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Concomitant Use of VAQTA™ with PedvaxHIB™ and Infanrix™in 12 to 17 Month Old Children

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Background

- VAQTA™ (Hepatitis A [HepA] vaccine, inactivated)
  - Immunization against hepatitis A virus in persons 12 months of age and older
  - A primary and booster dose administered 6 to 18 months apart
  - Efficacious, immunogenic, and well tolerated
- Infanrix™ (diphtheria/tetanus/acellular pertussis [DTaP] vaccine)
  - Immunization against diphtheria, tetanus and pertussis in infants and children 6 weeks to 7 years of age
  - DTaP components of Infanrix™ are the same as those respective components of Pediarix™
  - 3 doses, in 6- to 8-week intervals, beginning at 2, 4, and 6 months of age
  - 2 booster doses administered at 15 months and 4 to 6 years of age
- PedvaxHIB™ (*H. influenzae* type b [Hib] conjugate vaccine [Meningococcal protein conjugate])
  - Immunization against invasive disease caused by Hib in children 2 to 71 months of age
  - 2 primary doses administered at 2 to 4 months, and 1 booster dose at 12 to 15 months of age
  - Well tolerated and immunogenic
- Advisory Committee on Immunization Practices (ACIP), American Academy of Family Physicians (AAFP), and American Academy of Pediatrics (AAP) recommend that children 12 and 23 months of age receive vaccines with antigens including hepatitis B, DTaP, Hib, polio, pneumococcal, measles, mumps, rubella, and varicella
- HepA vaccine administered to children 12 to 23 months of age would likely be given concomitantly with one or more of the vaccines recommended by these recommending bodies

Study Design

- Evaluated the immunogenicity, safety, and tolerability of the of HepA vaccine administered concomitantly versus non-concomitantly with Hib and DTaP vaccines
- Open-label, multicenter, randomized, comparative clinical trial
  - Healthy children
  - Conducted across 53 sites in the United States
  - From April 2006 to June 2010
  - Stage 1: concomitant use (Groups 1-4; randomized 1:1 ratio)
    - ≥15 months old at study entry
    - Subjects must have received at least 2 doses of COMVAX™ or PedvaxHIB™ or 3 doses of ActHIB™ prior to 12 months of age
  - Stage 2: safety cohort sub-study (Group 5)
  - 12-17 months old at study entry
  - No Hib vaccination history requirement
  - Enrollment for Group 5 initiated after Stage 1 enrollment completed
- Study subjects assigned to five groups
  - Group 1: HepA + Hib + DTaP (investigational/concomitant group)
  - Group 2: Hib + DTaP followed by HepA (control/non-concomitant group)
  - Group 3: HepA + Hib (investigational/concomitant group)
  - Group 4: Hib followed by HepA (control/non-concomitant group)
  - Group 5: HepA alone (safety cohort sub-study) (no concomitant vaccinations)
- Immunogenicity hypotheses were evaluated using a sequential testing strategy
  - Noninferiority of HAV SPR in Groups 1+3 vs. Groups 2+4
  - Noninferiority of PRP response rate in Groups 1+3 vs. Groups 2+4
  - Noninferiority of pertussis GMTs in Group 1 vs. Group 2

Vaccination and Blood Draw Timelines

		Time Points					
		Visit 1	Visit 2	Visit 3		Visit 4	
Group	N	Day 1	Week 4	Week 24	Week 28	Week 28	Week 32
1*	155	HepA+Hib+DTaP (serology)	(serology)	HepA	NA	(serology)	NA
2†	151	Hib+DTaP (serology)	HepA (serology)	NA	HepA	NA	(serology)
3‡	159	HepA+Hib (serology)	(serology)	HepA	NA	(serology)	NA
4§	152	Hib (serology)	HepA	NA	HepA	NA	(serology)
5‖	654	HepA	NA	HepA	NA	NA	NA

* Serum samples from subjects in Group 1 were tested for antibodies to hepatitis A, PRP, diphtheria, tetanus, pertussis PT, FHA, and pertactin at Day 1; antibodies to PRP, diphtheria, tetanus, pertussis PT, FHA, and pertactin at Week 4; and hepatitis A at Week 28

† Serum samples from subjects in Group 2 were tested for antibodies to PRP, diphtheria, tetanus, pertussis PT, FHA, and pertactin at Day 1 and Week 4, and hepatitis A at Week 4 and at Week 32

‡ Serum samples from subjects in Group 3 were tested for antibodies to hepatitis A and PRP at Day 1; antibodies to PRP at Week 4; and hepatitis A at Week 28

§ Serum samples from subjects in Group 4 were tested for antibodies to PRP at Day 1 and Week 4, and hepatitis A at Week 4 and Week 32

‖ Safety Cohort Sub-Study; no other vaccines administered; no immunogenicity testing

Clinical Assessment Schedule

	Timing of Safety Data Collection		
Vaccination Time Point	Temperatures	Injection-Site AEs	Systemic AEs
Day 1 (Visit 1)*	Days 1 through 5	Days 1 through 5	Days 1 through 14
Days 1 through 5	Days 1 through 5	Days 1 through 5	Days 1 through 14
Week 24 or 28 (Visit 3)*	Days 1 through 5	Days 1 through 5	Days 1 through 14

* Safety cohort (Group 5) only collected safety data for Visit 1 and Visit 3 (Week 24).

Study Objectives

- HepA vaccine can be administered concomitantly with (1) Hib and DTaP vaccines or (2) Hib vaccine without impairing the antibody response to any of the antigens
- HepA vaccine administered concomitantly with Hib and DTaP vaccines is generally well tolerated
- Safety Cohort Sub-Study (Group 5): Demonstrate the safety and tolerability of 2 doses of HepA vaccine in children

Statistical Methods

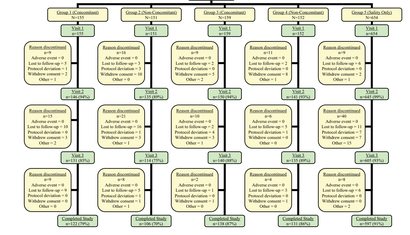
- Non-inferiority of the seroprotection rate (SPR) to hepatitis A corresponded to the lower bound of the 2-sided 95% CI on the difference in SPRs (Groups 1+3 minus Groups 2+4, or Group 1 minus Group 2), excluding a decrease of ≥10%
- Non-inferiority of the antibody response rate for PRP corresponded to the lower bound of the 2-sided 95% CI on the difference (Group 1+3 minus Group 2+4), excluding a decrease of ≥10%
- Non-inferiority of geometric mean titers (GMTs) for pertussis PT, FHA, and pertactin corresponded to the lower bound of the 2-sided 95% CI for the ratio of GMTs, Group 1/Group 2, being >0.5 for each antigen
  - secondary endpoint: diphtheria and tetanus GMTs (Groups 1 and 2 only) and proportions of subjects with anti-diphtheria and anti-tetanus titers ≥0.1 IU/mL (no hypothesis testing)
- All subjects who were vaccinated and had safety follow-up data were included in the safety analyses and summaries
- Analysis of safety data included risk differences, 95% CIs for the risk difference, and p-values for the comparisons of the groups for injection-site adverse experiences (including redness, swelling, and pain/tenderness) solicited on the vaccine report card (VRC) during Days 1 to 5
- Analysis of safety data also included a comparison between vaccination groups for body temperatures collected within Days 1 to 5

Demographics

	Group 1 (N=155)		Group 2 (N=151)		Group 3 (N=159)		Group 4 (N=152)		Group 5 (N=654)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gender										
Male	81	(52.3)	84	(55.6)	89	(56.0)	79	(52.0)	335	(51.2)
Female	74	(47.7)	67	(44.4)	70	(44.0)	73	(48.0)	319	(48.8)
Age (months)										
Mean [SD]	15.0 [0.14]		15.0 [0.00]		15.0 [0.11]		15.0 [0.11]		13.2 [1.49]	
Median	15		15		15		15		12	
Range	14 to 16		15 to 15		14 to 16		14 to 15		12 to 18	
Race										
White	102	(65.8)	98	(64.9)	102	(64.2)	92	60.5	432	(66.1)
Black	15	(9.7)	19	(12.6)	29	(18.2)	28	(18.4)	110	(16.8)
Hispanic	35	(22.6)	31	(20.5)	21	(13.2)	21	(13.8)	69	(10.6)
Other	3	(1.9)	3	(2.0)	7	(4.4)	11	(7.2)	43	(6.6)

N = Number of subjects randomized in the vaccination group
n = Number of subjects in each category

Subject Accounting



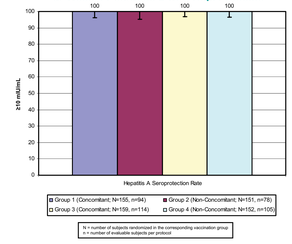
Results

Geometric Mean Titers at Week 4 Postdose 4

Parameter	Group 1 (Concomitant) N = 155			Group 2 (Non-Concomitant) N = 151			Group 3 (Concomitant) N = 159			Group 4 (Non-Concomitant) N = 152		
	n	Observed Response	(95% CI)	n	Observed Response	(95% CI)	n	Observed Response	(95% CI)	n	Observed Response	(95% CI)
Hepatitis A	94	3672.6	(2874.4, 4692.4)	78	4273.5	(3312.2, 5513.9)	114	3570.8	(2889.1, 4413.4)	105	5067.8	(4073.0, 6305.5)
Hib capsular PRP	106	17.9	(13.6, 26.3)	99	17.6	(13.0, 23.8)	110	18.4	(13.9, 24.3)	109	18.1	(13.7, 24.0)
Pertussis PT	85	69.2	(57.4, 83.5)	83	51.7	(41.5, 64.5)						
Pertussis FHA	85	253.8	(215.3, 299.2)	83	249.2	(200.6, 309.5)						
Pertactin	85	333.5	(267.3, 416.1)	83	358.5	(282.7, 454.7)						
Diphtheria	97	3.6	(3.1, 4.2)	69	4.3	(3.6, 5.1)						
Tetanus	98	8.3	(7.0, 9.8)	69	8.3	(6.4, 10.6)						

N = number of subjects randomized in the corresponding vaccination group
n = number of evaluable subjects per protocol

Hepitiitis A Seroprotection Rates at Week 4 Postdose 2 with HepA Vaccine



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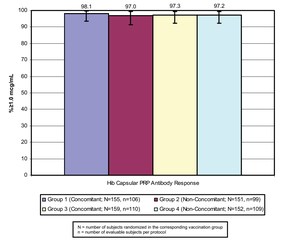
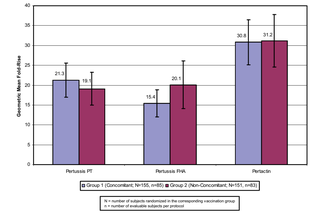
n = number of evaluable subjects per protocol

Hib Capsular PRP Antibody Response Rate at Week 4 Postdose with Hib Vaccine



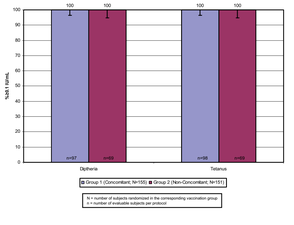
N = number of subjects randomized in the corresponding vaccination group
n = number of evaluable subjects per protocol

Pertussis PT, Pertussis FHA, and Pertactin Geometric Mean Fold-Rises at Week 4 Postdose with DTaP Vaccine



N = number of subjects randomized in the corresponding vaccination group
n = number of evaluable subjects per protocol

Diphtheria and Tetanus Responses at Week 4 Postdose with DTaP Vaccine



N = number of subjects randomized in the corresponding vaccination group
n = number of evaluable subjects per protocol

Statistical Analysis for Non-inferiority of Antibody Respoonses

Parameter	Groups 1 and 3 (Concomitant) N=314		Groups 2 and 4 (Non-concomitant) N=303		Difference	
	n	Estimated Response	n	Estimated Response	(95% CI)	P value
Seropositivity Rate Analysis (% Difference) for HepA Antibody						
% ≥10 mIU/mL	208	100%	183	100%	0.0% (-1.8, 2.1)	<0.001
Response Rate Analysis (% Difference) for PRP Antibody						
% >1.0 mcg/mL	216	97.7%	208	97.1%	0.6% (-2.8, 4.1)	<0.001
Geometric Mean Titer Analysis (Fold-Difference) for DTaP Components						
Pertussis PT	85	68.6	83	54.0	1.3 (1.0, 1.7)	<0.001
Pertussis FHA	85	253.9	83	256.6	1.0 (0.8, 1.3)	<0.001
Pertactin	85	345.8	83	330.1	1.0 (0.8, 1.4)	<0.001

Adverse Experiences Summary

	Groups 1 and 3 (Concomitant) (N=314)			Groups 2 and 4 (Non-Concomitant) (N=303)			Group 5 (Safety Cohort) (N=654)	
	n	Observed Response	(95% CI)	n	Observed Response	(95% CI)	Observed Response	(95% CI)
Subjects with follow-up	302	(96.2)		291	(96.0)		647	(98.9)
With one or more AE	240	(79.5)		228	(78.4)		466	(72.0)
Injection-site AEs*	190	(62.9)		179	(61.5)		249	(38.5)
Systemic AEs	170	(56.3)		163	(56.0)		395	(61.1)
With vaccine-related AEs†	201	(66.6)		190	(65.3)		328	(50.7)
Injection-site AEs*†	186	(61.6)		177	(60.8)		249	(38.5)
Systemic AEs†	78	(25.8)		80	(27.5)		147	(22.7)
With serious AEs	0	(0.0)		4	(1.4)		2	(0.3)
Serious vaccine-related AEs	0	(0.0)		0	(0.0)		0	(0.0)
Who died	0	(0.0)		0	(0.0)		0	(0.0)
Discontinued due to AE	0	(0.0)		0	(0.0)		0	(0.0)

N = Number of subjects randomized and vaccinated in the vaccination group
n = Number of subjects in each category
* Injection-site AE summary data include any injection-site at any visit
† Determined by the investigator to be possibly, probably, or definitely related to the vaccine
The same subject may appear in different categories, but counted only once in each category

VRC-Prompted Injection-Site Adverse Experiences (Days 1 to 5 Following Any Vaccination)

	Groups 1 and 3 (Concomitant)		Groups 2 and 4 (Non-Concomitant)		Group 5 (Safety Cohort)	
	n	%	n	%	n	%
Injection Site for HepA Vaccine Dose 1						
Number of Subjects Vaccinated	314		303		654	
Subjects with follow-up	302		256		647	
With ≥1 injection-site AE	136	(45.0)*	73	(28.5)*	161	(24.9)
Erythema	60	(19.9)	46	(18.0)	76	(11.7)
Pain/Tenderness	110	(36.4)*	56	(21.9)*	130	(20.1)
Swelling	43	(14.2)	26	(10.2)	46	(7.1)
Injection Site for HepA Vaccine Dose 2						
Number of Subjects Vaccinated	314		303		605	
Subjects with follow-up	261		242		599	
With ≥1 injection-site AE	87	(33.3)	85	(35.1)	170	(28.4)
Erythema	57	(21.8)	51	(21.1)	97	(16.2)
Pain/Tenderness	70	(26.8)	68	(28.1)	137	(22.9)
Swelling	27	(10.7)	23	(9.5)	42	(7.0)
Injection Site for Hib Vaccine						
Number of Subjects Vaccinated	314		303			
Subjects with follow-up	302		291			
With ≥1 injection-site AE	165	(54.6)	157	(54.0)		
Erythema	96	(31.8)	95	(32.6)		
Pain/Tenderness	128	(42.4)	123	(42.3)		
Swelling	68	(22.5)	63	(21.6)		
Injection Site for Hib Vaccine						
Number of Subjects Vaccinated	155		151			
Subjects with follow-up	150		145			
With ≥1 injection-site AE	89	(59.3)	77	(53.1)		
Erythema	51	(34.0)	47	(32.4)		
Pain/Tenderness	76	(50.7)	64	(44.1)		
Swelling	42	(28.0)	35	(24.1)		

* Risk difference p-value <0.001
The same subject may appear in different categories, but counted only once in each category
n = Number of subjects in the respective category

Elevated Temperatures (Days 1 to 5 After Any Dose of HepA Vaccine)

Temperature	Groups 1 and 3 (Concomitant)		Groups 2 and 4 (Non-Concomitant)		Group 5 (Safety Cohort)	
	n	%	n	%	n	%
<102.2 °F (<39.0 °C)	275	(94.2)	235	(94.0)	606	(95.3)
≥102.2 °F (≥39.0 °C)	17	(5.8)	15	(6.0)	30	(4.7)

N = Number of subjects vaccinated with follow-up
n = Number of subjects in the respective category

Serious Clinical Adverse Experiences

Adverse Experience	Age at Enrollment (months)	Day of Onset	Vaccine Relationship
Group 2 (Non-Concomitant)			
Buttock Abscess	16	12 days post-visit 2	Definitely Not
Asthma exacerbation	23	229 days post-visit 4	Definitely Not
Group 4 (Non-Concomitant)			
(1) Pyrexia	15	5 days post-visit 2	Definitely Not
(2) Vomiting		7 days post-visit 2	Probably Not
(3) Dehydration		8 days post-visit 2	Probably Not
(1) Otitis media	15	7 days post-visit 2	Definitely Not
(2) Pneumonia		7 days post-visit 2	Definitely Not
Group 5 (Safety Cohort Sub-Study)			
Lymphadenitis	12	5 days post-visit 2	Probably Not
Foreign body in lung	18	199 days post-visit 4	Definitely Not

Note: No serious AEs occurred in concomitant Groups 1+3

Conclusions

In healthy children 12 to 17 months of age with a negative clinical history of hepatitis A who received HepA vaccine as a 2-dose regimen at least 6 months apart administered concomitantly or non-concomitantly with DTaP and Hib vaccines or Hib vaccine:

- Immune responses to HepA, Hib and DTaP vaccines given concomitantly were non-inferior to each vaccine given non-concomitantly
- HepA vaccine displays an acceptable safety profile when given alone or concomitantly with DTaP and Hib vaccines or Hib vaccine
  - No vaccine-related serious AEs were observed
  - Incidence of VRC-prompted injection-site AEs at the Dose 1 HepA vaccine injection site was higher in the concomitant group than the non-concomitant group
    - Majority of injection-site AEs were mild (<1% severe in both groups)
  - No serious AEs occurred in concomitant Groups 1+3
- DTaP and Hib vaccines display acceptable safety profiles when administered concomitantly with HepA vaccine

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