BRIEFING PACKET

Antibody Responses to a Combined DTaP/Hib Vaccine with OPV or IPV; Variability of Anti-PRP Responses at Different Clinical Sites

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Objectives

- To compare the antibody responses to PRP 1 month after 3 doses of a DTaP/PRP-T vaccine when given with OPV or IPV at 2 and 4 months of age.
- To evaluate the antibody responses to diphtheria and tetanus toxoids, pertussis antigens (PT and FHA) and poliovirus.

Subjects

- Healthy 2 month old infants with no prior immunizations.
- Recruited from private pediatric practices in suburban Chicago and New Orleans.
- Original enrollment target was N= 450.

Study Design - I

Vaccination Schedule

	Age in Months			
	2	**4**	**6**	**7**
Group A	OPV	OPV		
Group B	IPV	IPV		
Other	DTaP/PRP-T Hepatitis B	DTaP/PRP-T Hepatitis B	DTaP/PRP-T	
Bleed	*			*

Study Design - II

Subjects with

* anti-PRP < 0.15 ug/ml
* anti-diphtheria < 0.01 U/ml
* anti-tetanus < 0.01 equi/ml

were offered an additional dose of PRP-T or DTaP.

FDA "clinical hold"

On June 16, 1998, the FDA placed a "clinical hold" on further enrollment. Preliminary results from a similar study being conducted by the NIH Vaccine Evaluation Units suggested interference in the immune response to PRP-T when DTaP/PRP-T was administered concurrently with IPV.

Results - I

- 356 subjects were enrolled at "clinical hold".
- 128 were excluded from the data analysis:
  - 110 - subjects had completed < 3 of the scheduled immunization visits.
  - 18 - moved, no-compliance, adverse reaction, parental request.
- 228 subjects were included in the analysis.

Results - II

N = 228

Gender - 118 male

110 female

Ethnicity - 205 Caucasian

11 African-American

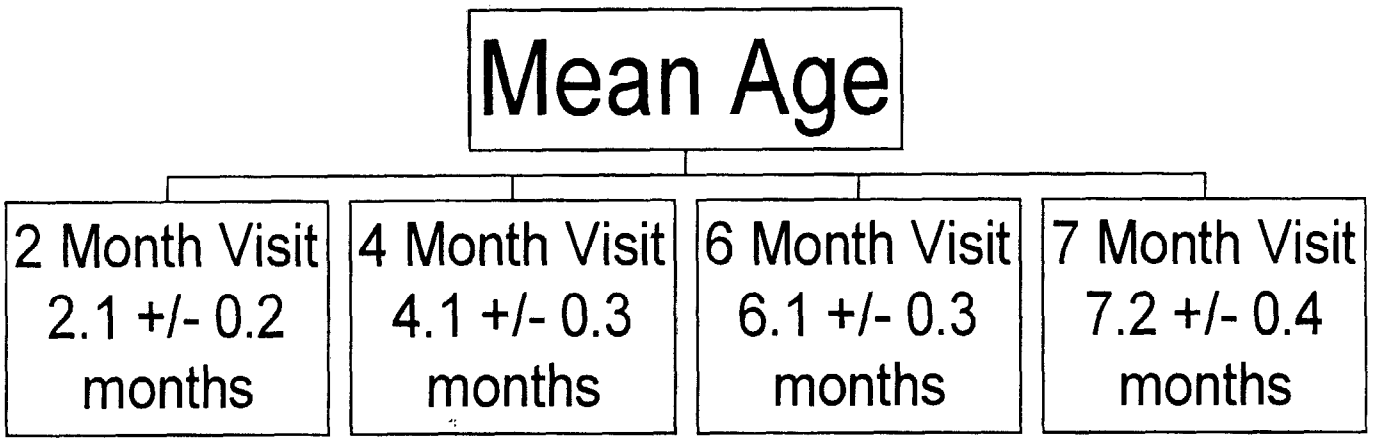
8 Hispanic

1 Asian

3 of "mixed" descent

Results - III

N = 228



Anti-PRP Ab Response (µg/ml) - I

GMT (95% CI)*

Group	N	2 Months	7 Months	7 Months	
Overall				% ≥ 0.15	% ≥ 1.00
A (OPV)	125	0.09 (0.07, 0.12)	3.12 (2.39, 4.07)	95.2 (91.5, 99.0)	76.8 (69.4, 84.2)
B (IPV)	103	0.07 (0.05, 0.09)	2.44 (1.73, 3.42)	90.3 (84.6, 96.0)	73.8 (65.3,82.3)
Total	228				

*GMT = Geometric Mean Titer, CI = Confidence Interval

Ab response to other antigens

- The type of polio immunization received did not influence the Ab response to:

  anti-diphtheria

  anti-tetanus

  anti-PT (ELISA & CHO)

  anti-FHA

  anti-poliovirus, type 3.

- Types 1 & 2 - OPV significantly higher.

Anti-PRP Ab Response (μg/ml) - II

Group	N	2 Months	7 Months	7 Months	
				% ≥ 0.15	% ≥ 1.00
Chicago					
A (OPV)	62	0.09 (0.06, 0.13)	4.52[1] (3.18, 6.42)	100.0[3] (94.2, 100)	80.7 (70.9, 90.5)
B (IPV)	64	0.07 (0.05, 0.09)	3.32[2] (2.29, 4.79)	95.3[4] (90.1, 100)	81.3[5] (71.8, 90.9)
Total	126				
New Orleans					
A (OPV)	63	0.09 (0.07, 0.13)	2.17[1] (1.47, 3.19)	90.5[3] (83.3, 97.7)	73.0 (62.0, 84.0)
B (IPV)	39	0.07 (0.05, 0.10)	1.47[2] (0.76, 2.84)	82.0[4] (69.9, 94.1)	61.5[5] (46.2, 76.8)
Total	102				

[1] $P = 0.0057$, [2] $P = 0.0331$, [3] $P = 0.028$, [4] $P = 0.039$, [5] $P = 0.048$

Anti-PRP Ab Response (µg/ml) - III

Group	N	2 Months	7 Months	7 Months	
Site				% ≥ 0.15	% ≥ 1.00
Chicago	126	0.08 (0.06, 0.10)	3.86[1,2] (3.00, 4.97)	97.6[4] (95.0, 100.0)	81.0[6] (74.1, 87.8)
Metairie	76	0.08 (0.06, 0.11)	2.43[1,3] (1.67, 3.55)	92.1[5] (86.1, 98.2)	75.0[5] (65.3, 84.7)
Destrehan	26	0.08 (0.05, 0.14)	0.86[2,3] (0.42, 1.78)	73.1[4,5] (56.0, 90.1)	50.0[6,5] (30.8, 69.2)

[1] $P = 0.03$, [2] $P = 0.0001$, [3] $P = 0.005$, [4] $P < 0.001$, [5] $P = 0.03$, [6] $P = 0.001$

Ab response to other antigens

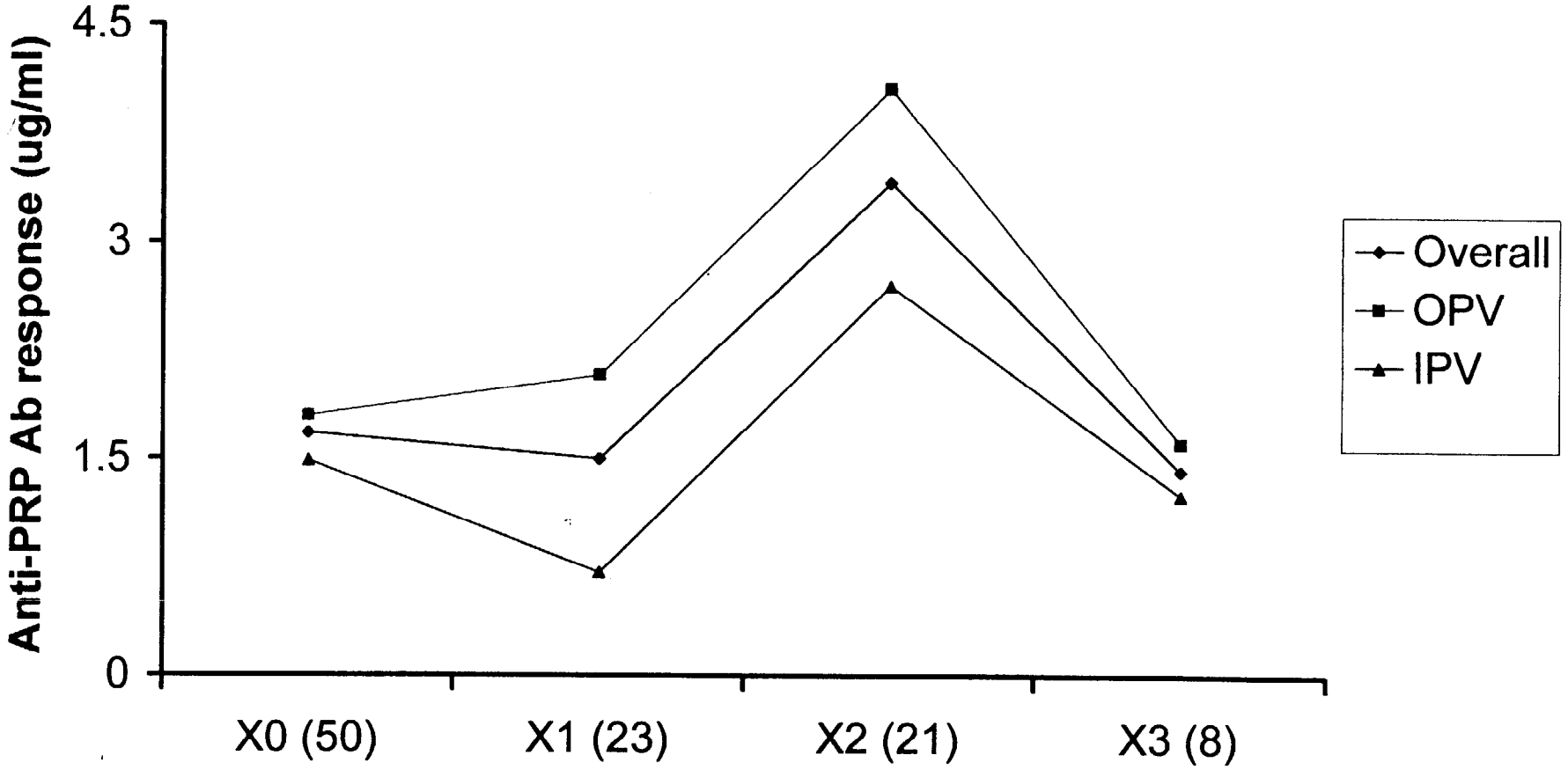
(stratified by sites)

- Mean antibody concentrations for all other vaccine antigens did not differ among infants from Destrehan, Metairie, and Chicago with 1 exception.
- Anti-poliovirus, type 1 was significantly lower for Metairie infants compared to Chicago infants.

Possible Explanations for Site Differences in the Mean Anti-PRP Ab Response

- Differences in vaccine and sera transportation.
- Differences in handling and mixing vaccines.
- "Faulty" refrigerator/freezer at the New Orleans site.
- Differences in vaccine administration.

Impact of "faulty" refrigerator



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Impact of the "faulty" refrigerator/freezer Anti-PRP Ab response (μg/ml) - I

GMT (95% CI)

Group	N	Overall	Group A	Group B
X_0	50	1.68 (1.02, 2.76)	1.80 (1.08, 3.02)	1.49 (0.51, 4.38)
X_1	23	1.50 (0.72, 3.10)	2.08 (0.92, 4.69)	0.71 (0.12, 4.16)
X_2	21	3.41 (1.88, 6.20)	4.06 (1.64, 10.04)	2.70 (1.09, 6.71)
X_3	8	1.42 (0.15, 13.25)	1.61 (0.02, 138.98)	1.25 (0.01, 139.37)

Impact of the "faulty" refrigerator/freezer Anti-PRP Ab response (μg/ml) - II

		% ≥ 0.15			% ≥ 1.00		
Group	N	Overall	Group A	Group B	Overall	Group A	Group B
X_0	50	88.0 (79.0, 97.0)	93.6 (86.8, 100)	79.0 (67.7, 90.3)	62.0 (48.5, 75.5)	61.3 (47.8,75.0)	63.2 (49.8, 76.6)
X_1	23	87.0 (73.3, 100)	87.5 (73.9, 100)	85.7 (71.4, 100)	73.9 (56.0, 91.8)	81.3 (65.4, 97.2)	57.1 (36.9, 77.3)
X_2	21	95.2 (86.1, 100)	91.7 (79.9, 100)	100.0 (83.9, 100)	81.0 (64.2, 97.8)	91.7 (79.9, 100)	66.7 (46.5, 86.9)
X_3	8	62.5 (29.0, 96.0)	75.0 (45.0, 100)	50.0 (15.3, 84.6)	62.5 (29.0, 96.0)	75.0 (45.0, 100)	50.0 (15.4, 84.6)

Site Differences in Vaccine Administration Technique

	Chicago	New Orleans
Needle length	5/8	1
Needle gauge	25	23
Angle of injection	90°	45°
Skin around injection site	tented	flat

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Non-Responders - I

- 16 subjects had an anti-PRP Ab response < 0.15 μg/ml.
- 15 received an additional dose
  - 3 Chicago, IL.
  - 5 Metairie, LA.
  - 7 Destrehan, LA.

Non-Responders - II

N = 12

	Pre	Post
Age	11.8 ± 0.9 m	13.6 ± 1.1 m
Anti-PRP (μg/ml)	0.04	5.24
>1.0 (μg/ml)	0/12	11/12 (92%)

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Conclusions - I

- Concurrent IPV administration with DTaP/PRP-T did not result in significant interference.
- The mean anti-PRP Ab response was significantly lower for New Orleans infants compared with Chicago infants.

Conclusion - II

- The difference in the mean anti-PRP Ab response among sites does not appear to be caused by the "faulty" refrigerator/freezer or vaccine administration technique differences.
- 11/12 non-responders had an anti-PRP Ab response > 1.0 μg/ml after an extra dose of PRP-T.