Alternative strategies for neonatal protection against Hib and Pneumococcus

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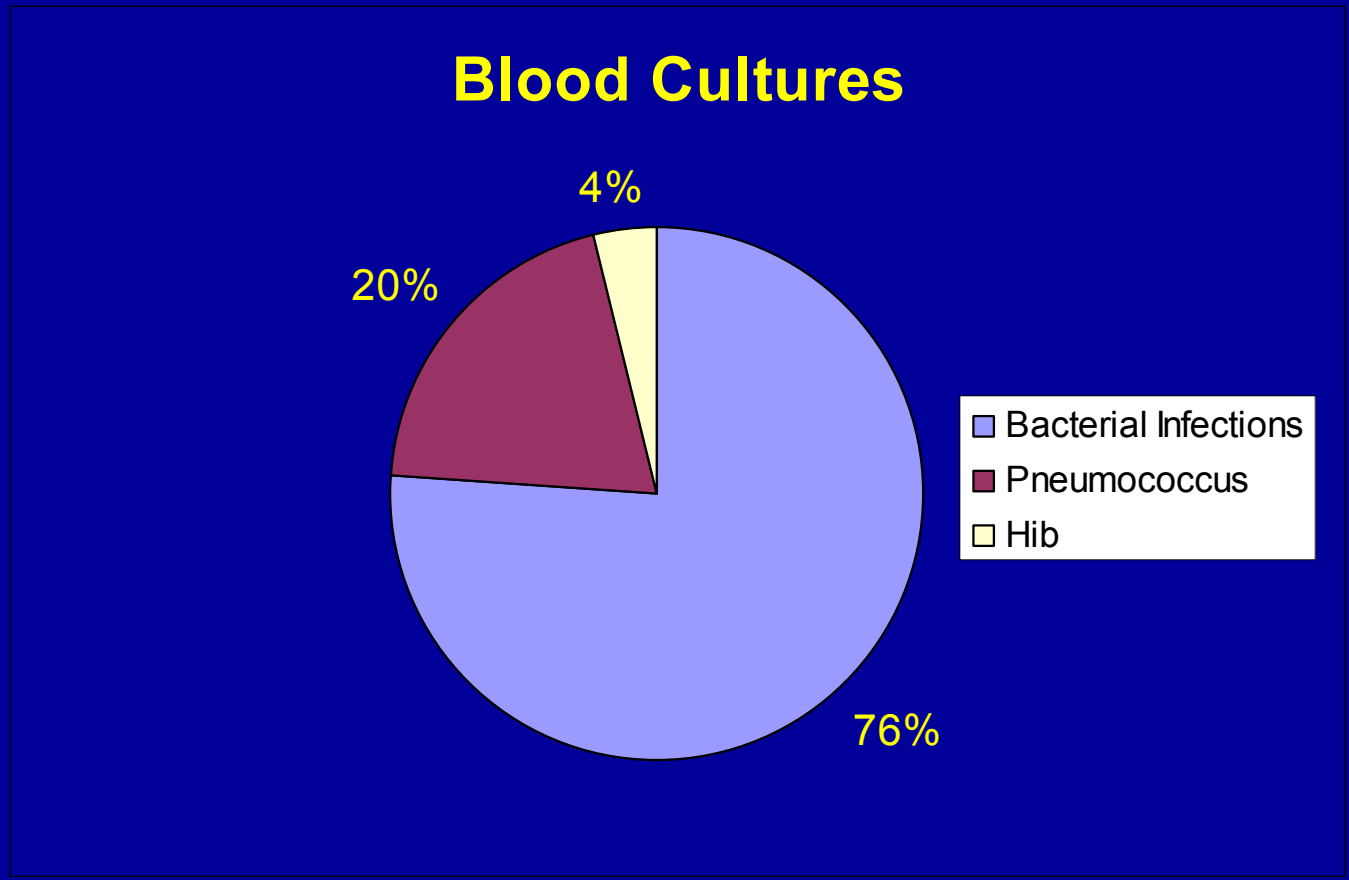
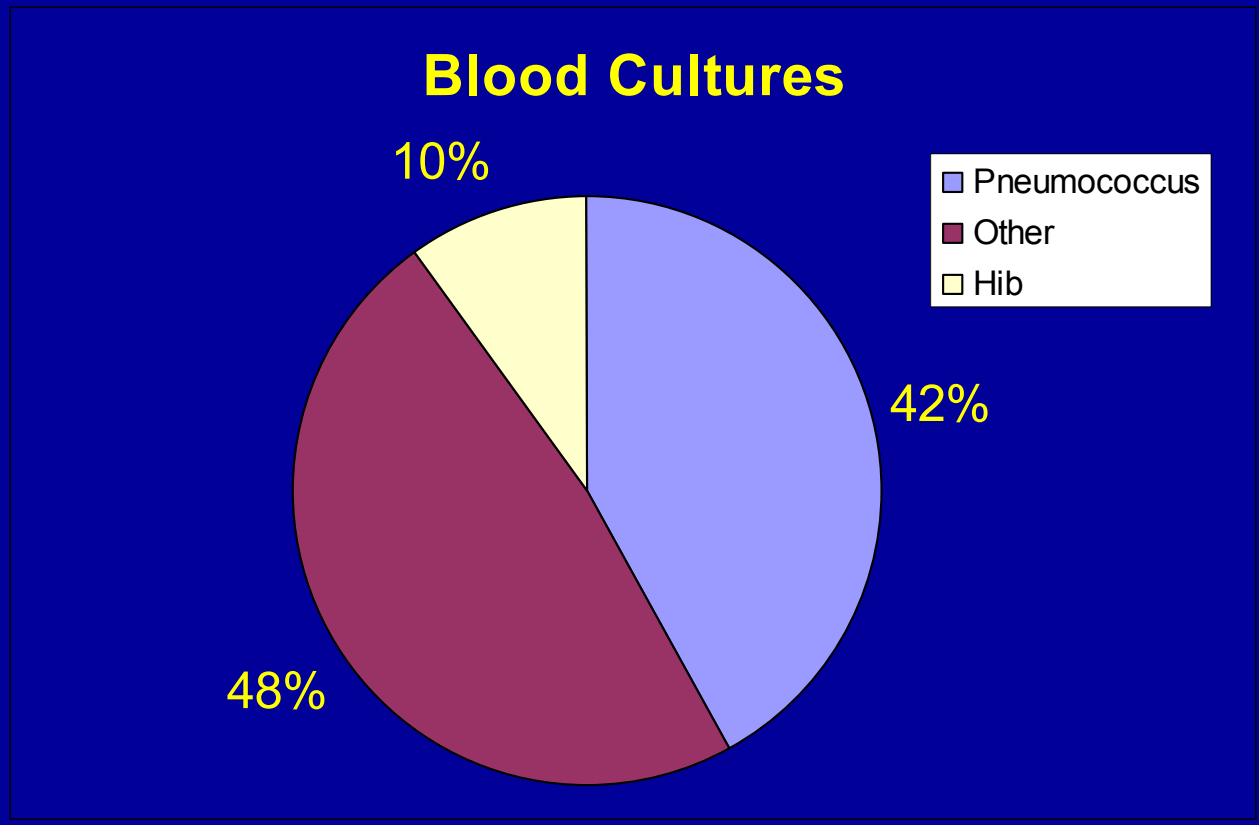
WHO Young Infant Study Group 0-90 Days



167 positive cultures of 2452 samples

WHO Study Group, PIDJ 1999; 18:S17

CSF Cultures 0-90 Days



40 positive cultures

WHO Study Group, PIDJ 1999; 18:S17

Alternative strategies for protection of Neonates against Hib and Pneumococcal Disease

- Passive immunization
- Neonatal Immunization
- Maternal Pre-pregnancy immunization
- Maternal Pregnancy immunization
- Post-partum immunization

Passive Immunization

Bacterial Polysaccharide Immune Globulin

Preparation

1. Immunization of plasma donors
    a. *H. influenzae* type b polysaccharide or conjugate
    b. Polyvalent *N. meningitidis* (2 or 4 serotypes)
    c. Polyvalent *S. pneumoniae* (14 or 23 serotypes)
2. Plasmapheresis of donors 2X/week
3. Plasma pooled and fractionated by cold ethanol procedure of Cohn and Oncley to prepare an im globulin
4. Characterization of antibody concentrations

Santosham et al, NEJM 1987

Bacterial Polysaccharide Immune Globulin Efficacy Trial

White Mountain Apache Infants
Randomized to Receive BPIG or
Placebo at 2, 6 and 10 months of age

Santosham et al, NEJM 1987

Bacteremic Hib Infections

(within 3 months of BPIG/Placebo)

	BPIG	Placebo	
No. children at risk	353	350	
No. of doses given	858	838	
Invasive Hib disease			
1-90 days after immunization*	0	7	p=0.007
1-120 days after immunization**	1	7	p=0.04

*Efficacy 100% (95% CI=46.7-100%)

**Efficacy 85.8% (95% CI=-11.4-99.7%)

Santosham et al, NEJM 1987

BPIG Use In Alaska, YK Delta July 31st to Dec 31st 1990

- 620 of 966 newborns received BPIG at birth
- 1 case of Hib among BPIG recipients vs. 7 cases in non-recipients

p=.007

Singleton R, personal communication

Maternal Immunization Pre-Pregnancy

Pre-Pregnancy Immunization Study - Sacaton, AZ

Healthy non-pregnant women randomized to receive:

-HbOC

-PRP-OMP

-23 Valent pneumococcal vaccine

Santosham PIDJ 2001; 20:931

Schedule for Immunization

Non-pregnant mothers			Birth		Infants			
Mos.	0 13	1	18	19	0	2	4	>12
Grp A	HbOC	HbOC				PRP-OMP	PRP-OMP	PRP-OMP
Grp B	PRP-OMP	PRP-OMP				PRP-OMP	PRP-OMP	PRP-OMP
Grp C	PS-23					PRP-OMP	PRP-OMP	PRP-OMP
Sera	X X	X	X	X	X	X	X	X

Santosham PIDJ 2001; 20:931

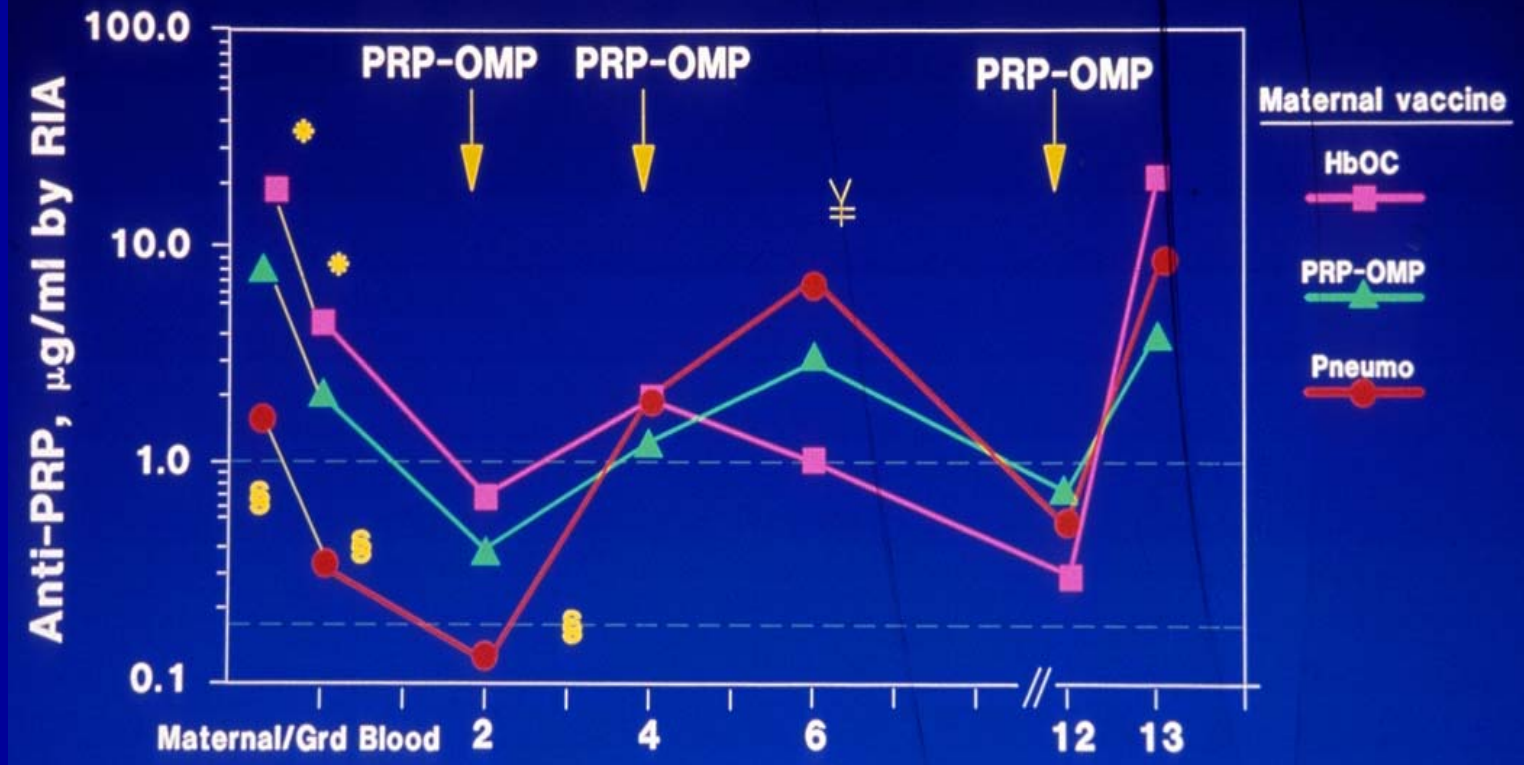
Persistence of total anti-PRP levels in women after primary immunization

	Geometric mean (μg/ml)			
	HbOC	PRP-OMP	Control	*p*
Pre	2.2	2.9	2.3	NS
1 mo. Post	111	33.3	2.7	<0.01
21 mo. Post	16.7	6.6	2.13	<0.01
37 mo. Post	14.6	5.4	2.0	<0.01

Santosham PIDJ 2001; 20:931

MATERNAL IMMUNIZATION BEFORE PREGNANCY

- Hib Antibody Response in Infants -



* p <.01 HbOC vs PRP-OMP

† p <.05 HbOC vs PRP-OMP

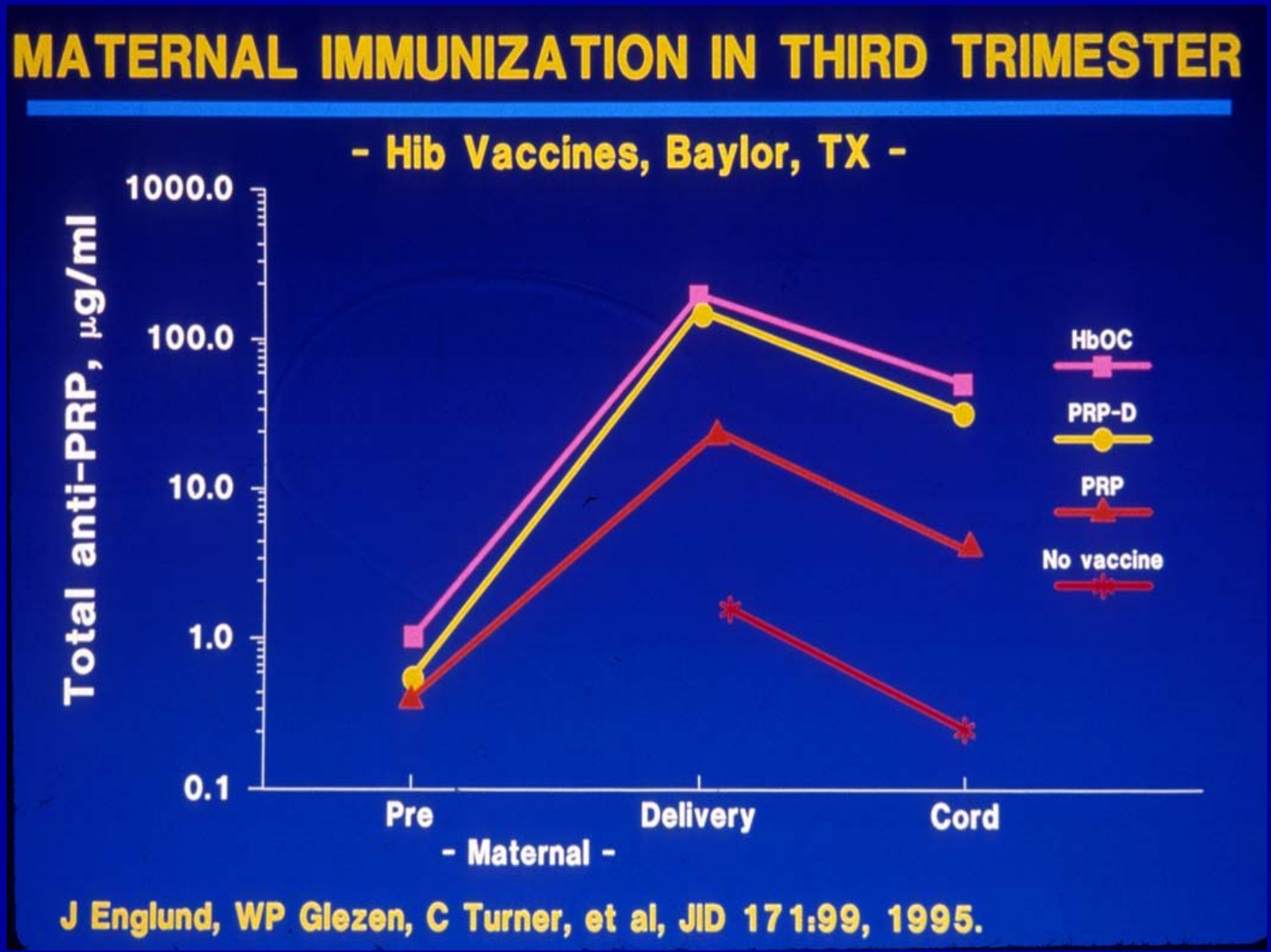
§ p <.01 Pneumo vs Hib vaccines

¥ p <.05 Pneumo vs Hib vaccines

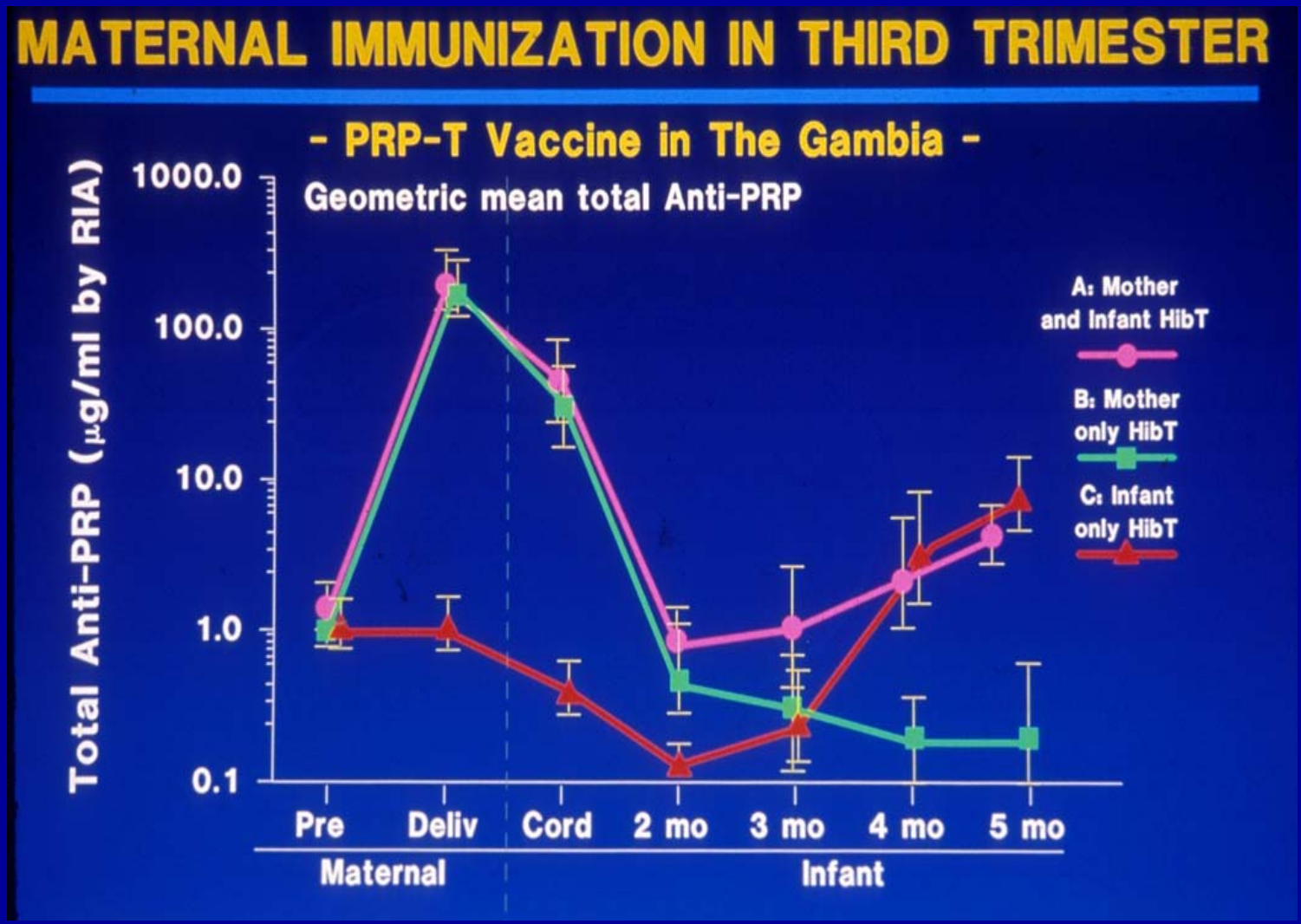
G Siber et al, Ped Res 35:196A, 1994.

Maternal Immunization Pregnancy

MATERNAL IMMUNIZATION IN THIRD TRIMESTER



J Englund, WP Glezen, C Turner, et al, JID 171:99, 1995.



Mulholland et al; JAMA 1996; 275:1183

CORD PRP AB IN CORD FOLLOWING MATERNAL IMMUNIZATION

VACCINE	CORD TOTAL PRP Ab (RIA)	% Mat:Fetal	% infants with >1 ug/ml PRP
PRP	2.9	14	75
PRP-D	17.5	12	89
HbOC-10ug	28.8	17	95
HbOC 2 ug (early)	3.5	--	95
PRP-T	1.92	22	22
NONE: US	0.3	42	13
Gambia	0.3	36	19

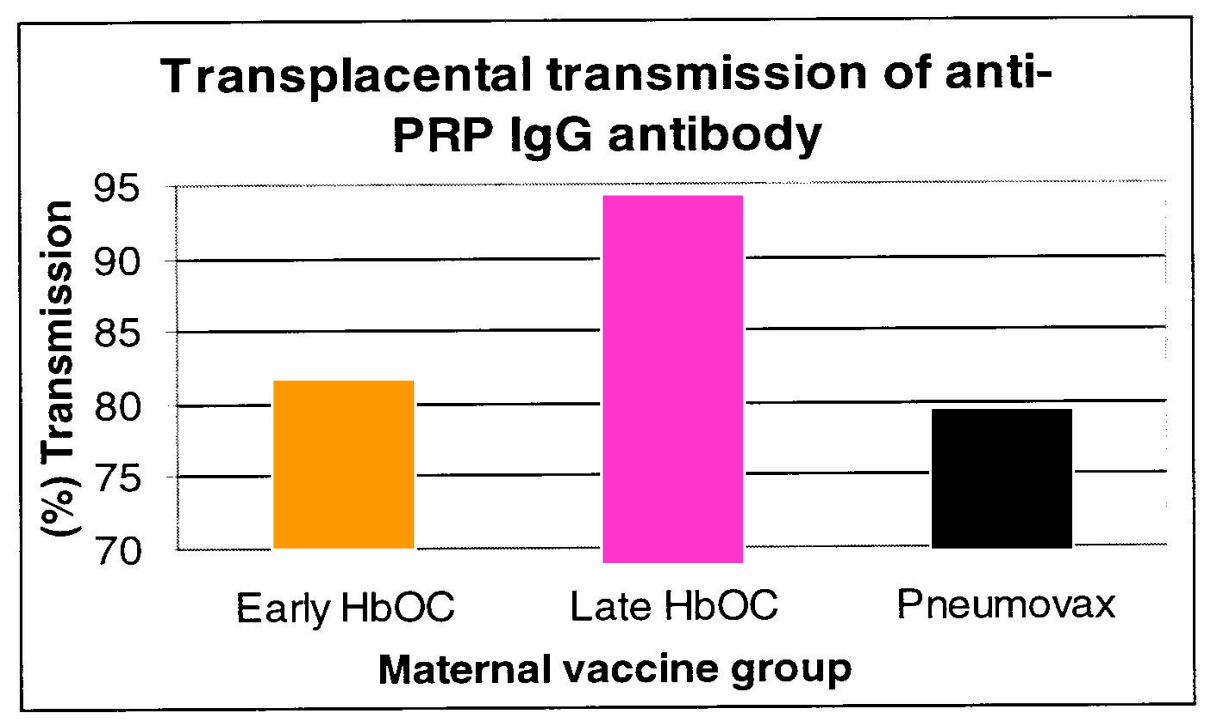
TIMING OF VACCINE: IS THERE AN ADVANTAGE TO IMMUNIZATION DURING RATHER THAN PRIOR TO PREGNANCY?

Timing of Hib Vaccine	IgG Anti-PRP(ug/ml) Mother	Infant	% Transmision
Pre-Pregnancy (HbOC) Sacaton, AZ[1]	20	11	73%
3rd Trimester:			
Houston, TX[2] (HbOC)	78	47	60%
The Gambia[3] (PRP-T)	4	2	61%

[1] Santosham et al,PIDJ 2001;20:931; [2] Englund et al JID 1995; 171:99
[3] Mulholland et al. JAMA 1996;275:1182

TIMING OF VACCINE DURING PREGNANCY: RELATIVE TRANSMISSION OF MATERNAL ANTIBODY

- PRP-CRM at 2 ug/dose or pneumococcal PS vaccine administered to 60 pregnant women at 32 or 36 weeks gestation:



PRP AB IN STUDY INFANTS AT TWO MOS.

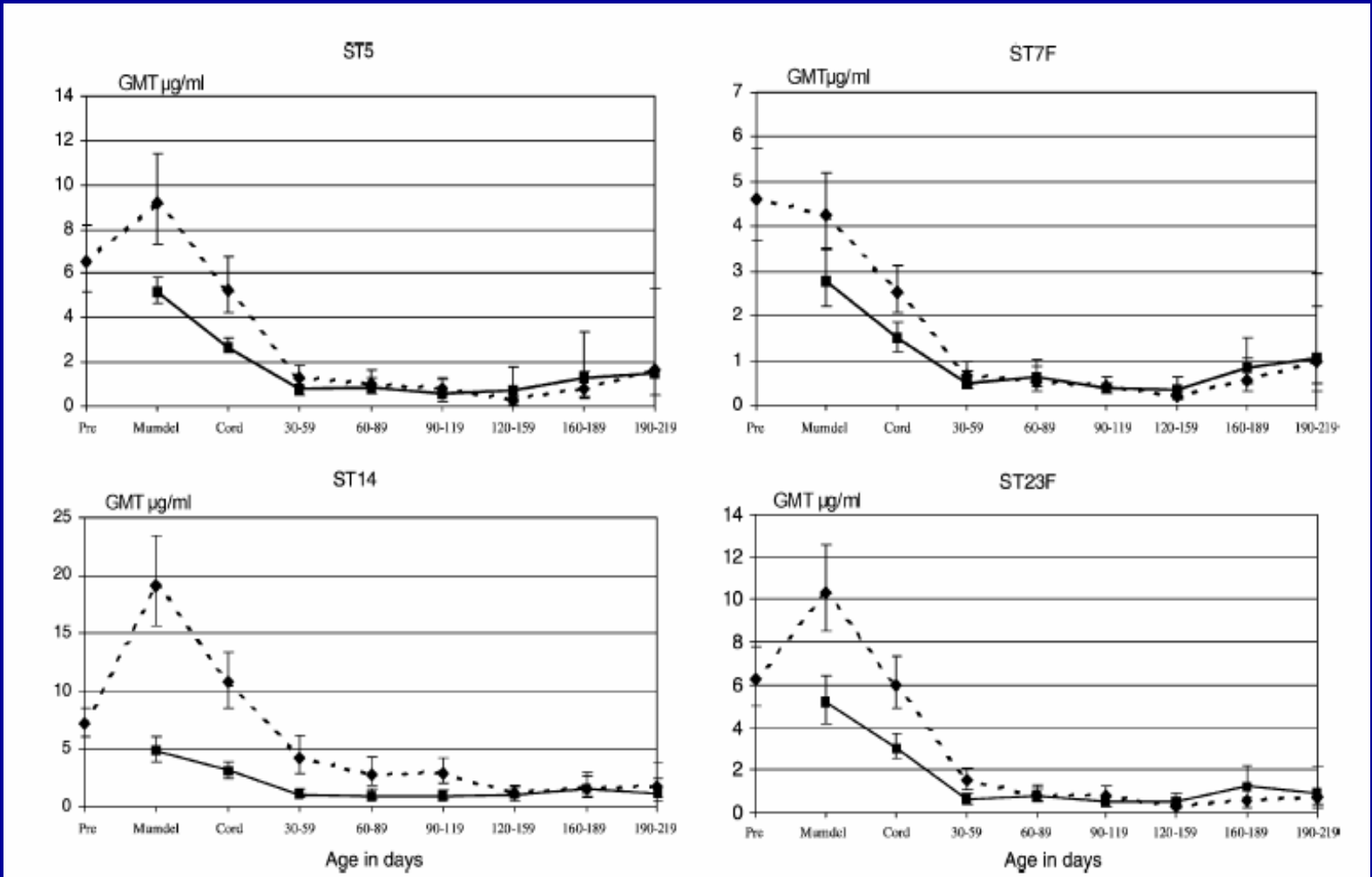
	Mean total PRP Ab (ug/ml)	% infants > 0.15 ug/ml	% infants > 1.0 ug/ml
CONTROL	0.10	17	0
US: PRP	1.5	82	36
US: PRP-D	14.4	100	93
US: HbOC	20.4	100	83
Gambia: PRP-T	0.35	61	26
Pre-Preg. HbOC	0.83	87	45
Pre-Preg. OMP	0.4	78	22

PREFERENTIAL TRANSMISSION OF IgG1 SUBCLASS

	IgG1				IgG2		
VACCINE	Mat	Cord	%		Mat	Cord	%
CONTROL	.29	.32	127%		.49	--	111%
PRP	3.84	2.15	99 %		2.01	.62	22 %
PRP-D	41.9	18.9	74 %		12.9	3.38	46 %
HbOC	24.5	18.1	91 %		9.46	3.82	59 %
PrePreg HbOC	2.4	2.7	136%		4.4	2.4	60 %

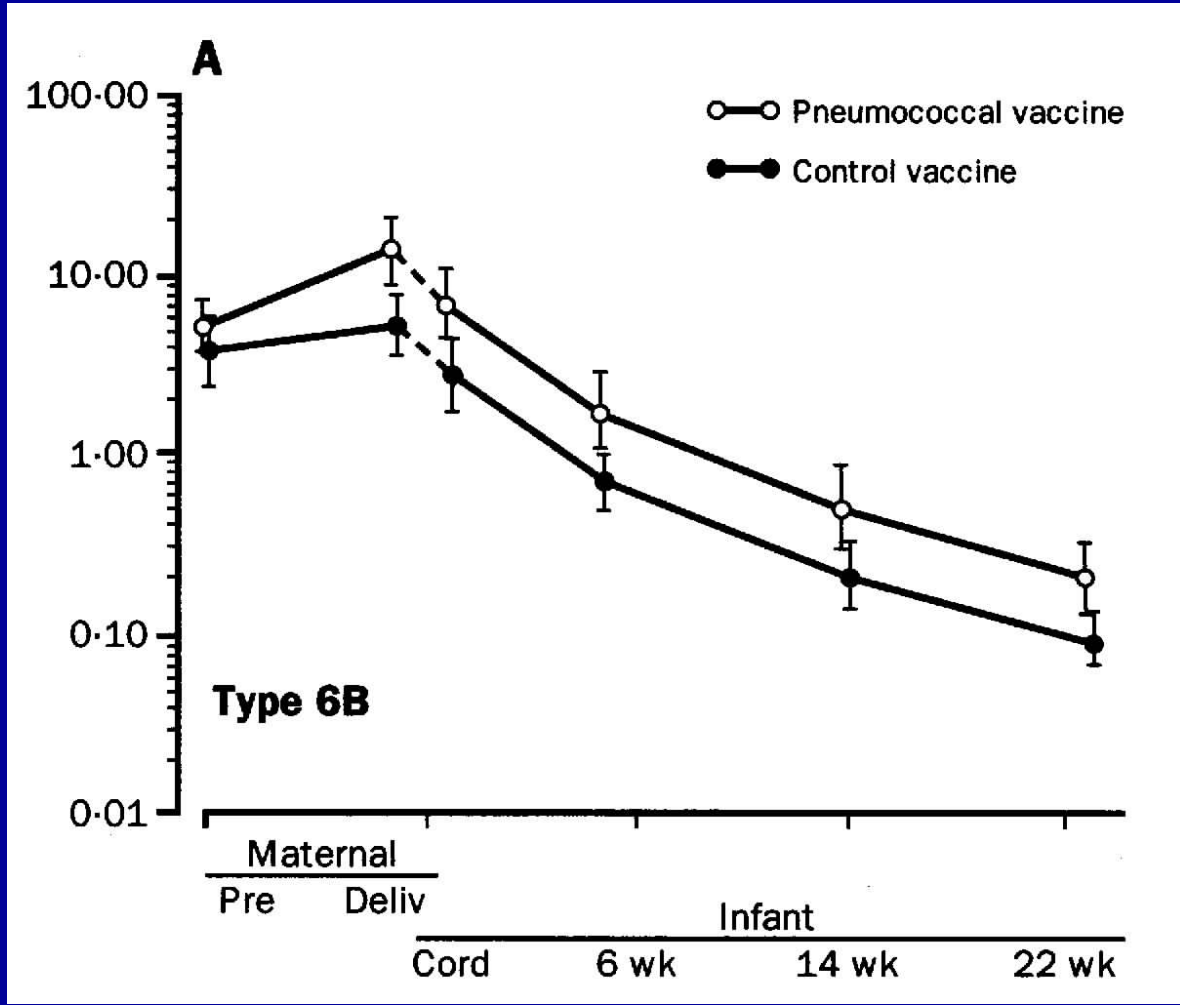
Maternal Immunization with Pneumococcal Vaccines

GMT IgG antibody to Pnc serotypes 5, 7F, 14 and 23F - maternal immunization with PS-23



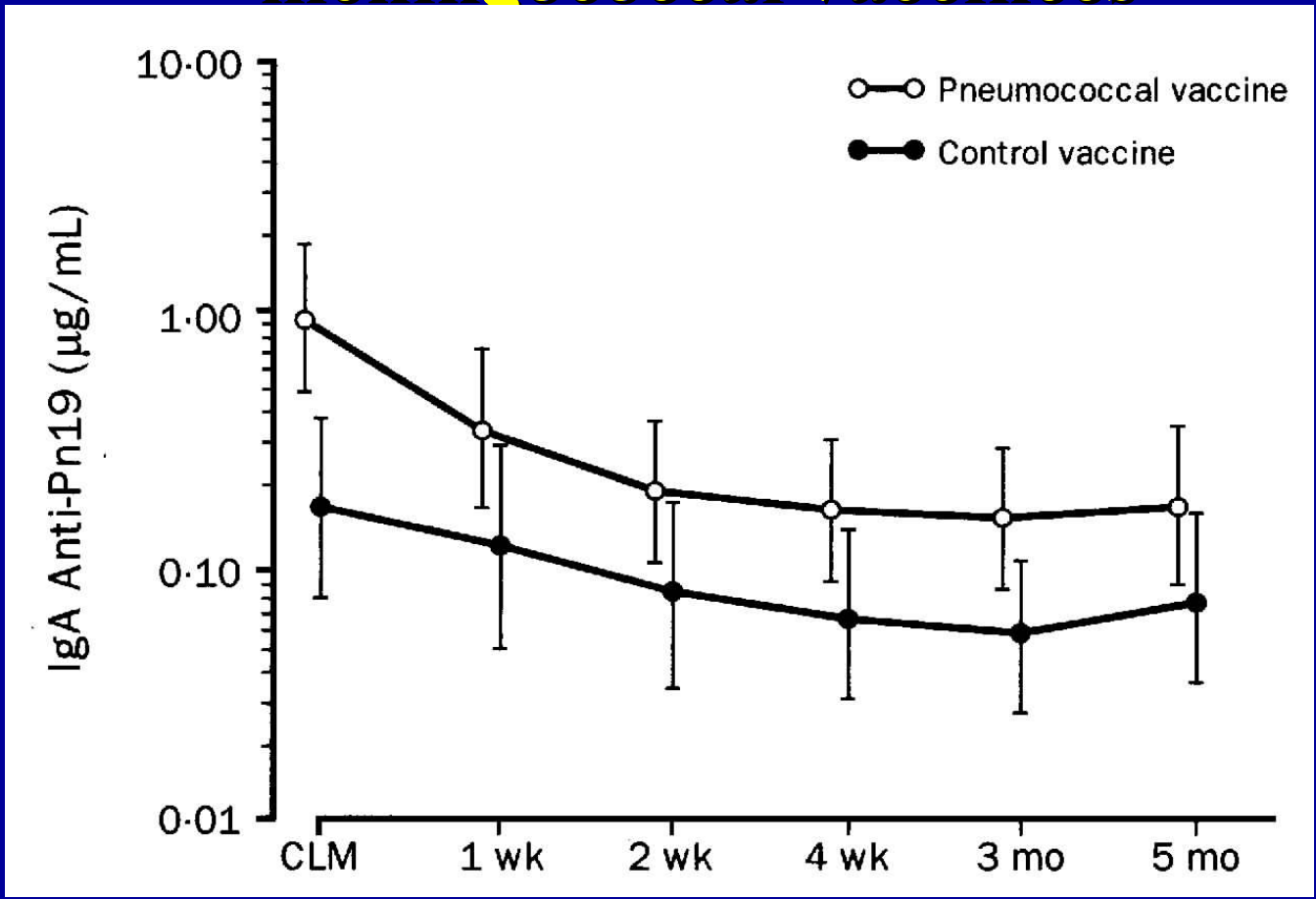
Lehmann D, Vaccine 2003; 21: 3446-3450

Pneumococcal serum IgG antibody in mothers and infants



Source: Shahid Steinhoff Lancet 1995

Breast milk pneumococcal type 19F antibody concentrations in pneumococcal and meningococcal vaccinees



Source: Shahid Steinhoff Lancet 1995

Cord Blood/Maternal Blood Pneumococcal antibody levels (%) – Women Vaccinated with Pneumococcal Vaccine – influence of Malaria

Serotype	Active infection placenta (N=4)	Non-infected placenta (N=11)
1	24	46
3	25	54
5	27	47
6	21	44
14	9	28
19	13	40

Adapted from Dempsey et al: Vaccine 1996:14:963-70

Efficacy of maternal immunisation with 14-valent pneumococcal polysaccharide vaccine in prevention of pneumonia in their children, Tari, Papua New Guinea 1973-1976

	Pneumonia episodes/ No. mothers		Efficacy	p
Age	Vaccine	Placebo		
In utero at time of maternal immunisation followed for **3 years**	57/84	73/93	14%	0.1
Child age 1-17 months at time of maternal immunisation followed over **next 5 months**	84/286	133/310	32%	0.003
Child age 1-17 months at time maternal immunisation followed over **next 3 years**	218/286	284/310	17%	0.02

Riley ID & Douglas RM; Rev Infect Dis 1981;3:233.

TRANSPLACENTAL TRANSPORT OF PRP ANTIBODIES DEPENDS ON MULTIPLE FACTORS

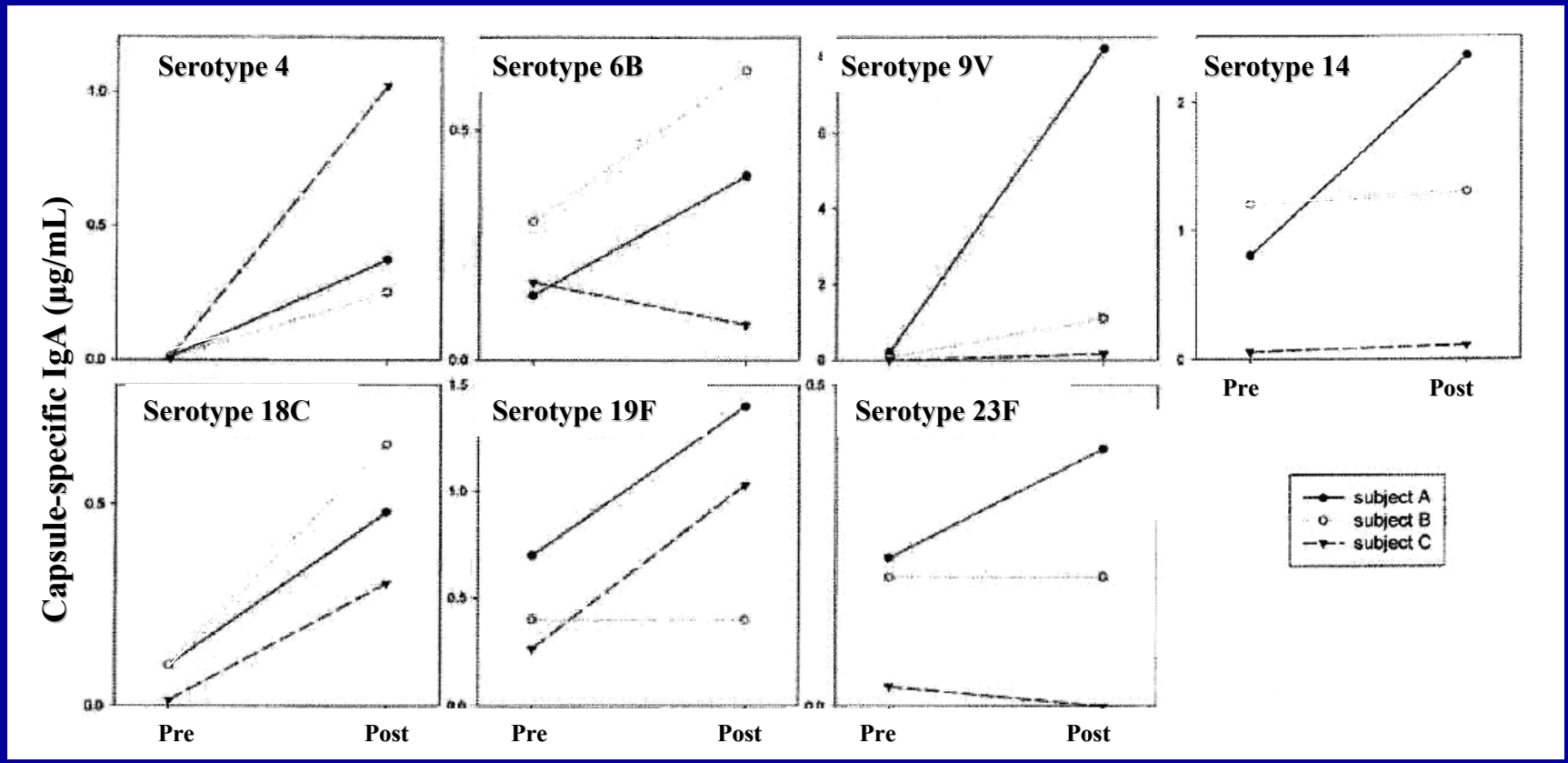
- Vaccine administered
- TIME:
  - gestational age of fetus at birth
  - time between maternal vaccination and delivery
- Maternal IgG level
- IgG subclass
- Placental abnormalities - such as malaria

OTHER FACTORS WHICH MAY VARY IN DIFFRERENT POPULATIONS

- Maternal IgG concentrations
- Integrity of the placenta
- Recent or repeated immunization with carrier protein, such as tetanus
- Maternal immune system (HIV)

Post-Partum Immunization

S. pneumoniae Capsule-specific IgA in Breast Milk After Immunization with 23-valent Vaccine



Finn, et. al. J Infect Dis 2002; 186:1422

Primary Objectives

- **To determine whether infants of women immunized with PNCRM-9 and infants of control women who receive placebo during the third trimester of pregnancy have equivalent anti-capsular polysaccharide (PS) IgG antibody responses to PNCRM-7 measured one month after the third vaccine injection given at 6 months of age.**

- **To compare local and systemic adverse events among women immunized with PNCRM-9 or placebo.**

Daly KA et al. MIVS Poster PAS 2003

Study Design

Mother

- 22-28 wks: Enroll
- 32-35 wks: Study Product administration
- Delivery: Blood sample
- 2 mos: Breast milk & blood sample
- 6 mos: Blood sample
- 13 mos: Blood sample

Vaccine safety assessment

Infant

- Birth: Cord blood
- 2 mos: Prevnar dose #1
- 4 mos: Prevnar dose #2
- 6 mos: Prevnar dose #3, blood sample
- 7 mos: Blood sample
- 12 mos: Prevnar dose #4, blood sample
- 13 mos: Blood sample

Daly KA et al. MIVS Poster PAS 2003

Reasons Eligible Women Refused to Participate (n = 558)

Concern about vaccination during pregnancy……46%

Partner or family member objects……10%

Too busy……7%

Dislikes blood draws for self or infant…….. 5%

Opposes immunizations……..5%

Dislikes placebo control……<1%

No reason given……26%

Daly KA et al. MIVS Poster PAS 2003

Conclusions - 1

Pre- Pregnancy Immunization

Advantageous

- Avoids concerns re. complications of pregnancy

Disadvantageous

- Uncertainty about time of delivery to time of vaccination
- Lack of routine scheduled visit

Conclusion 2

Maternal Immunization during Pregnancy

Advantageous

- Coverage with maternal immunization with tetanus toxoid high
- Relatively easy to deliver the intervention

Disadvantageous

- Perceptions of adverse effects during pregnancy