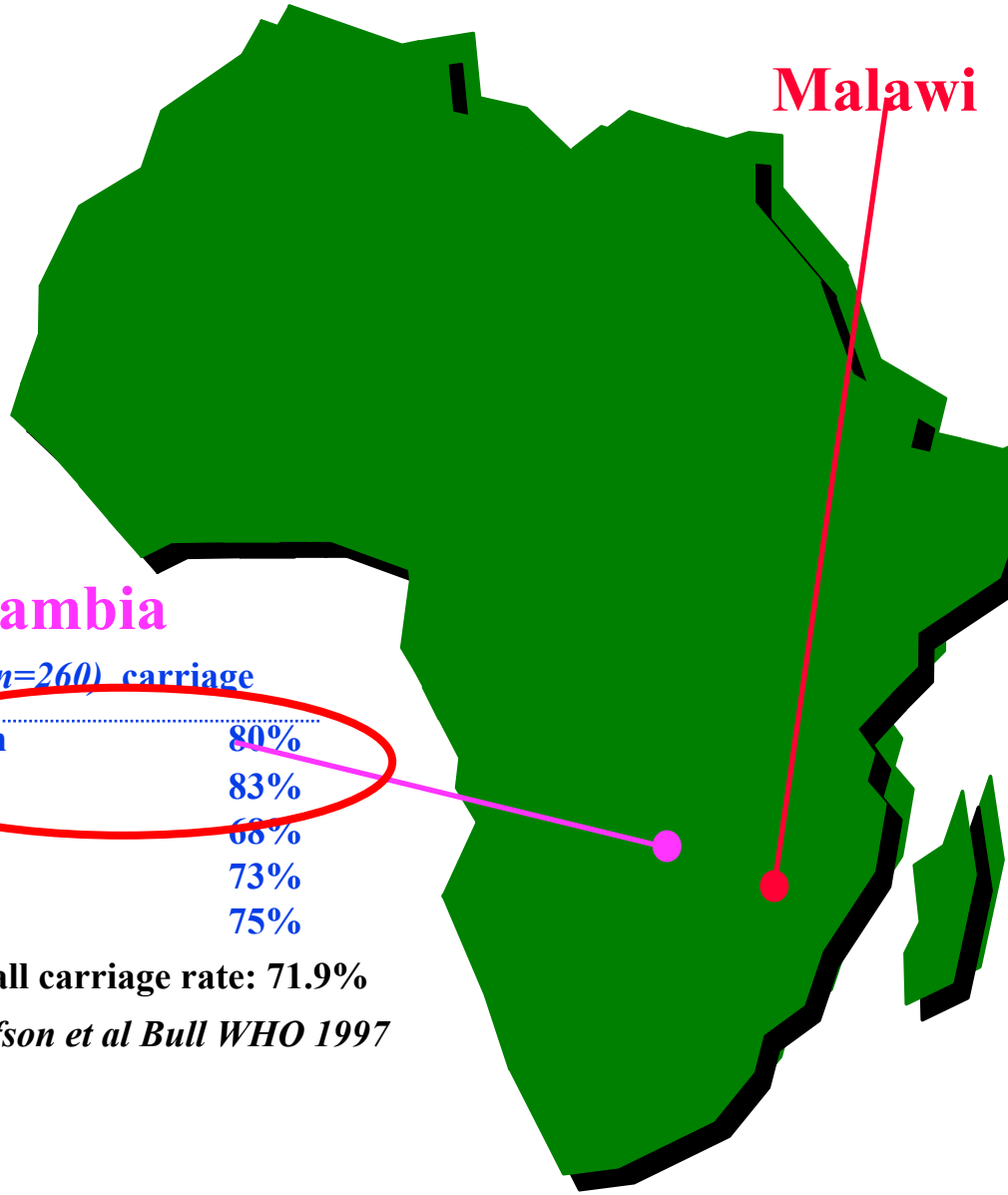


FIG. 2. Cumulative proportion of infants with nasopharyngeal colonization by bacterial species and age (days). ●, *Moraxella catarrhalis*; ■, *Haemophilus influenzae*; ×, *Streptococcus pneumoniae*.

Leach et al Pediatr Inf Dis J 1994;13:983-9



Malawi

Age	*n*	carriers (%)
0-2m	*47*	16 (34)
3-5m	*53*	27 (51)
6-8m	*37*	19 (51)
9-11m	*31*	18 (58)
1-5y	*32*	15 (47)

Overall carriage rate: 47.5%

[illegible]no et al Ann Trop Paed 1997

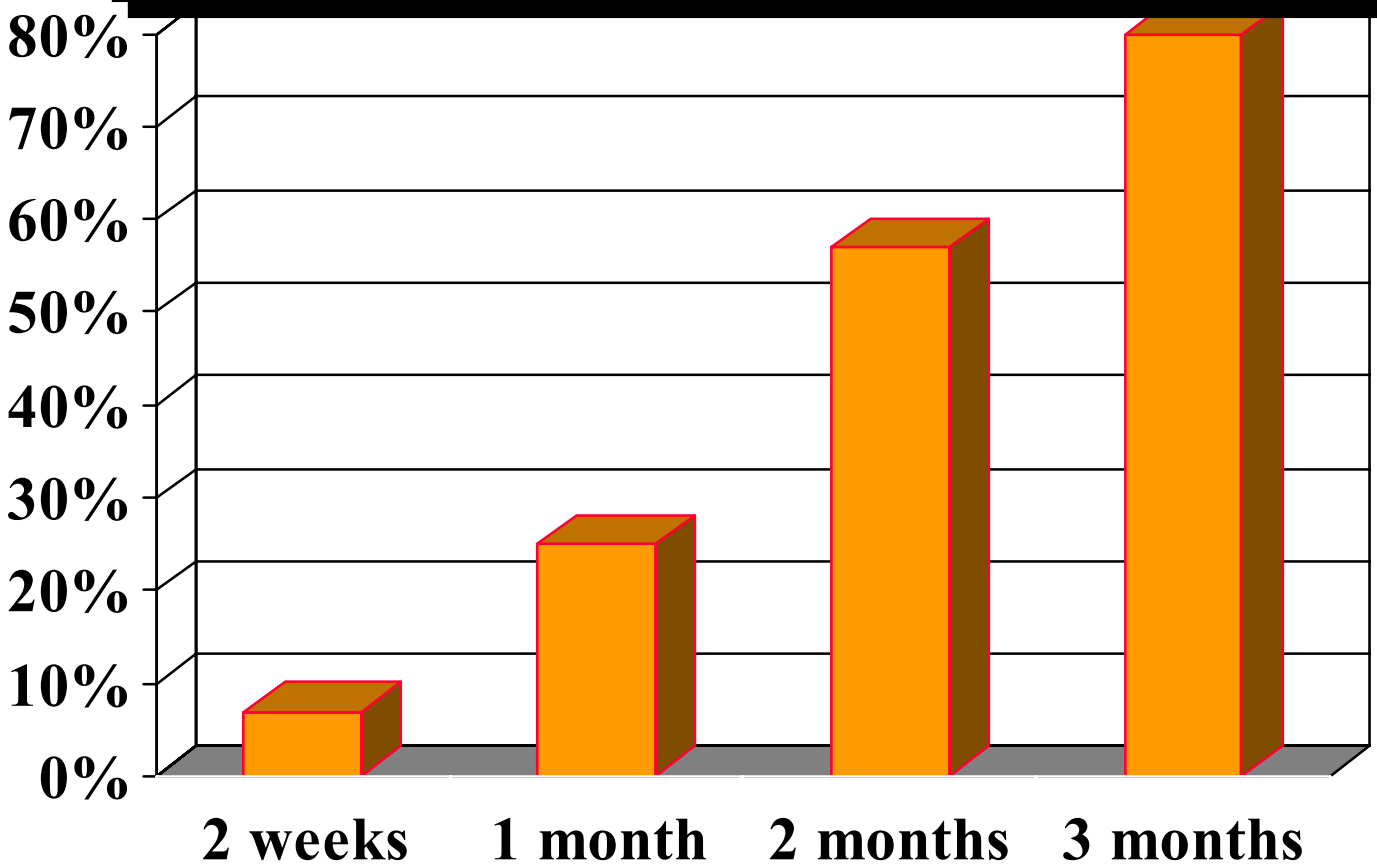
Zambia

Age (*n=260*)	carriage
by 3m	80%
6m	83%
9m	68%
12m	73%
24m	75%

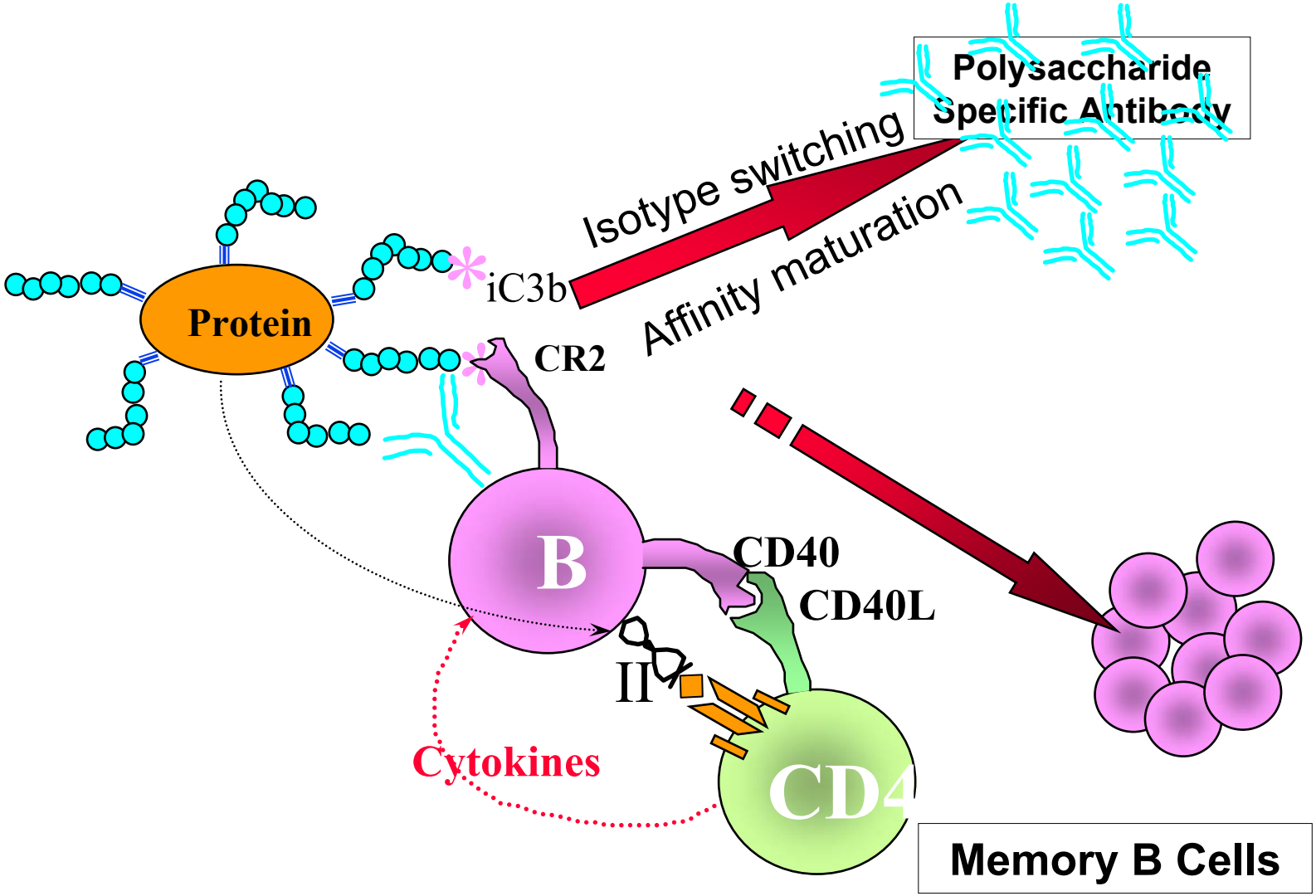
Overall carriage rate: 71.9%

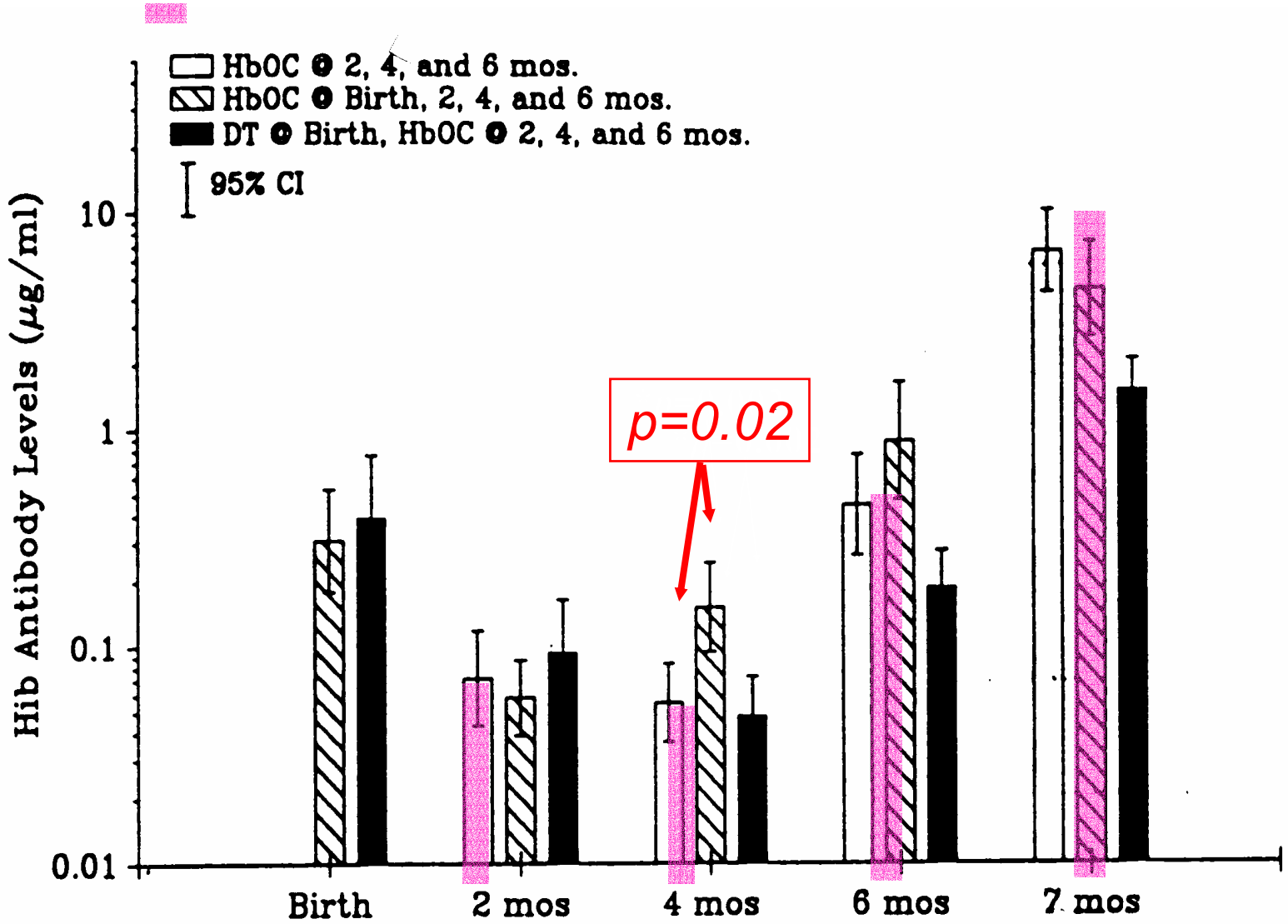
Woolfson et al Bull WHO 1997

Pneumococcal Carriage in Bangladesh



Zakaria et al ISPPD 02


Polysaccharide
Specific Antibody
Isotype switching
Affinity maturation
Protein
iC3b
CR2
B
CD40
CD40L
II
Cytokines
CD4
Memory B Cells



Lieberman et al J Pediatr 1995

Neonatal PRP-T recipients classified:

Non-responders (*n*=24)

Responders (*n*=31)

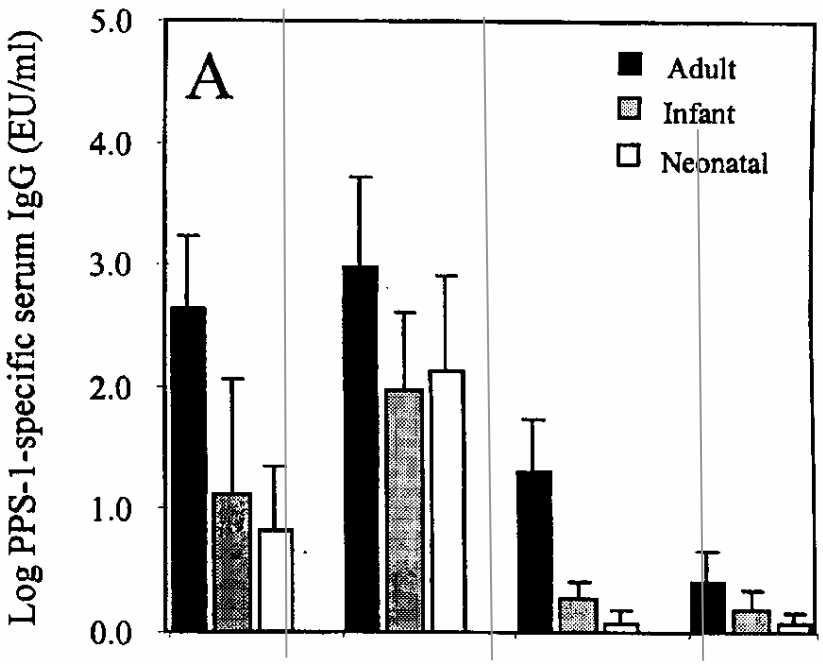
All (*n*=55)

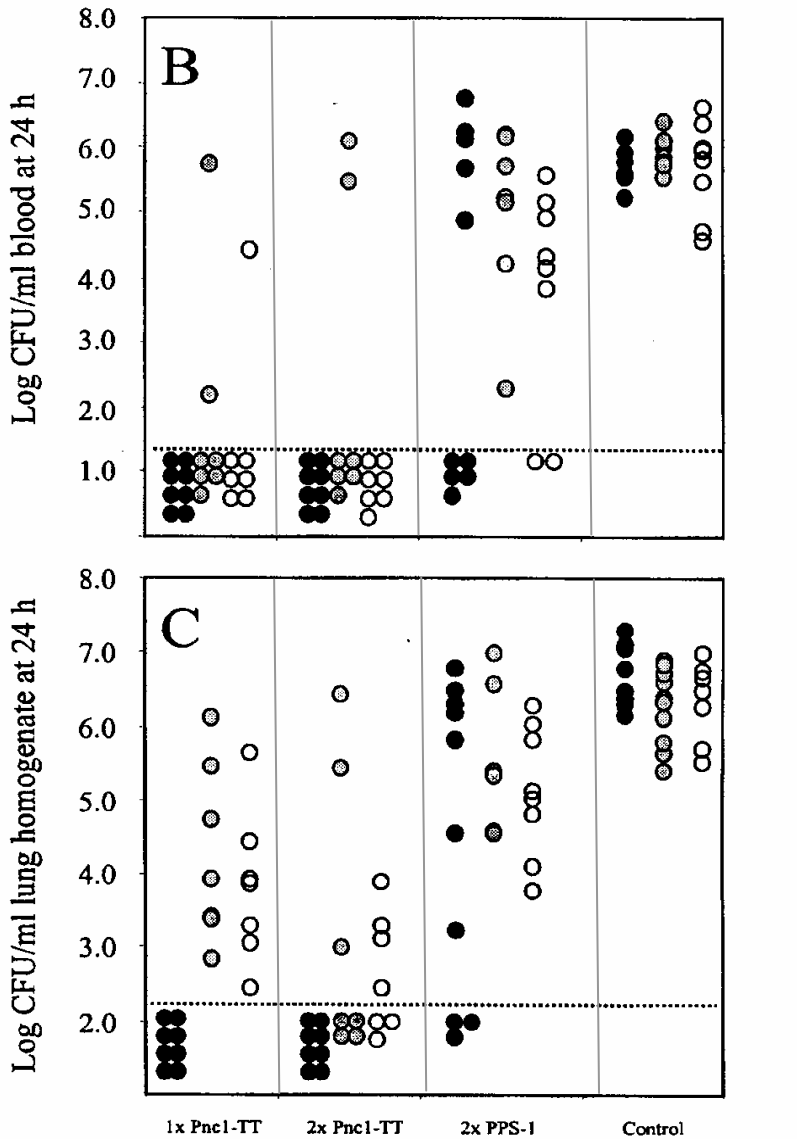
Kurikka et al Pediatrics 1995 95:815-822

Neonatal PRP-T Recipients classified:		Anti-Hib PS responses 2 months after Hib PS booster given at 2 months of age		
		≥ 2 fold	≥ 4 fold	≥ 10 fold
Non-responders	(*n*=24)	9 (37%)	4 (17%)	1 (4%)
Responders	(*n*=31)	25 (81%)	16 (52%)	7 (23%)
All	(*n*=55)	34 (62%)	20 (36%)	8 (14%)

Kurikka et al Pediatrics 1995 95:815-822

Pnc1-TT is immunogenic in infant & neonatal mice when administered s.c. and provides protection against lethal pneumococcal infections after i.n. challenge





Jakobsen et al I&I 2002

Evaluation of Neonatal Immunisation with Pneumococcal Conjugate Vaccine

- Safety
- Primary Immunogenicity
  - Neonatal Immunity
  - Maternal Antibodies
- Priming
  - Immunological Memory
  - Hyporesponsiveness
- Efficacy?
  - Effect on carriage

Wyeth Vaccines


KEMRI
CENTRE FOR GEOGRAPHIC
MEDICINE RESEARCH COAST
AND
WELLCOME TRUST
RESEARCH LABORATORIES

The case for pneumococcal conjugate at birth in Kenya

- 16% of pneumo deaths in under 2's occur before 6 weeks of age
- 23% occur under 14 weeks of age
- Only 70% have received a 2nd DPT by 14w
- Conversely, 70% receive BCG by 6w of age

PHASE I	**Age in weeks**				
	0	6	10	14	18
Group 1 (n=30)					
PNC♦	✓		✓	✓	
Hib♥		✓	✓	✓	
BCG	✓				
DPT&P/HBV		✓	✓	✓	
Group 2 (n=30)					
PNC		✓	✓	✓	
Hib♥		✓	✓	✓	
BCG	✓				
DPT&P/HBV		✓	✓	✓	
All Groups					
Blood samples	✓†	✓‡	✓‡	✓‡	✓

PHASE II	*Age in weeks*						
	0	6	10	14	18	36 (9 months)	37
Group 1 (n=150)							
PNC♦	✓		✓	✓		✓*	
Hib♥		✓	✓	✓			
BCG	✓						
DPT&P/HBV		✓	✓	✓			
Measles						✓	
Group 2 (n=150)							
PNC		✓	✓	✓		✓*	
Hib♥		✓	✓	✓			
BCG	✓						
DPT&P/HBV		✓	✓	✓			
Measles						✓	
All Groups							
NP swabs					✓	✓	
Blood samples	✓	✓‡	✓‡	✓‡	✓	✓	✓

Randomised to pneumococcal conjugate or a fractional dose of pneumococcal polysaccharide (0.1ml/5µg)

Summary

- Hib conjugates appear to prime for subsequent responses when given close to birth
- Animal models of neonatal responses to pneumo polysaccharides are encouraging too.
- Priming neonates for responses to pneumo polysaccharides may result in boosted immunity rather than disease following colonisation in early life
- A clinical study will start in 6-8 weeks to test these hypotheses.

PROS

In developing country settings:

Potential to provide earlier protection

Possibly help improve vaccine coverage

CONS

Potential safety issues

Potential failure to induce responses

Potential negative effects on subsequent responses