

Accelerating Immunity to Hib in the First Six Months of Life



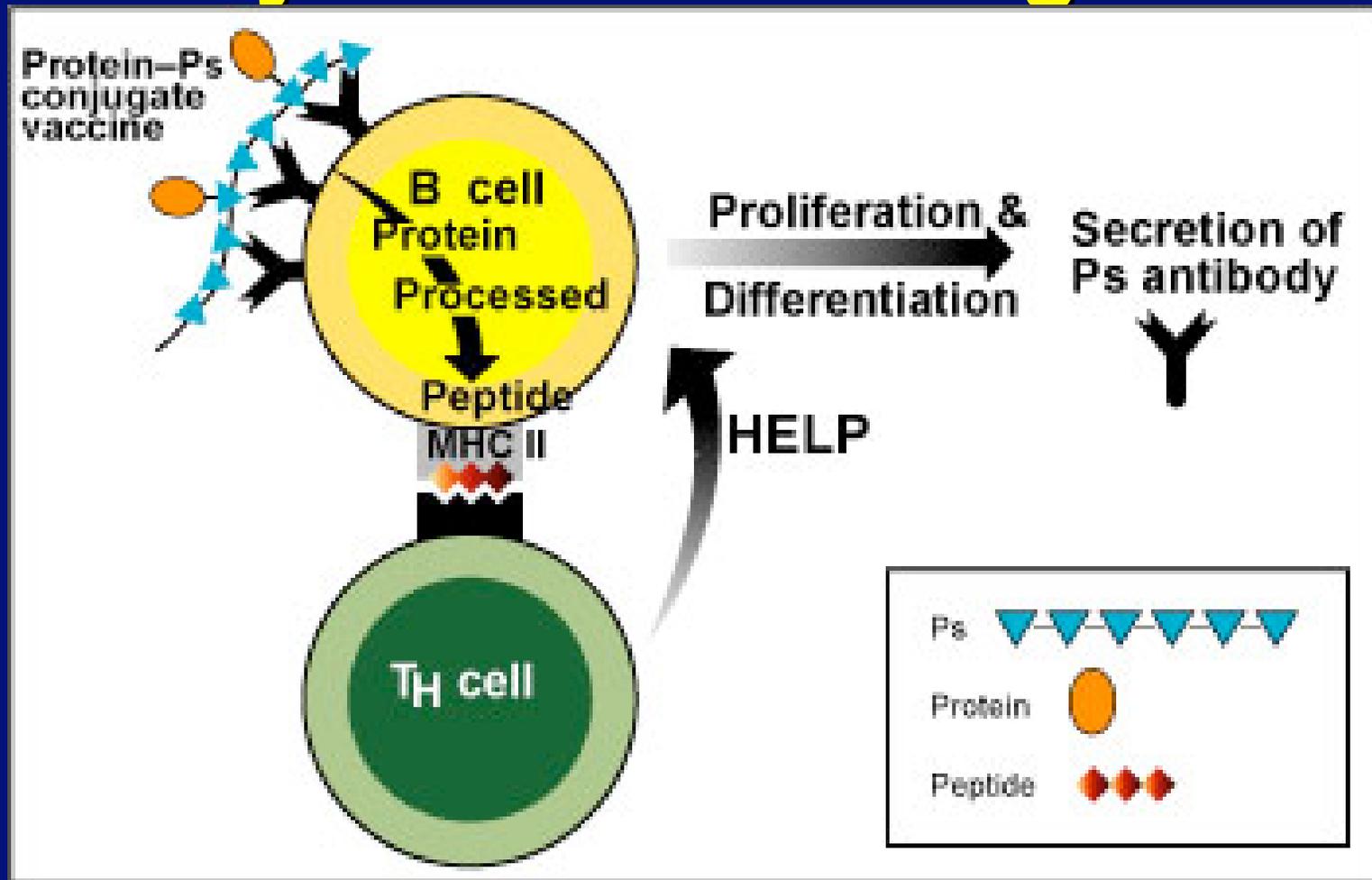
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**Neonatal Vaccination
Workshop, March 2, 2004**

Three PRP-Protein Conjugate Vaccines

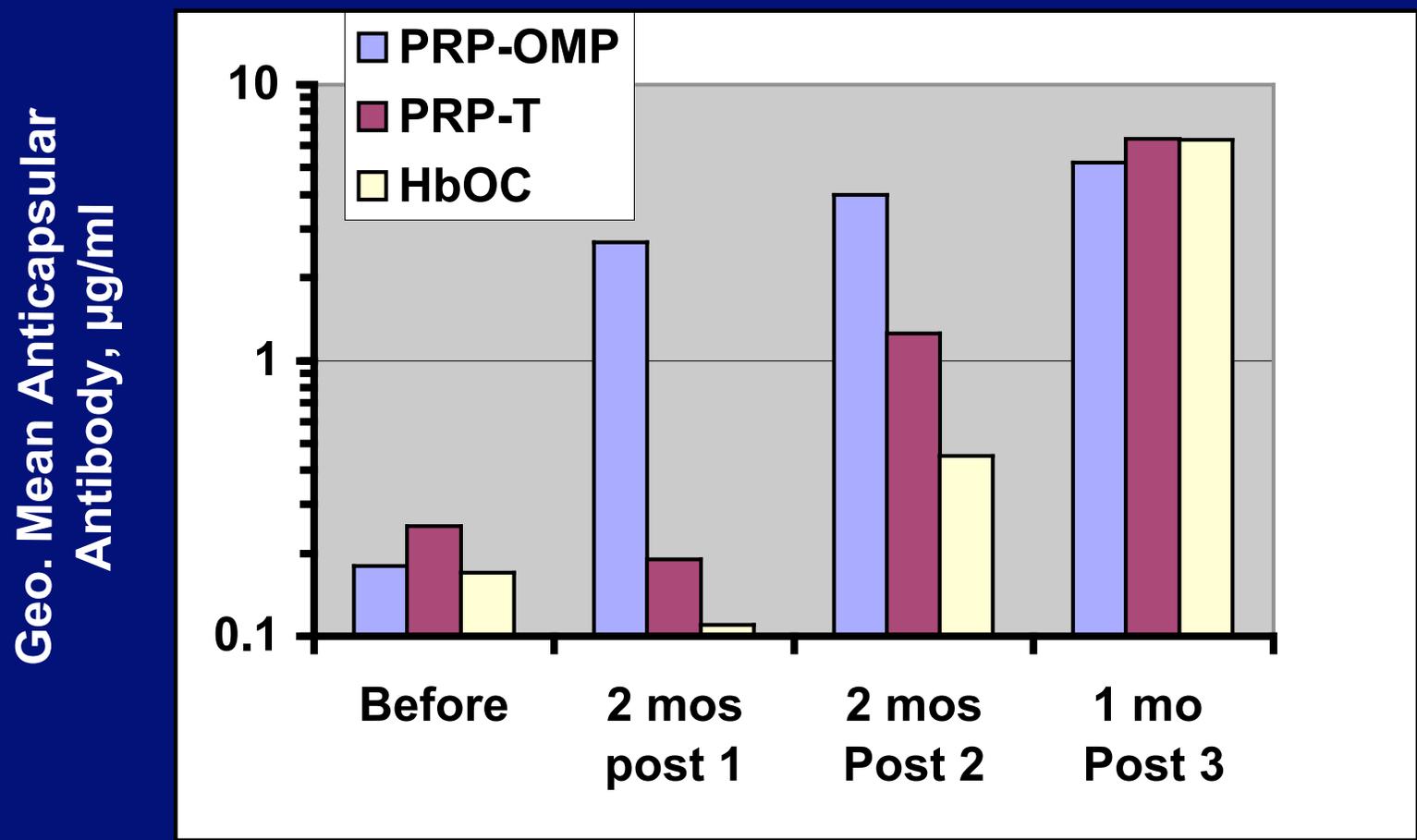
- Outer membrane protein (PRP-OMP, Merck)
- Tetanus toxoid (PRP-T, Aventis, GSK)
- Cross-reactive mutant diphtheria toxin, CRM₁₉₇ (HbOC, Wyeth)

Recruiting T Cell Help For Polysaccharide Antigens



Modified from Siber, Science 1994

Immunogenicity of Hib Conjugates in Infants Immunized at 2, 4 and 6 mos



N=149 subjects per vaccine group

Granoff et al,
J. Pediatrics, 1

***Neisseria meningitidis* OMP Complex**

- **Contains PorB (class 2 porin protein), a potent adjuvant**
 - **Increases expression of B cell co-stimulatory molecule, B7-2**
 - **Requires Toll-like receptor 2 (TLR2)**
 - **Delivers second signal for activation of Ig secretion by B cells in response to TI-2 antigens**
 - **Ability to elicit anti-PRP body response after one dose may be related to induction of cytokines by T cells and macrophages**

Wetzler et al, J. Exp Med 1996

Snapper et al, Infect Immun 1997

Massari et al, J. Immunol 2002

Latz et al, J. Immunol 2004

Qualitative Differences in Anti-PRP Antibody in Infants Immunized at 2, 4 and 6 Months of Age

Vaccine	Bactericidal Activity*	Avidity (Ka, nM ⁻¹)	Percent of Infants	
			HibId-1 Expression	HibId-2 Expression†
HbOC	+++	+++	68†	18††
PRP-T	++	++	64†	10††
PRP-OMP	+	+	33†	47††

*µg/ml for killing 50% of Hib with human C

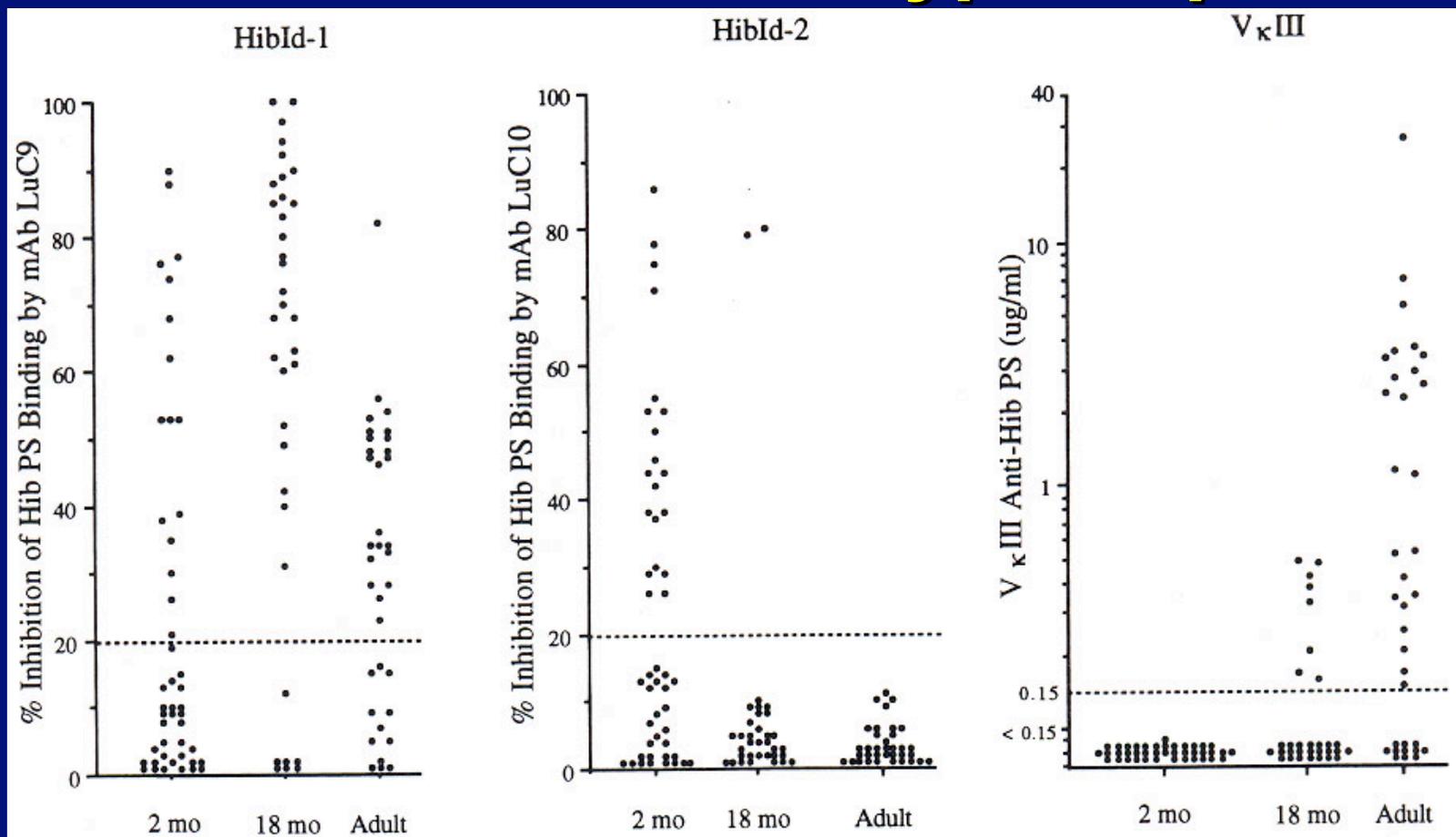
HibId-1 and HibId-2 are idiotypic markers of V α II and V α VII usage, respectively

†P<0.001

††P<0.001

Granoff et al, JCI 1993 and
Schlesinger and Granoff, JAMA 1992

Effect of Age of PRP-OMP Immunization on Cross-Reactive Idiotypic Expression



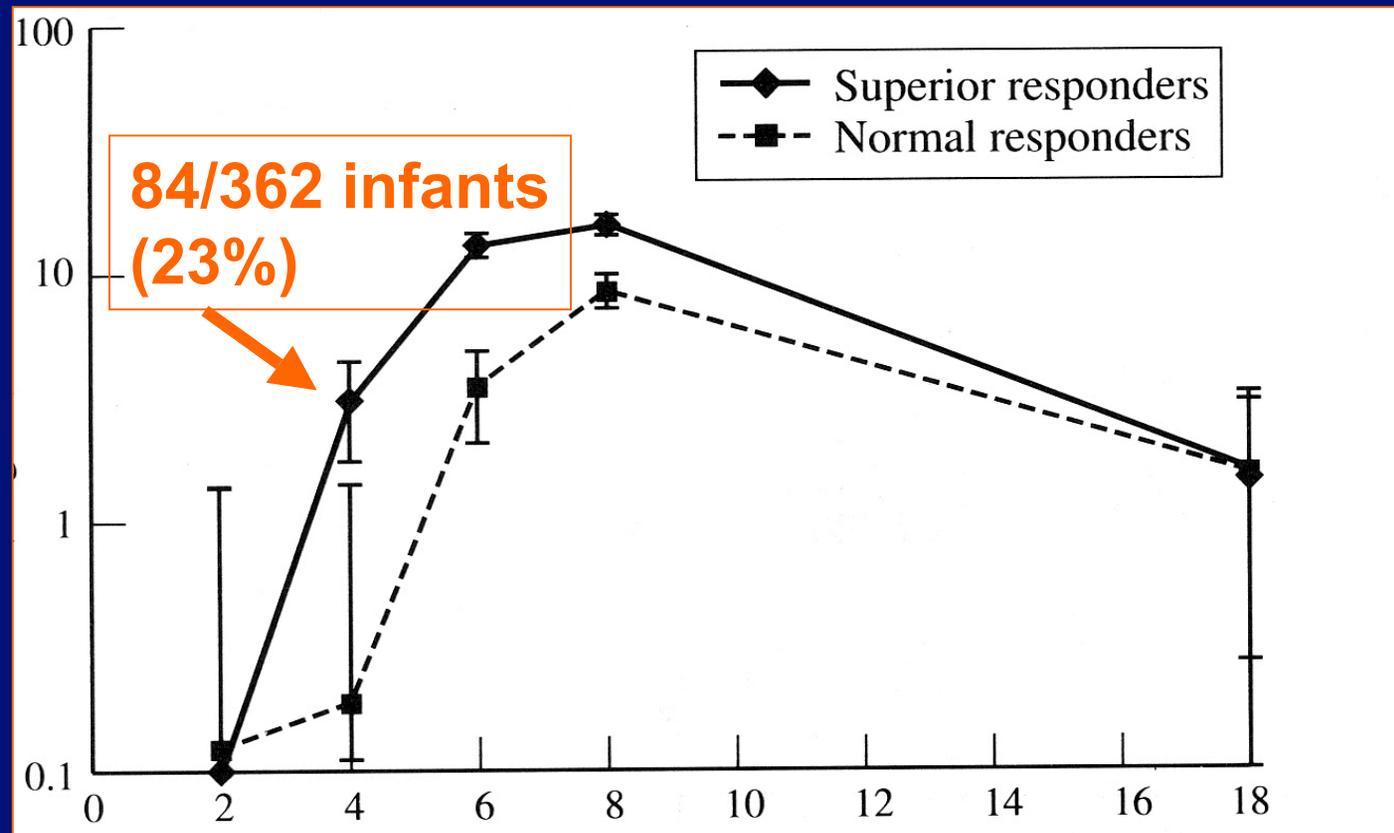
One injection of vaccine

Lucas et al, J. Immunol. 1993

Accelerating Immunity to Hib

Superior Responders to PRP-T Vaccination at 2 Mos. of Age in Chile ($\geq 1 \mu\text{g/ml}$)

Geo. Mean Anticapsular Antibody, $\mu\text{g/ml}$



Age in Mos.

Levine, OS et al
Vaccine 1997

Superior PRP-T Responders

- Higher anti-tetanus toxoid antibody ($P < 0.01$) but not higher diphtheria toxoid antibody responses ($P > 0.1$)
- Associated with crowding and lower maternal education ($P \leq 0.05$)
 - Reflection of different pre-natal or post-natal environmental exposures (cross-reacting *E. coli* or tetanus toxoid)?
- Biologic plausibility at attempts to accelerate Hib immunity

Levine et al, Vaccine 1997

Approaches to Accelerate Acquisition of Immunity to *Hib*

- Maternal Immunization and/or passively administered antibody
- Neonatal immunization
 - Conjugate vaccine
 - Carrier priming

Newborn Hib Immunization

- Two published studies
 - PRP-T: Kurikka et al, Pediatrics 95:815, 1995
 - HbOC: Lieberman et al, J. Pediatrics 126:198, 1995
- Two unpublished abstracts of PRP-OMP presented at ICAAC
 - Keyserling and Wickliffe, 1990
 - Ward et al, 1992

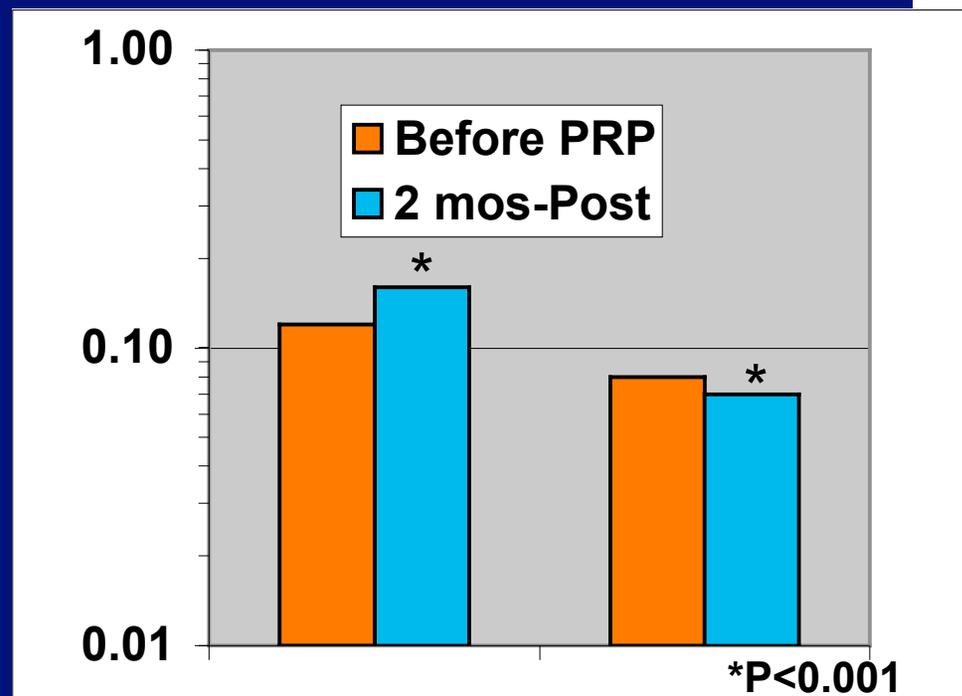
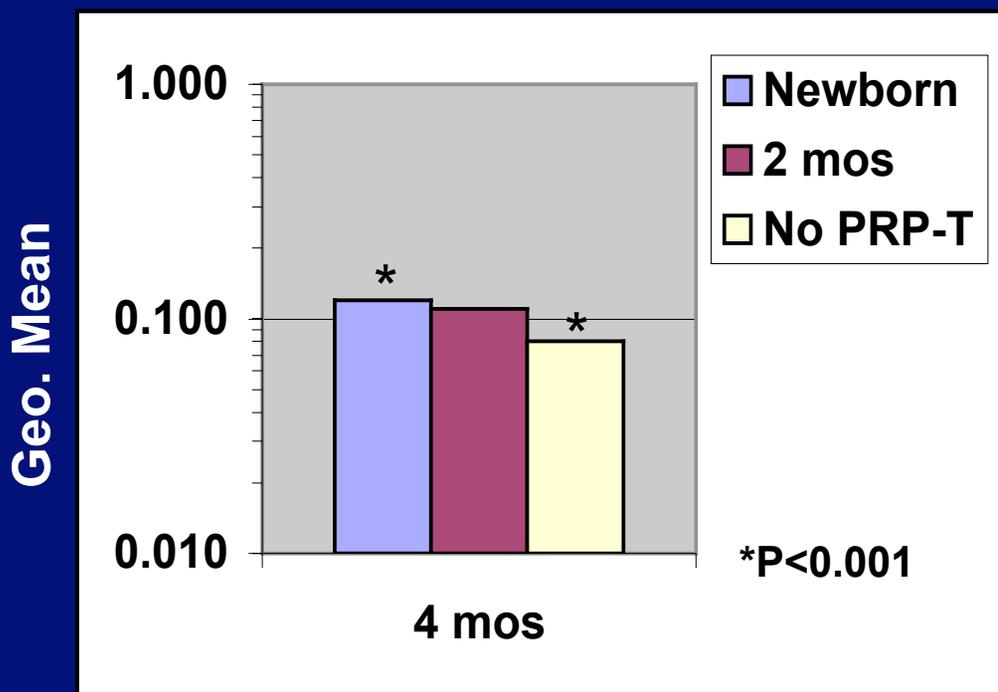
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PRP-T Conjugate Vaccination of Finnish Newborns (2 days)

One dose of PRP-T

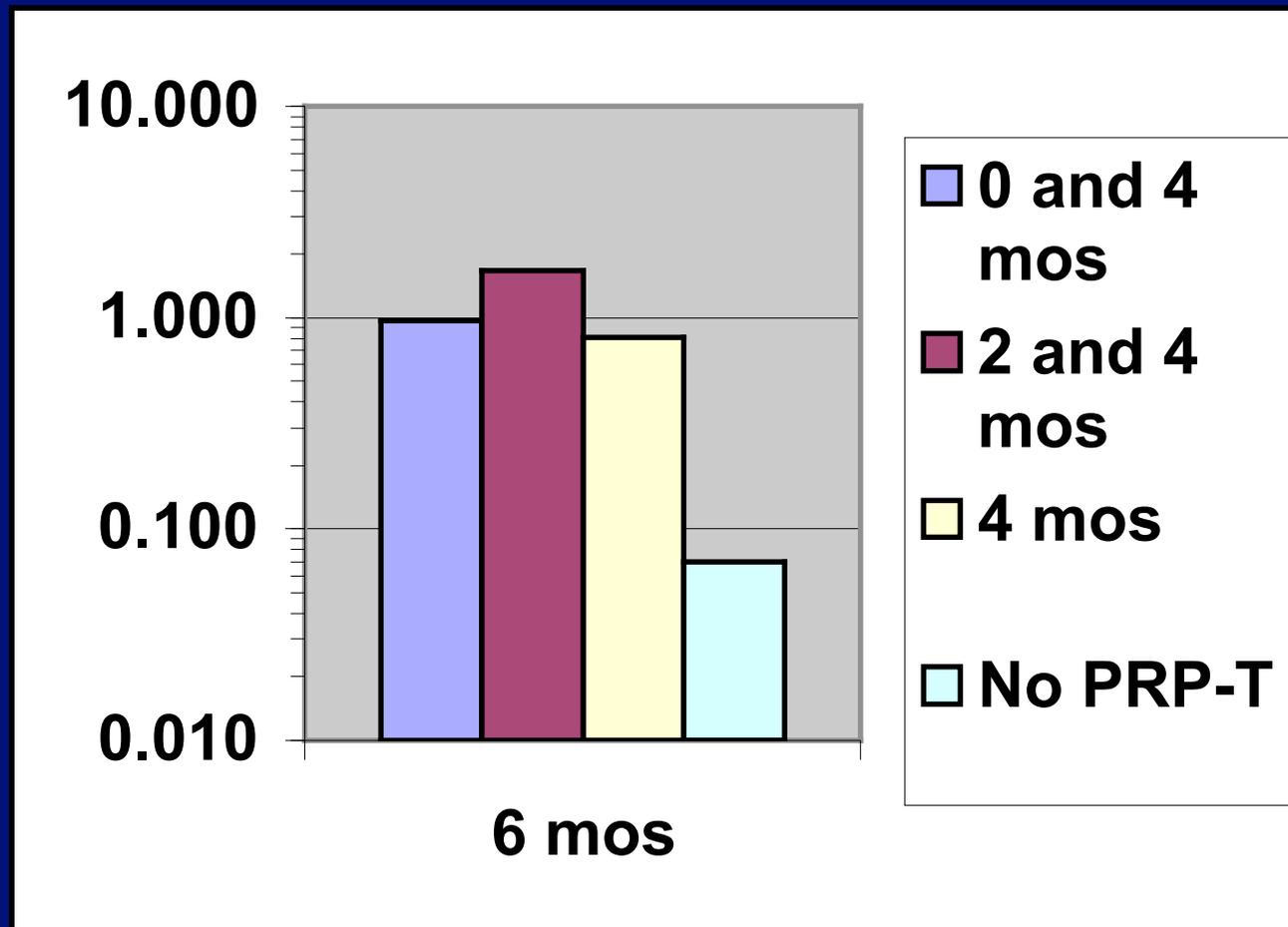
PRP Boost at 4 mos



Evidence of antibody production at 4 months with modest priming

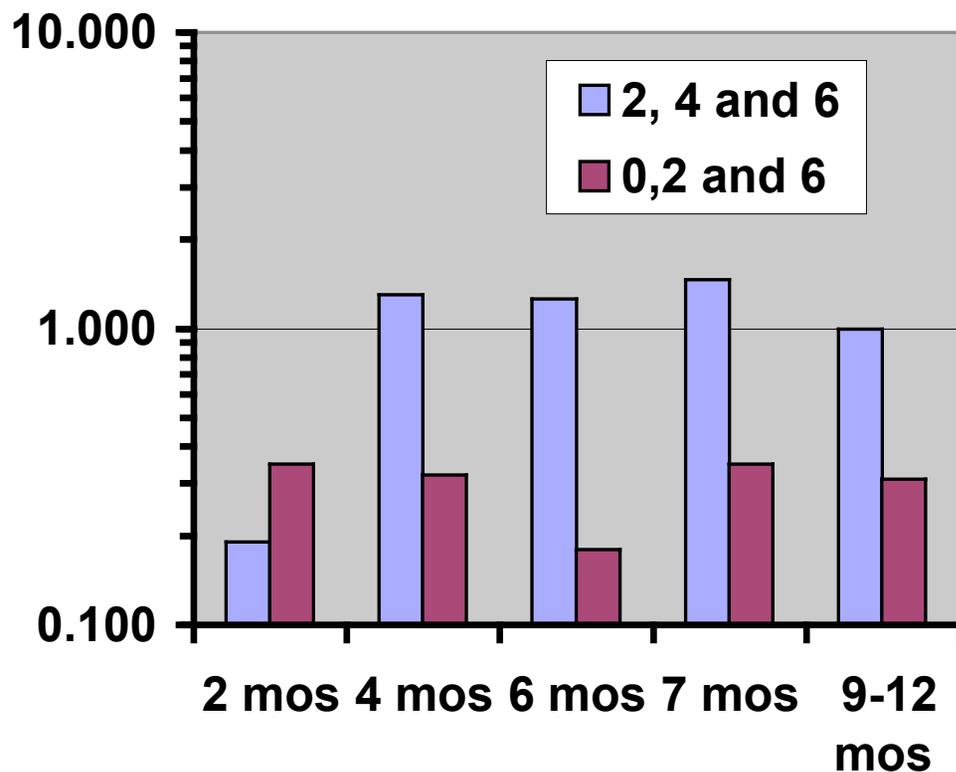
Kurikka et al, Peds 1995

Anti-PRP Antibody Levels at 6 mos. in Infants Immunized with PRP-T at Birth



Kurikka et al,
Pediatrics 1995

Newborn PRP-OMP Vaccination of Native Alaskans



Conclusions

Evidence of anti-PRP antibody production at 2 mos but subsequent suppression

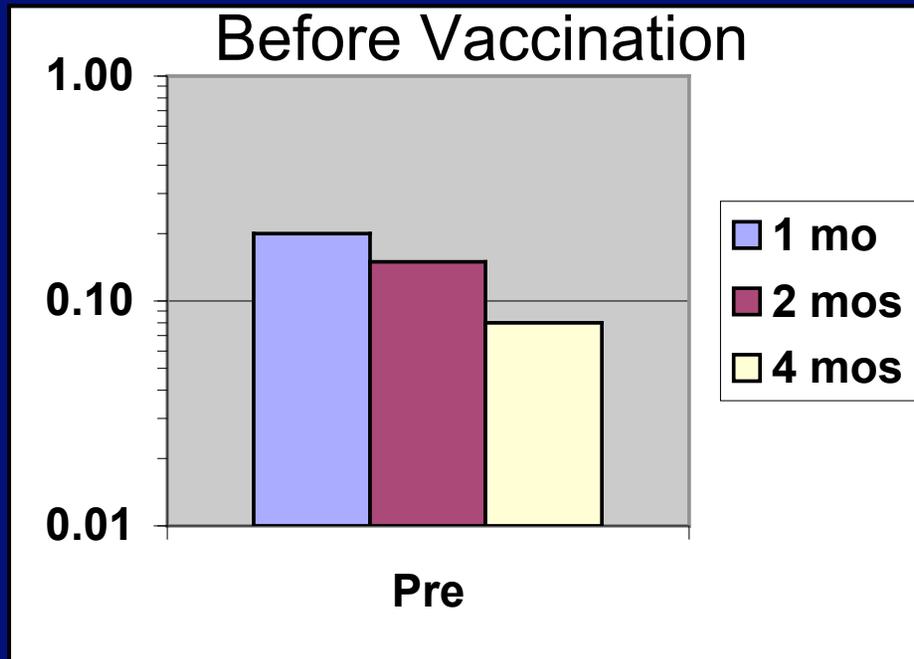
Ward et al,
ICAAC, 1992

Summary of Newborn Hib Conjugate Immunization

- HbOC and PRP-T elicited minimal increases in antibody levels at 4 mos. of age, which were not sustained
- PRP-OMP - elicited antibody production at 2 mos. but subsequent hyporesponsiveness
 - Mechanism unknown
 - May be related to unusual properties of OMP carrier protein

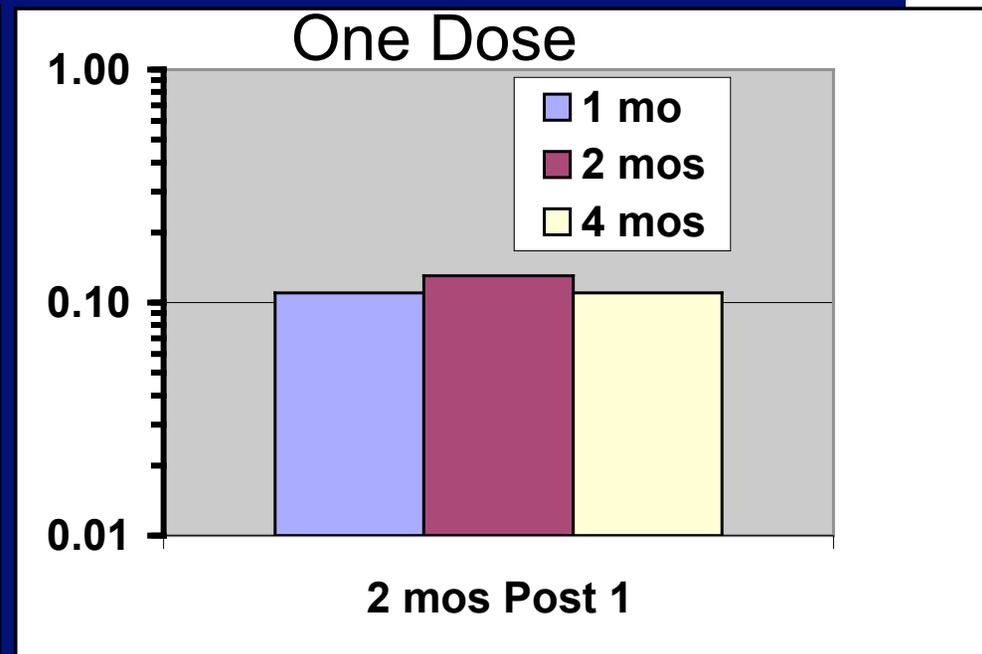
PRP-T Vaccination of Finnish Infants at Different Schedules[†]

Anti-PRP, µg/ml
Geo. Mean



Pre- antibody levels decreased with age

[†]Given with DTwP

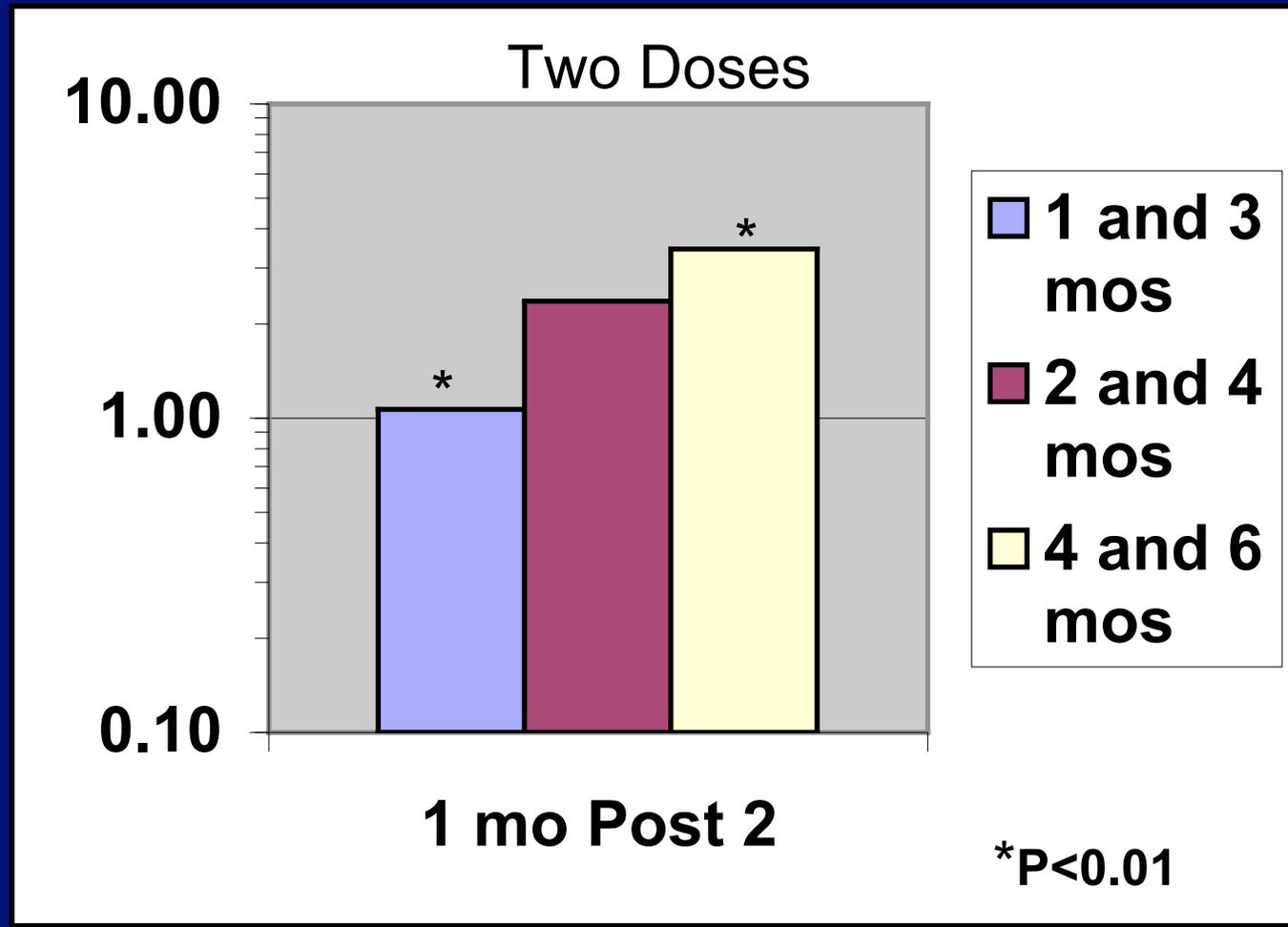


No significant differences after 1 dose at the different ages

Kurikka et al, J Pediatr 1996

PRP-T Vaccination of Finnish Infants at Different Schedules

Anti-PRP, $\mu\text{g/ml}$
Geo. Mean



Kurikka et al,
J Peds 1996

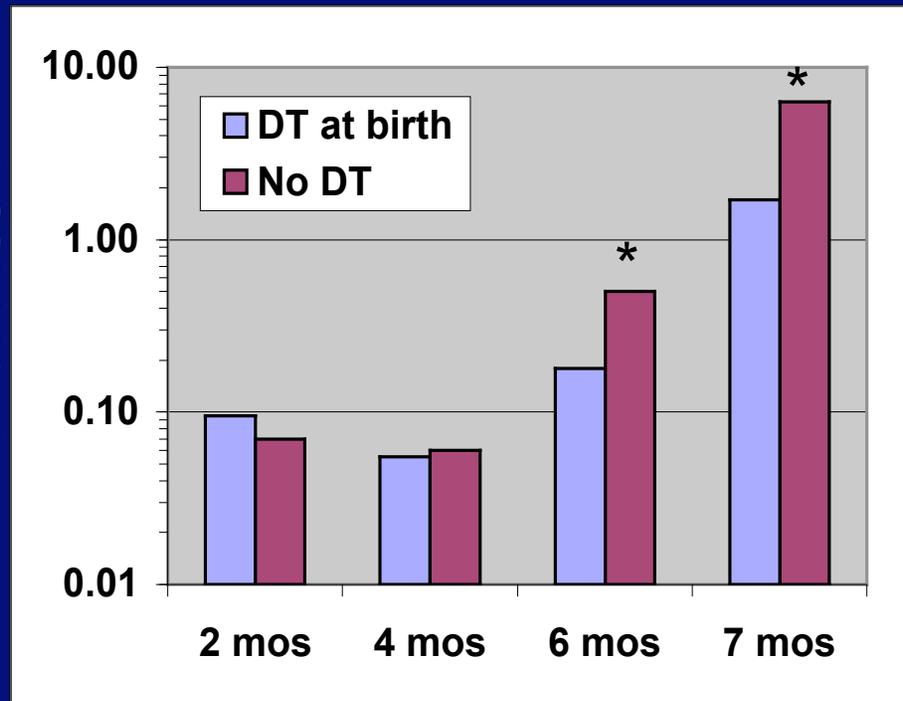
Conclusions

- **Immunization with PRP-T at 1 month elicits antibody production and avoids modest decline in maternally-derived anti-PRP antibodies in unimmunized infants between 2 and 4 months**
- **Earlier immunization results in lower anti-PRP antibody levels at 7 months than when beginning PRP-T at 4 months**

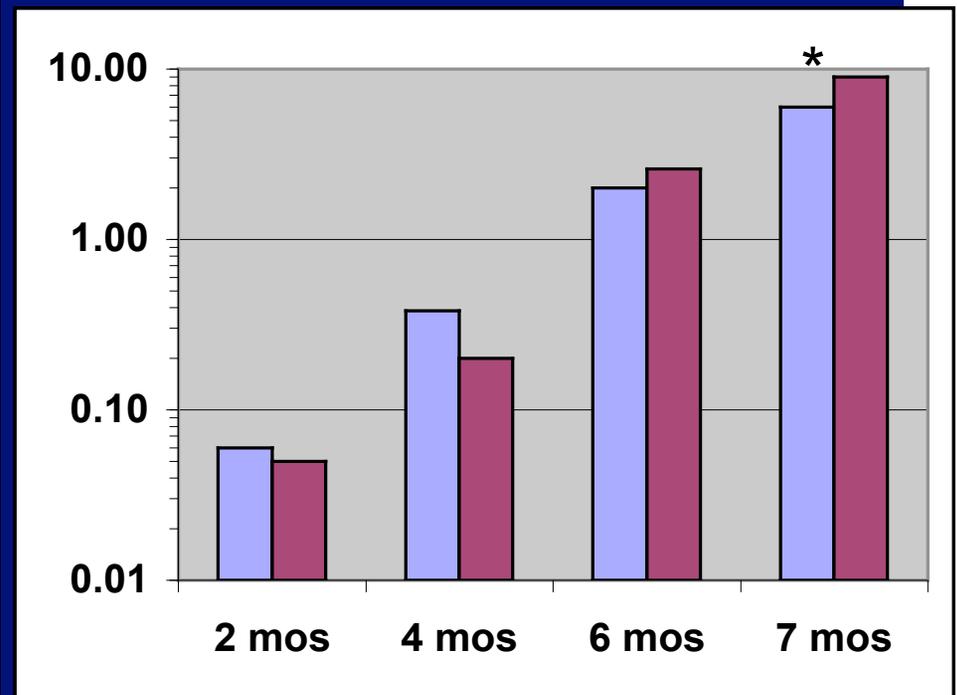
Accelerating Acquisition of Hib Immunity by Carrier Priming

Newborn Priming with Diphtheria and Tetanus Toxoid Vaccine (DT)

Response to HbOC*



Response to PRP-T*



*P<0.01

*2, 4 and 6 mos. with separate DTwP

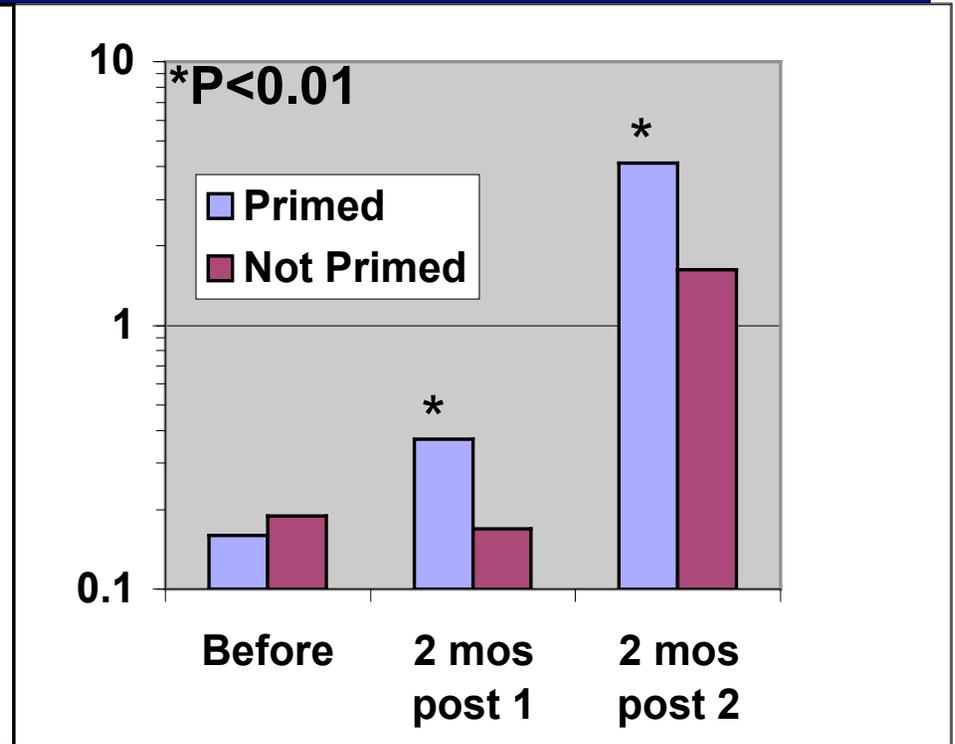
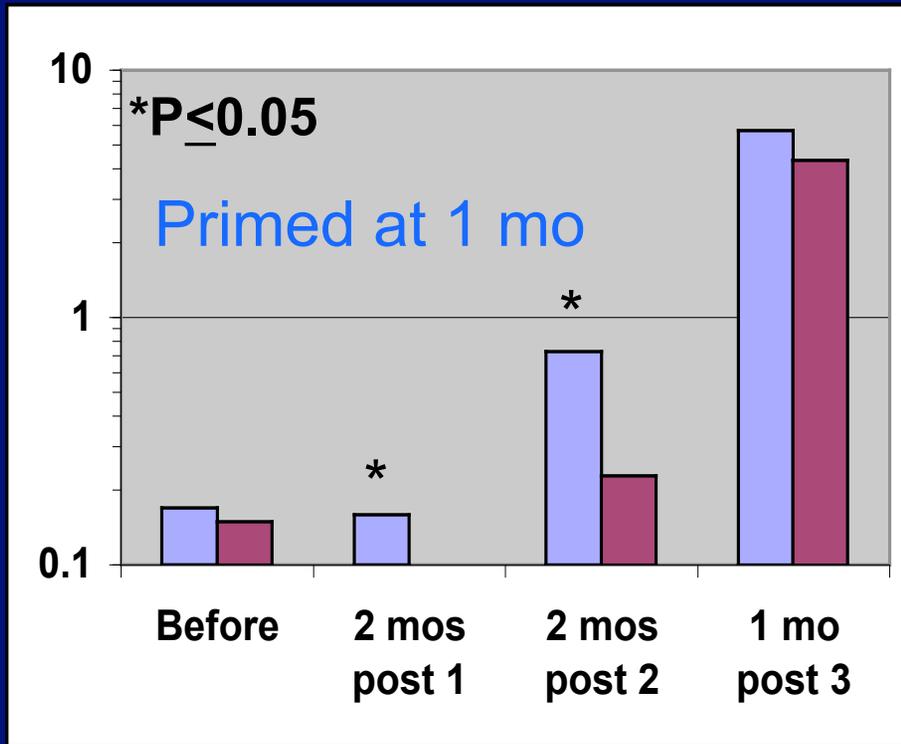
Lieberman et al, J. Pediatrics 1995

Priming with Diphtheria and Tetanus Toxoids at 1 Mo.

HbOC†

PRP-T†

Geo. Mean



Granoff et al
JAMA 1994

†2, 4 & 6 mos
with DTwP

†Post 3 PRP-T: 13 µg/ml for primed Vs.
7.4 µg/ml for unprimed (P<0.05)

Response to Plain PRP Booster at age 12 mos.

Anti-PRP (Geometric Mean $\mu\text{g/ml}$)

DT Primed	HbOC-Immunized		PRP-T-Immunized	
	Before	1 mo Post	Before	1 mo Post
Yes	1.2	6.0	2.6	24.4*
No	0.9	6.9	1.5	8.4*

*P<0.05

Granoff et al, JAMA 1994

Summary of Newborn Hib Immunization or Carrier Priming

- **Conjugate vaccines** - Slight enhancement of antibody levels at 4 months, which are not sustained (PRP-T or HbOC), or which are associated with depressed anti-PRP antibody levels up to 1 year (PRP-OMP)
- **DT priming on anti-PRP antibody levels**
 - No significant enhancement
 - Depression at 6 to 7 months

Summary of DT Carrier Priming at 1 Month of Age

- **HbOC**

- 2 to 3-fold enhanced anti-PRP antibody levels at 4 and 6 months, as compared to that of unprimed infants
- No effect on PRP booster response

- **PRP-T**

- 2- to 3-fold enhanced anti-PRP antibody levels at 4, 6 and 7 months, and 3-fold increase in antibody response to PRP booster at 12 months

PRP-OMP Immunization at Age 1 mo?

- One injection of PRP-OMP at 2 mos. of age is immunogenic without suppression
 - 80% $\geq 1 \mu\text{g/ml}$ of antibody (Granoff et al, J Peds 1992)
- PRP-OMP beginning at age 2 mos. also
 - Highly effective in eliminating disease in Alaskan natives
 - Primes for high booster antibody responses to PRP-T or HbOC

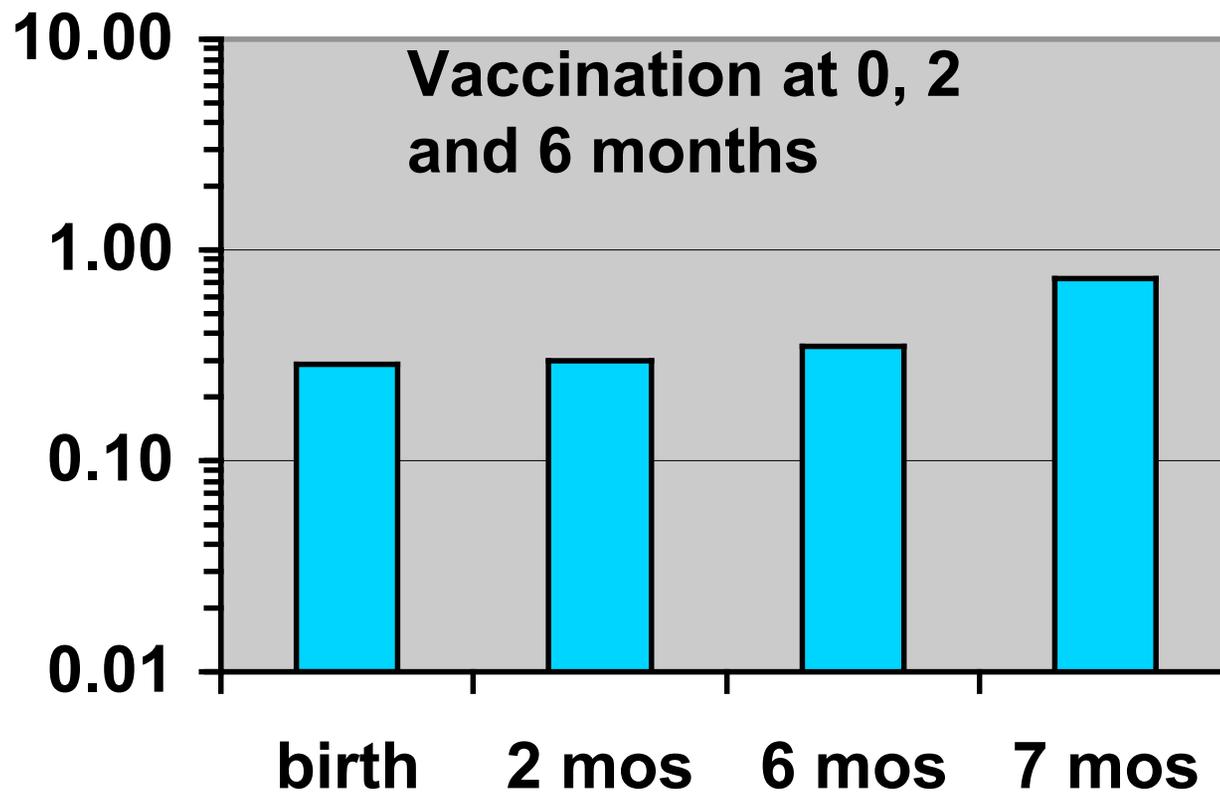
Acknowledgements

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 - Yechiel Schlesinger and Jacob Amir
 - Sandra Holmes and Farukh Azmi

Extra Slides Not Shown

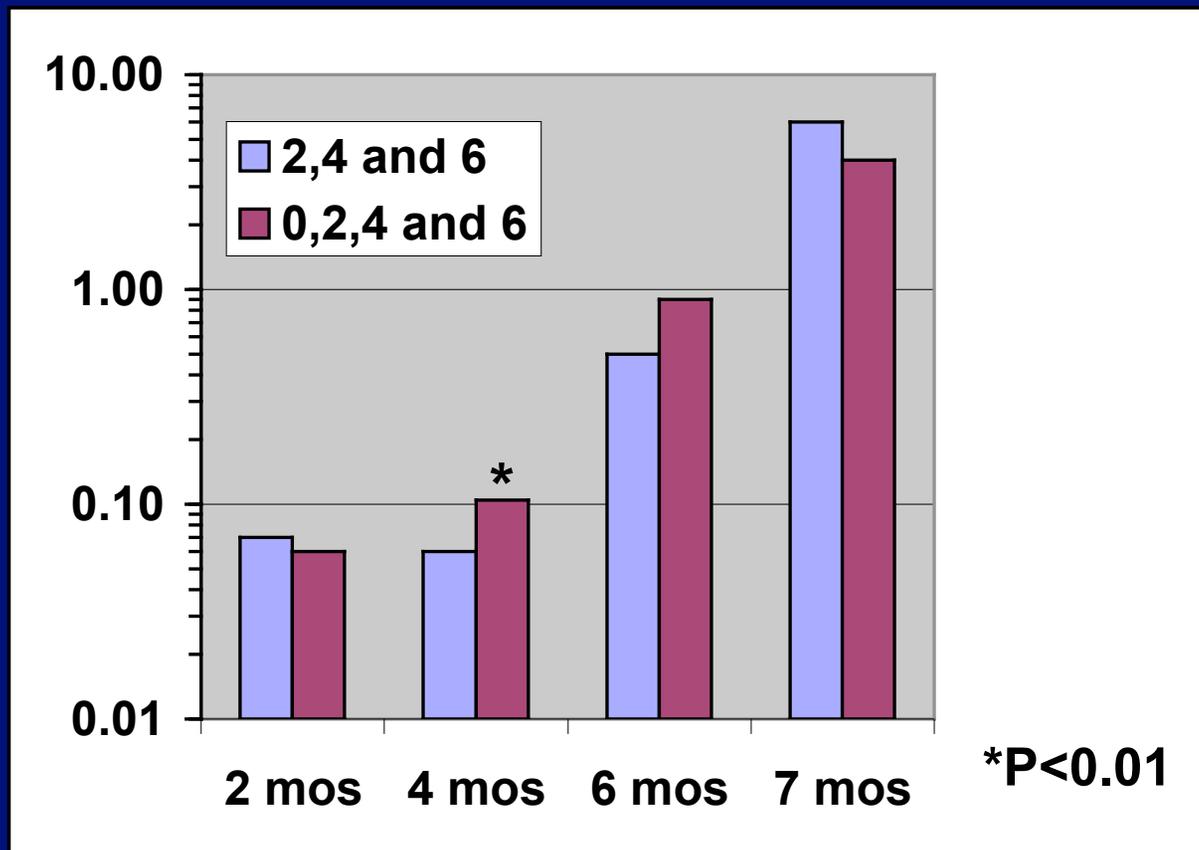
PRP-OMP Vaccination of Newborns in Atlanta GA

Anti-PRP, $\mu\text{g/ml}$
Geo. Mean



Keyserling and
Wickliffe, ICAAC,
1990

Newborn HbOC Vaccination



Conclusions

Transient increase in anti-PRP antibody levels at 4 months of age, which were not sustained

Lieberman et al,
J. Pediatrics 1995