Pentacel®

DTaP-IPV/Hib Combined

Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and *Haemophilus* b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined

VRBPAC Briefing Document

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse Event
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CPDT	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Daptacel, formerly TRIPACEL™)
DTaP-IPV/Hib	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and *Haemophilus* b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined (Pentacel)
DTwP	Diphtheria, Tetanus, whole-cell Pertussis Vaccine
eBLA	Electronic Biologic License Application
ELISA	Enzyme-linked Immunosorbent Assay
FDA	Food and Drug Administration
FE	Formulation Equivalent
FHA	Filamentous Hemagglutinin
FIM	Fimbriae Types 2 and 3
GMT	Geometric Mean Titer
HCPDT	Component Pertussis Vaccine with Diphtheria and Tetanus Toxoids Adsorbed
HCPDT-IPV	Component Pertussis Vaccine with Diphtheria and Tetanus Toxoids Adsorbed and Inactivated Poliomyelitis Vaccine (Quadracel)
HHE	Hypotonic-Hyporesponsive Episode
Hib	*Haemophilus influenzae* type b
IMPACT	Health Canada Immunization Monitoring Program, Active
IND	Investigational New Drug
LOQ	Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles, Mumps and Rubella vaccine
NA	Not applicable
NEC	Not Elsewhere Classified

NOS	Not Otherwise Specified
PI	Package Insert
PP	Per-Protocol
PRN	Pertactin
PRP-T	Polyribosylribitol Phosphate conjugated to Tetanus Toxoid
PT	Pertussis Toxoid
SAE	Serious Adverse Event
SC	Standard of Care
SIDS	Sudden Infant Death Syndrome
SOC	System Organ Class

1 Overview

The clinical and epidemiological data summarized in this document support the following observations for Pentacel® vaccine:

- The clinical safety profile of Pentacel vaccine compares favorably to that of the separate administration of its licensed-equivalent component vaccines (Daptacel, IPOL, and ActHIB vaccines) or formulation-equivalent components (HCPDT, Poliovax, and ActHIB). Subjects who received Pentacel vaccine were equally or less likely to experience vaccine reactions (i.e., solicited local and systemic) than were subjects who received the separate administration of its licensed-equivalent vaccines or formulation-equivalent components. There were no SAEs or seizures that the Investigators considered to be related to Pentacel vaccine, and no HHEs were reported. Pentacel has a proven track record of safety with over 9 years of exclusive use in Canada.
- The efficacy of Pentacel vaccine based on immunogenicity outcomes has been demonstrated to be comparable to the separate administration of the US-licensed equivalent vaccines (Daptacel®, IPOL®, and ActHIB®) in Study P3T06; to the separate administration of its constituent components in Study 494-01, and to the antibody levels associated with 85% efficacy against Word Health Organization-defined pertussis in the Pertussis Serology Bridge Study, and is supported by the comparable immune responses elicited by Pentacel vaccine in study M5A07.
- Pentacel does not adversely affect the immunogenicity of concomitantly administered vaccines, nor do concomitantly administered vaccines affect the immunogenicity of Pentacel.
- Data from surveillance studies in Canada demonstrate that the use of Pentacel and Quadracel® (HCPDT-IPV) vaccines over the past 9 years has led to sustained control of pertussis among infants and children aged <10 years.
- Similarly, Pentacel vaccine use in Canada has been associated with excellent control of invasive Hib disease in children aged <5 years.

Pentacel vaccine has the advantage of integrating easily into the current routine and recommended immunization schedule of the Advisory Committee on Immunization Practices and American Academy of Pediatrics.

Background Information

Pentacel vaccine is diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, and *Haemophilus* b conjugate (tetanus toxoid conjugate) vaccine combined. The components of Pentacel are included, individually (ActHIB) or in combination (the HCPDT and IPV components), in products that are licensed and commercially available in numerous markets around the world, including the United States. The compositions of the vaccines referenced in this document are shown in Table 1. Daptacel (which is licensed and distributed in the US as a stand-alone vaccine) and HCPDT (the DTaP component of Pentacel vaccine, which is not licensed or used as a stand-alone vaccine) differ in the amount of PT and FHA antigens that they contain. Poliovax® (the IPV component of Pentacel vaccine, which is licensed but not co-administered with HCPDT and ActHIB) and IPOL (the IPV vaccine licensed and distributed in the US) contain the same 3 polio antigens, but differ in their manufacturing technology. ActHIB is the same vaccine as the currently licensed standard of care in the US. Pentacel vaccine consists of the

combined liquid HCPDT and Poliovax components, packaged with and used to reconstitute the ActHIB component at the time of immunization, thereby delivering 5 vaccines with a single injection.

Table 1: Composition of Pentacel and Control Vaccines

Antigen	Pentacel	Standard of Care (SC)			Formulation Equivalent (FE)		
		Daptacel	IPOL	ActHIB	HCPDT [1]	Poliovax	ActHIB
Diphtheria Toxoid	15 Lf	15 Lf			15 Lf		
Tetanus Toxoid	5 Lf	5 Lf			5 Lf		
PT [2]	20 µg	10 µg			20 µg		
FHA [3]	20 µg	5 µg			20 µg		
PRN [4]	3 µg	3 µg			3 µg		
FIM [5]	5 µg	5 µg			5 µg		
Poliovirus Type 1	40 DAU [6]		40 DAU			40 DAU	
Poliovirus Type 2	8 DAU		8 DAU			8 DAU	
Poliovirus Type 3	32 DAU		32 DAU			32 DAU	
PRP-T [7]	10 µg			10 µg			10 µg

[1] Component Pertussis Vaccine with Diphtheria and Tetanus Toxoids Adsorbed
[2] Pertussis toxoid
[3] Filamentous hemagglutinin
[4] Pertactin
[5] Fimbriae types 2 and 3
[6] D antigen units
[7] 10 µg Polyribosylribitol Phosphate conjugated to 24 µg Tetanus Toxoid, containing antigens against *H. influenzae* type b

An important feature of HCPDT-IPV (DTaP-IPV) is the fact that the acellular pertussis component consists of 5 purified antigens (PT, FHA, PRN, and FIM Types 2 and 3) that have been shown to be highly protective against whooping cough in infants (1). The sanofi pasteur 5-component acellular pertussis combination vaccines are unique among currently available vaccines in containing the FIM components. FIM has been shown to play a significant role in protection against pertussis and contributes importantly to the multiple protective antigens in the 5-component vaccine (2) (3) (4).

Pentacel vaccine is proposed to be indicated for active immunization against *H. influenzae* type b, *Bordetella pertussis, Corynebacterium diphtheriae*, *Clostridium tetani*, and Poliovirus Types 1, 2, and 3, beginning at age 2 months in a 3-dose Infant Series at 2, 4, and 6 months of age concluding at age 15 to 18 months with a 4th Dose.

Pentacel vaccine was first registered in Canada on 12 May 1997, and is currently licensed in Argentina, Australia, Brazil, Canada, Colombia, Israel, and Mexico. Between 1 May 1997 and 30 April 2006, a total of 13,546,580 doses of Pentacel were distributed worldwide, 12,543,855 (92%) of them in Canada.

Pentacel Clinical Development Program

The investigational new drug application (IND) for Pentacel vaccine was submitted to the Food and Drug Administration (FDA) on 21 July 1999. The clinical development program executed under this IND (BB-IND No. 8502) studied Pentacel vaccine with the intent of providing a combination vaccine that would align well with the existing US childhood immunization schedule and replace separate injections of DTaP, IPV and *H. influenzae* type b (Hib) conjugate vaccines in the first and second years of life. The overall goal of the clinical development program for Pentacel vaccine licensure in the United States was to demonstrate that this vaccine is safe and immunogenic when given as a 4-dose series for the prevention of *H. influenzae* type b disease, pertussis, diphtheria, tetanus, and poliomyelitis in infants and toddlers from 2 to 18 months of age. The electronic Biologics License Application (eBLA) for Pentacel vaccine was submitted to the Center for Biologics Evaluation and Research (CBER) on 26 July 2005.

The summary of the clinical development program for Pentacel vaccine is presented in Section 2 of this document. A total of 4 pivotal studies (Studies P3T06, 494-01, 494-03, and 5A9908) and 1 additional study (Study M5A07) were submitted to the eBLA and are described herein. These clinical studies were all Phase 3, randomized, multi-center trials conducted under BB-IND 8502. Four of the studies (Studies 494-01, 494-03, P3T06 and M5A07) were carried out in the United States, and the other (Study 5A9908) was conducted in Canada. The 4 clinical studies performed in the United States each consisted of 2 stages (Infant Series and 4th Dose), while the Canadian study looked at the 4th Dose only, in children who had already received 3 doses of Pentacel (which has been licensed in Canada since May 1997) as part of the Canadian standard of care. Two of the studies (P3T06 and 494-01) were controlled. Study P3T06 compared Pentacel vaccine to the US-licensed separate vaccines Daptacel, IPOL, and ActHIB, which represent a current standard of care in the United States and the use of which is likely to be replaced by use of Pentacel, if licensed (collectively, these 3 vaccines are referred to as the "licensed-equivalent vaccines" or "licensed standard-of-care vaccines"). Study 494-01 compared Pentacel to its constituent components (HCPDT, Poliovax, and ActHIB; collectively, termed "formulation-equivalent components"). Study 494-03 was designed to assess the safety and immunogenicity of a 4th Dose of Pentacel on other recommended vaccines during the second year of life. Study M5A07 was designed to assess the effect of Prevnar® on the immunogenicity of Pentacel throughout the 4-dose series (only the immunogenicity of the Infant Series was part of the licensing submission). The Pertussis Serology Bridge Studies were laboratory bridge studies designed to compare the anti-Pertussis responses from Studies P3T06 and 494-01 to those from the Sweden I Efficacy Trial which established the clinical efficacy of Daptacel against pertussis disease (1). The Canadian study (Study 5A9908) was designed to assess the safety and immunogenicity of a 4th Dose of Pentacel vaccine when administered at 15 to 16 versus 17 to 18 months of age in subjects who had received 3 doses of Pentacel as part of the recommended schedule of immunization in Canada.

Populations for Analyses

The Safety Population included all enrolled subjects who received at least 1 dose of Pentacel or Control vaccine. The assessments of the safety data after each dose of the Infant Series and 4th Dose (Toddler dose) were performed according to the vaccine actually received. For the overall Infant Series (3 doses combined), the assessment was performed according to randomization. The Safety Population definitions for the 4 pivotal studies (P3T06, 494-01, 494-03 and 5A9908) were identical.

The total safety population for the 4 pivotal studies combined consists of 8466 subjects, of whom 5980 received at least one dose of Pentacel. In the Infant Series studies, of the 6697 subjects randomized in the trials, 4198 subjects received at least 1 dose of Pentacel, 1032 received HCPDT, and 1454 received Daptacel. At the 4th Dose, 5033 subjects received Pentacel, 739 received HCPDT, and 418 received Daptacel. Only Group 1 from Study P3T06 4th Dose (Daptacel and ActHIB at 15 months of age) is presented in this document.

The immunogenicity results presented in this document are based on the Per-Protocol (PP) Immunogenicity Populations. The PP Immunogenicity Population for all studies consisted of subjects who satisfied the eligibility criteria, received the study Infant Series or 4th-dose vaccines (Pentacel or Control) according to randomization, the immunizations and blood sample visits occurred within the specified time intervals, and there was at least 1 valid serology result. For the Serology Bridge Study, the PP Immunogenicity Population was defined as above for Study 494-01 4th Dose with the addition that all subjects had to have received 3 doses of Prevnar vaccine concurrently with Pentacel vaccine during the Infant Series.

For all studies combined, there were 2670 Pentacel subjects and 1570 Control subjects after the Infant Series and 2207 Pentacel subjects and 640 Control subjects after the 4th Dose that were included in the PP Immunogenicity Population.

Table 2: Infant Series: Summary of the Analyzed Populations

Study	Safety Population		Intent-to-Treat Immunogenicity Population		Per-Protocol Immunogenicity Population	
	Pentacel	**Control**	**Pentacel**	**Control**	**Pentacel**	**Control**
P3T06	485	1454	404	1243	374	1167
494-01	2506	1032	1268 [1]	458 [1]	1136 [1]	403 [1]
494-03	1207	NA	307 [1]	NA	274 [1]	NA
M5A07	NA	NA	965	NA	886	NA
Total	**4198**	**2486**	**2944**	**1701**	**2670**	**1570**

[1] By study design, sera were only obtained from a subset of the enrolled subjects

Table 3: 4th Dose: Summary of the Analyzed Populations

Study	Safety Population		Intent-to-Treat Immunogenicity Population		Per-Protocol Immunogenicity Population	
	Pentacel	**Control**	**Pentacel**	**Control**	**Pentacel**	**Control**
P3T06	431	418	405	389	371	349
494-01	1862	739	974	339	883	291
494-03	958	-	237	-	218	-
5A9908	1782	-	756 [1]	-	735 [1]	-
Total	**5033**	**1157**	**2372**	**728**	**2207**	**640**

[1] By study design sera were only obtained from a subset of the enrolled subjects

2 Pentacel Clinical Development Program

A total of 4 pivotal studies (Studies P3T06, 494-01, 494-03, and 5A9908) and 1 additional study (Study M5A07) were submitted to the BLA and are described in this document.

All clinical trials in support of Pentacel vaccine licensure were conducted in the US and Canada using the US schedule of immunization. They were performed using a 3-dose Infant Series with immunizations at 2, 4, and 6 months followed by a 4th Dose at 15 to 16 months of age (except for one study that explicitly compared administration of the 4th Dose at 15-16 or 17-18 months).

Comparison to Licensed Separate Injections to Demonstrate Efficacy

- Study P3T06 - The immunogenicity of Pentacel vaccine compared to that of the separately administered US-licensed standard of care vaccines Daptacel, IPOL, and ActHIB.

Lot Consistency

- Study 494-01 (Infant Series) - Comparison of the safety and immunogenicity of 3 Pentacel vaccine consistency lots at 2, 4, and 6 months.

Comparison to Formulation-equivalent Separate Injections

- Study 494-01 - The immunogenicity of Pentacel vaccine compared to that of the separately administered components HCPDT (the internal code name for the DTaP components of Pentacel; HCPDT is not licensed or used as a stand-alone vaccine), Poliovax (an IPV licensed in Canada and US, but not co-administered with HCPDT and ActHIB) and ActHIB vaccine.

Immunogenicity Bridge for Pertussis Efficacy

- The comparison of the immunogenicity of Pentacel vaccine to the immunogenicity of Daptacel in the Sweden I Efficacy Trial.

Co-Administration

- Study P3T06 (Infant Series) - Comparison of the immunogenicity of other recommended pediatric vaccines when co-administered with Pentacel vaccine or its licensed-equivalent components.
- Study 494-03 (4th Dose) - Comparison of the immunogenicity of Pentacel vaccine when co-administered with or without other recommended pediatric vaccines.
- Study M5A07 (Infant Series) - Comparison of the immunogenicity of Pentacel vaccine when co-administered with or without Prevnar.

Age Range of 4th Dose

- Study 5A9908 - Comparison of the safety and immunogenicity of a 4th Dose of Pentacel vaccine when administered at 15 to 16 versus 17 to 18 months of age.

Comparison to Control Vaccines to Demonstrate Safety

- Study P3T06 - Comparison of the safety of Pentacel vaccine to the separate administration of its licensed-equivalent standard of care vaccines (Daptacel, IPOL, and ActHIB).
- Study 494-01 - Comparison of the safety of Pentacel vaccine to the separate administration of its formulation-equivalent components (HCPDT, Poliovax, and ActHIB).

To assess the possible effect of the co-administration of Prevnar on the immune responses to the Pertussis and PRP-T antigens elicited by either Pentacel vaccine (Study M5A07) or Daptacel and

ActHIB vaccines (Study P3T07) (5), 2 separate studies were conducted. Given that previous reports have raised questions of possible suppression of immune responses to pertussis and Hib antigens when given concomitantly with Prevnar, FDA requested that the immunogenicity results of these 2 studies be submitted to the IND prior to eBLA submission.

Table 4 through Table 8 present the study designs for the 4 pivotal trials and Study M5A07.

Table 4: P3T06 Study Design

Group(s)	Vaccine	Months of Age / Dose Number						
		2	4	6	7	12	15-16	16-17
1, 2, 3	Daptacel (1 of 3 consistency lots), IPOL, ActHIB, and Prevnar	❶	❷	❸				
1	Daptacel and ActHIB						❹	
	Prevnar					❹		
	M-M-R_{II}® and Varivax®					❶		
2	Daptacel, ActHIB and Prevnar						❹	
	M-M-R_{II} and Varivax						❶	
3	Daptacel							❹
	ActHIB and Prevnar						❹	
	M-M-R_{II} and Varivax						❶	
4	Pentacel	❶	❷	❸			❹	
	Prevnar	❶	❷	❸		❹		
	M-M-R_{II} and Varivax					❶		
All	Recombivax HB [1]	❷		❸				
All	Blood Sample	❶			❷		❸	❹

[1] The 1st dose of Hepatitis B vaccine was administered a minimum of 30 days prior to receipt of Dose 1 of study vaccine.

Table 5: 494-01 Study Design

	Vaccine	Months of Age / Dose Number						
		2	4	6	7	12	15	16
Lot 1, 2, 3	Pentacel (1 of 3 consistency lots)	❶	❷	❸			❹	
Control	HCPDT, Poliovax, and ActHIB	❶	❷	❸			❹	
All	Hepatitis B [1]	❷		❸				
	Prevnar	❶	❷	❸		❹		
	M-M-R_{II} and Varivax					❶		
All	Blood Sample	❶			❷		❸	❹

[1] The 1st dose of Hepatitis B vaccine was administered a minimum of 30 days prior to receipt of Dose 1 of study vaccine.

Table 6: 494-03 Study Design

Group(s)	Vaccine	Months of Age / Dose Number						
		2	4	6	7	12	15	16
All	Pentacel and Prevnar	❶	❷	❸				
1	Pentacel						❹	
	Prevnar					❹		
	M-M-R_{II} and Varivax					❶		
2	Pentacel						❹	
	Prevnar					❹		
	M-M-R_{II} and Varivax						❶	
3	Pentacel and Prevnar						❹	
	M-M-R_{II} and Varivax					❶		
4	Pentacel							❹
	Prevnar						❹	
	M-M-R_{II} and Varivax						❶	
All	Blood Sample				❶		❷	❸

Note: Hepatitis B vaccine was received at either 0, 2, and 6 or 2, 4, and 6 months of age.

Table 7: 5A9908 Study Design

Group(s)	Vaccine	Months of Age / Dose Number				
		12	15	16	17	18
1	Pentacel		❹			
2	Pentacel			❹		
3	Pentacel				❹	
4	Pentacel					❹
All	M-M-R_{II} and Varivax	❶				

Note: M-M-R_{II} and Varivax were optional at 12 months of age.
Blood samples were collected prior to and 1 month after immunization with Pentacel.

Table 8: M5A07 Study Design

Group(s)	Vaccine	Months of Age / Dose Number					
		2	3	4	5	6	7
All	Pentacel	❶		❷		❸	
	Hepatitis B [1]	❷					❸
Concomitant	Prevnar	❶		❷		❸	
Staggered	Prevnar		❶		❷		❸
All	Blood Sample	❶					❷

[1] The 1st dose of Hepatitis B vaccine was administered a minimum of 30 days prior to receipt of Dose 1 of study vaccine.

2.1 Subject Disposition and Demographics

During the conduct of Studies 494-01, 494-03 and P3T06, a total of 4198 subjects received at least the 1st dose of Pentacel vaccine, and 3251 subjects received all 4 doses. In addition, 1782 subjects who had received the Infant Series of Pentacel vaccine as part of their normal immunization schedule in Canada received the 4th Dose while participating in Study 5A9908, totaling 5980 subjects exposed to at least 1 dose of Pentacel vaccine.

2.1.1 Infant Series

A summary of the subject disposition of the Safety Population is provided in Table 9 for the Infant Series. Overall, the safety population for the Infant Series includes 4198 subjects who received Pentacel vaccine and 2486 subjects who received Control vaccines.

Of all vaccine recipients that discontinued study participation during the Infant Series, only 22 of 433 Pentacel vaccine recipients, 3 of 152 HCPDT recipients, and 5 of 105 Daptacel vaccine recipients withdrew because of an adverse event or contra-indication. In 3 of the cases (2 Pentacel vaccine recipients and 1 Control subject) withdrawal occurred because of death. None of these deaths were deemed related to vaccination by the investigator (see Section 2.2.10).

The most frequently reported adverse events or contraindications leading to withdrawal were afebrile or febrile seizures, as these events were defined in the protocol as a possible reason to preclude subjects from receiving any subsequent study vaccines.

The demographics for subjects included in the Safety Population are presented in Table 10. The mean age of subjects at the time of enrolment was comparable across studies, ranging from 2.1 to 2.2 months. For all studies, there was an approximately even distribution of males and females, with only slightly more females than males. The predominant race/ethnicity of subjects in all studies was Caucasian, followed by Hispanic, and then African American. The “Other” category was predominantly used to indicate >1 ethnic/race background.

Table 9: Summary of Subject Disposition for the Infant Series (Safety Population)

	P3T06		494-01		494-03	All Studies Combined
	Pentacel n	Control [1] n	Pentacel N	Control [1] n	Pentacel n	Pentacel n
Subject participation by randomized treatment	**484**	**1455**	**2506**	**1032**	**1207**	**4197**
Received Dose 1 of Pentacel or Control [2]	485	1454	2506	1032	1207	4198
Received 2 doses of Pentacel or Control	469	1400	2374	945	1115	3958
Received all 3 doses of Pentacel or Control	461	1376	2294	900	1077	3832
Did not complete 60-day safety follow-up post–Dose 3 [3,4]	32	105	255	152	146	433
Withdrawal due to an adverse event or contra-indication [n (%)]	1 (3.1)	5 (4.8)	8 (3.1)	3 (2.0)	13 (8.9)	22 (5.1)

1 "Control" means Daptacel, IPOL, and ActHIB vaccines for Study P3T06, and HCPDT, Poliovax, and ActHIB components for Study 494-01.

2 Subjects have been classified by the actual treatment received at Dose 1.

3 Subjects have been classified by the treatment to which they were randomized.

4 Subjects terminated at any time between receipt of Dose 1 and the post-Dose 3 60-day safety follow-up telephone call.

Table 10: Infant Series: Summary of Subject Demographics (Safety Population)

Infant Series	P3T06				494-03		494-01				Total	
	Pentacel (N=485)		Control [1] (N=1454)		Pentacel (N=1207)		Pentacel (N=2506)		Control [1] (N=1032)		Pentacel (N=4198)	
Age (months) [2]												
Mean	2.1		2.2		2.2		2.1		2.1		2.1	
Range	(1.4, 3.0)		(1.3, 3.5)		(1.4, 3.0)		(1.4, 3.3)		(1.4, 3.3)		(1.4, 3.3)	
Sex [n (%)]												
Male	243	(50.1)	703	(48.3)	601	(49.8)	1246	(49.7)	509	(49.3)	2090	(49.8)
Female	242	(49.9)	751	(51.7)	606	(50.2)	1260	(50.3)	523	(50.7)	2108	(50.2)
Race/Ethnicity [n (%)]												
Caucasian	375	(77.3)	1123	(77.2)	703	(58.2)	1489	(59.4)	623	(60.4)	2567	(61.1)
African American	34	(7.0)	91	(6.3)	103	(8.5)	273	(10.9)	111	(10.8)	410	(9.8)
Hispanic	33	(6.8)	95	(6.5)	265	(22.0)	333	(13.3)	135	(13.1)	631	(15.0)
Asian	5	(1.0)	13	(0.9)	23	(1.9)	153	(6.1)	67	(6.5)	181	(4.3)
Other	38	(7.8)	132	(9.1)	113	(9.4)	258	(10.3)	96	(9.3)	409	(9.7)

[1] "Control" means Daptacel, IPOL, and ActHIB vaccines for Study P3T06, and HCPDT, Poliovax, and ActHIB components for Study 494-01.

Notes: 'n' is the number of subjects in the demographic subcategory.
'N' is the number of subjects in the Safety Population.
"Age" is age at the time of the first dose.

2.1.2 4th Dose

A summary of the subject disposition of the Safety Population is provided in Table 11 for Dose 4. Overall, 5033 subjects and 1988 subjects received a 4th Dose of Pentacel or Control vaccines, respectively.

In the 4th Dose studies, 1 subject of the 47 in the combined Pentacel vaccine groups and no subjects in the Control groups withdrew due to an adverse event or contra-indication. The withdrawal, in Study P3T06, was the single case of a reported death. The death was assessed by the Investigator as unrelated to the study vaccine (see Section 2.2.10).

The demographics for subjects in the 4th Dose Safety Population are presented in Table 12. The mean age of subjects at the 4th Dose was comparable across studies with the exception of Study 5A9908, which, by design, enrolled subjects ranging in age from 15 to 18 months. For all studies, there was an approximately even distribution of males and females, with only slightly more females than males. The predominant race/ethnicity of subjects in all studies was Caucasian, followed by African American, and then Hispanic.

Table 11: Summary of Subject Disposition for the 4th Dose (Safety Population)

	P3T06		494-01		494-03	5A9908	All Studies Combined
	Pentacel	Control [1]	Pentacel	Control [1]	Pentacel	Pentacel	Pentacel
	n	n	n	n	n	n	n
Completed 60-day post-Dose 3 safety follow-up but terminated before receiving Dose 4 [2]	22	27	356	175	105	NA	483
Due to an adverse event or contra-indication [n (%)]	0 (0.0)	4 (14.8)	11 (3.1)	3 (1.7)	5 (4.8)	NA	16 (3.3)
Safety Population (received the 4th Dose of Pentacel or Control vaccine) [3]	**431**	**418**	**1862**	**739**	**958**	**1782**	**5033**
Did not complete 60- or 180-day safety follow-up post-Dose 4	14	13	13	8	11	9	47
Withdrawal due to an adverse event or contra-indication [n (%)]	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)

[1] "Control" means Daptacel and ActHIB vaccines for Study P3T06, and HCPDT, Poliovax, and ActHIB components for Study 494-01.

[2] Subjects have been classified by the treatment to which they were randomized during the Infant Series.

[3] Subjects have been classified by the actual treatment received at Dose 4.

NA=Not applicable.

Table 12: 4th Dose: Summary of Subject Demographics (Safety Population)

4th Dose	P3T06				494-03		494-01				5A9908 (Canada)		Total	
	Pentacel (N=431)		Control [1] (N=418)		Pentacel (N=958)		Pentacel (N=1862)		Control [1] (N=739)		Pentacel (N=1782)		Pentacel (N=5033)	
Age (months) [2]														
Mean	15.6		15.6		15.7		15.5		15.5		16.9		16.0	
Range	(14.7, 18.3)		(15.0, 19.5)		(14.2, 19.1)		(14.1, 20.8)		(14.2, 19.4)		(14.5, 19.6)		(14.1, 20.8)	
Sex (n [%])														
Male	216	(50.1)	205	(49.0)	463	(48.3)	925	(49.7)	356	(48.2)	861	(48.3)	2465	(49.0)
Female	215	(49.9)	213	(51.0)	495	(51.7)	937	(50.3)	383	(51.8)	921	(51.7)	2568	(51.0)
Race/Ethnicity (n [%])														
Caucasian	340	(78.9)	328	(78.5)	601	(62.7)	1221	(65.6)	491	(66.4)	1532	(86.0)	3694	(73.4)
African American	25	(5.8)	19	(4.5)	71	(7.4)	168	(9.0)	76	(10.3)	34	(1.9)	298	(5.9)
Hispanic	25	(5.8)	24	(5.7)	189	(19.7)	195	(10.5)	68	(9.2)	15	(0.8)	424	(8.4)
Asian	4	(0.9)	2	(0.5)	17	(1.8)	100	(5.4)	40	(5.4)	77	(4.3)	198	(3.9)
East Indian [3]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	35	(2.0)	35	(0.7)
Native Indian [3]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	9	(0.5)	9	(0.2)
Other	37	(8.6)	45	(10.8)	80	(8.4)	178	(9.6)	64	(8.7)	80	(4.5)	375	(7.5)

[1] "Control" means Daptacel and ActHIB vaccines for Study P3T06 (Group 1), and HCPDT, Poliovax, and ActHIB components for Study 494-01.
[2] Age for subjects is calculated from 4th Dose as: (vaccination date-date of birth+1)/(365.25/12).
[3] The 'East Indian' and 'Native Indian' categories applied only to Study 5A9908 conducted in Canada.
'n' is the number of subjects in the demographic subcategory; 'N' is the number of subjects in the Safety Population.
NA=Not Applicable.

2.2 Safety Results

2.2.1 Safety Endpoints

The clinical development program was designed to determine the safety and tolerability of Pentacel vaccine in infants and toddlers at 2 to 18 months of age. Specifically, the following objectives were addressed: to compare the safety of Pentacel vaccine with the safety of the US-licensed standard of care vaccines (termed "licensed-equivalent") and with the separately administered constituent components of Pentacel vaccine (HCPDT, Poliovax, and ActHIB, collectively termed "formulation-equivalent components"), to compare the safety of Pentacel vaccine when co-administered with other pediatric vaccines, and to compare the safety of 3 Pentacel vaccine consistency lots.

2.2.2 Safety Collection

The parents or legally authorized representatives were asked to record in the diary cards, daily for the evening of and 7 days after vaccination, the occurrence (or measurement, as applicable) and the severity of solicited local and solicited systemic reactions. An instruction sheet was provided to ensure consistency of reporting. They were also asked to record in the diary any adverse events (AEs) that in their view represented a change in the health status of their child. A summary of the types of safety data collected is presented in Table 13.

Table 13: Summary of Safety Variable Collection and Timing

Safety Parameters	Timing of Collection
Immediate reactions	30 minutes after each vaccination
Solicited local reactions (redness, swelling, tenderness, and change in limb circumference [4th Dose only]), **Solicited systemic reactions** (fever, less active [decreased activity], crying, diarrhea, fussiness, anorexia, vomiting, and rash)	Collected daily from Day 0 to 7 after each vaccination
Unsolicited adverse events (defined as any change in the health status of the child)	Collected from Day 0 to 7 after each vaccination
Unsolicited adverse events requiring healthcare provider contact (telephone call, office, emergency room or hospital visit)	Collected from Day 8 to 60 after each vaccination
Specific Unsolicited Events: chronic events, and events of possible autoimmune origin	Collected from Day 61 to Day 180 after Dose 4 in Study P3T06
Serious adverse events (SAEs)	Anytime during the study, from the first study-related procedure through Day 60 following the 4th Dose of Pentacel or Control vaccines (through Day 180 for Study P3T06)

The severity of immediate reactions, solicited local and systemic reactions, and unsolicited adverse events was established using the definitions listed in Table 14.

The relationship of unsolicited AEs to the study vaccines was evaluated by the Investigator as follows:

- **Unrelated** was applied to those AEs in which evidence existed that the symptom was definitely related to an etiology other than the study product (e.g., auto accident) or a symptom suggestive of another illness that was not accepted to be a possible event of the study product.
- **Possible** was applied to those AEs that had a timely relation to the study product; however, a potential alternative etiology existed which could have been responsible for the symptom (e.g., fever or irritability when other symptoms were present that suggested another etiology).
- **Probable** was applied to those AEs that had a timely relation to the study product, but a potential alternative etiology was not apparent (e.g., fever or irritability when no other symptoms suggestive of an illness were present).
- **Definite** was applied to those AEs that had a timely relation to the study vaccine and no alternative etiology was present. It must have occurred within a reasonable temporal sequence of the study product administration, must have been reasonably explained, and must have followed a known pattern of response.

Table 14: Severity Assessments: Immediate Reactions, Solicited Local and Systemic Reactions, and Unsolicited Adverse Events

Adverse Event	Rating		
	Mild	Moderate	Severe
Immediate Reactions			
Any adverse reaction occurring within 30 minutes of vaccination	Easily tolerated	Discomforting enough to cause interference with usual activity	Incapacitating, causing inability to do usual activity
Solicited Local Reactions			
Redness [1]	>5 to <25 mm	≥25 to 50 mm	>50 mm
Swelling [1]	>5 to <25 mm	≥25 to 50 mm	>50 mm
Tenderness	Subject whimpers when injection site is touched; no crying	Subject cries when injection site is touched	Subject cries when leg or arm is moved
Change in Limb Circumference [2] (4th Dose only)	>5 to <20 mm increase over baseline limb measurement (same arm at Day 0)	≥20 to 40 mm increase over baseline limb measurement (same arm at Day 0)	>40 mm increase over baseline limb measurement (same arm at Day 0)
Solicited Systemic Reactions			
Decreased activity (Less active)	Symptoms present (daily activity not affected, subject interactive)	Discomfort (interferes with and limits daily activity, subject less interactive)	Disabling (subject not interested in usual daily activity, cannot be coaxed to interact with caregiver)
Body temperature (Fever) [3]	≥38.0°C - ≤38.5°C	>38.5°C - ≤39.5°C	>39.5°C
Crying	Crying for <1 hour	Crying for 1 to 3 hours	Crying for >3 hours
Diarrhea [4]	1 to 3 diarrhea stools	4 to 5 diarrhea stools	>5 diarrhea stools
Fussiness (Irritability)	Fussy for <1 hour	Fussy for 1 to 3 hours	Fussy for >3 hours
Anorexia (Infant series)	Refuses 1 feed	Refuses 2 feeds	Refuses ≥3 feeds
Anorexia (4th Dose)	Refuses 50% of a meal	Skips 1 meal	Skips ≥2 meals
Vomiting	1 episode	2 episodes	≥3 episodes
Rash[5]	Present		

Table 14: Severity Assessments: Immediate Reactions, Solicited Local and Systemic Reactions, and Unsolicited Adverse Events

Adverse Event	Rating		
	Mild	Moderate	Severe
Unsolicited adverse events	Easily tolerated	Discomforting enough to cause interference with usual activity	Incapacitating, causing inability to do usual activity

[1] Redness and Swelling: parents measured the longest diameter in millimeters (mm) using a plastic ruler, except for Study 5A9908 in which a template with graduated circumferences in mm was used. These measurements were recorded daily.

[2] Only performed for Dose 4. The parent or legally authorized representative recorded the circumference measurement of both arms daily in the diary card. For the purposes of statistical analysis, the limb circumference variable was calculated by subtracting the left (injected) arm baseline circumference (pre-immunization measurement obtained at the study site) from those measurements obtained in the same arm for each day.

[3] All temperatures measured in Fahrenheit were converted to Celsius by Biostatistics. Fever Rates are all based upon the actual temperature recorded with no adjustments for route.

[4] Diarrhea: Defined as “looser than normal stools”, per 24 hours.

[5] For Studies 494-01, 494-03, and 5A9908, a “rash” event was intended to capture those subjects with an allergic reaction to the vaccine that was manifested by hives. Definition: well-circumscribed wheals or welts with red raised irregular borders with blanched centers that may coalesce to become giant wheals. Therefore, obvious causes of rash such as diaper rash, poison ivy, or rash associated to viral syndromes were excluded from this definition of solicited reactions and entered as an unsolicited AE. In Study P3T06, all rash events were captured as well as information on the date of 1st appearance, location, height, itchy (4th Dose only), whether or not the rash lost color when pressed, color, and duration.

2.2.3 Comparison Criteria

The statistical comparisons used to evaluate the safety of Pentacel vaccine are described in Table 15.

The objective of comparing the safety of 3 different Pentacel vaccine lots is addressed in Study 494-01 (Infant Series), by using equivalency testing to determine consistency of fever rates.

The objective of comparing the safety of Pentacel to the safety of its separately administered individual components is addressed by Studies P3T06 and 494-01 (Infant Series and 4th Doses). Data from Pentacel recipients are compared with data from recipients of the licensed-equivalent standard of care vaccines (Daptacel, IPOL, and ActHIB vaccines) in Study P3T06, and data from recipients of the formulation-equivalent components (HCPDT, Poliovax, and ActHIB) in Study 494-01. Study 494-01 assessed the non-inferiority of fever rates, and for the purposes of this document, the same analysis was performed in Study P3T06.

Table 15: Criteria for Safety Endpoints

Endpoint	Study	Non-inferiority Criteria	Equivalence Criteria (Lot Consistency)
Fever[1] (≥38.0°C) occurring within 3 days	494-01 Infant Series	Upper limit of the 2-sided 90% confidence interval (CI) of (Pooled Pentacel – Control [HCPDT, Poliovax, and ActHIB]) is <10%	Upper limit of each 2-sided 90% CI is <10% and the lower limit is >-10% for Lot 2-Lot 1, Lot 3-Lot 1 and Lot 3-Lot 2.
	494-01 Dose 4	Upper limit of the 2-sided 90% CI of (Pentacel - Control) is <10%	Not Applicable
	P3T06 Infant Series	Upper limit of the 2-sided 90% CI of (Pooled Pentacel – Control [Daptacel, IPOL, and ActHIB]) is <10%	Not Applicable
	P3T06 Dose 4	Upper limit of the 2-sided 90% CI of (Pentacel - Control) is <10%	Not Applicable
Solicited reactions occurring within 3 days	494-03 Dose 4	Upper limit of the 2-sided 90% CI of the ratio of Group 2/Group 1 was <3 (co-administration of Pentacel, varicella, and MMR vaccines compared to Pentacel alone)	Not Applicable
		Upper limit of the 2-sided 90% CI of the ratio of Group 3/Group 1 is <3 (co-administration of Pentacel and Prevnar compared to Pentacel alone)	Not Applicable

[1] In agreement with FDA, the statistical assessments of fever were performed using all temperatures, regardless of the route of measurement, without conversion to a standard temperature.

All other local and systemic solicited events as well as unsolicited events, including immediate reactions and serious adverse events, were evaluated by descriptive comparisons.

2.2.4 Overall Summary of Safety

Summary information on immediate reactions, solicited systemic reactions, non-serious unsolicited adverse events, and serious adverse events is presented in Table 16 for the Infant Series and in Table 17 for the 4th Dose. Since solicited local reactions required additional analyses in the Control groups due to multiple injection sites, those reactions are presented separately, in Table 18 (Infant Series) and Table 19 (4th Dose).

In the tables for the Infant Series (Table 16 and Table 18), the events shown are the total of those that occurred following any of the 3 doses.

Table 16: Infant Series: Percentage of Subjects with Immediate, Solicited Systemic Reactions, Non-Serious Unsolicited Adverse Events, and Serious Adverse Events of Any Severity Within the Specified Time Period

	P3T06		494-01		494-03	All Studies Combined
	Pentacel N=484	Control [1] N=1455	Pentacel N=2506	Control [1] N=1032	Pentacel N=1207	Pentacel N=4197
	%	%	%	%	%	%
Immediate Reactions (within 30 minutes)	0.0	0.2	<0.1	0.1	0.0	<0.1
Solicited Systemic Reactions						
0-3 days	96.8	96.5	92.5	93.8	95.5	93.8
0-7 days	97.7	97.1	93.5	94.4	95.7	94.6
Non-serious Unsolicited Adverse Events						
0-7 days	71.5	69.1	57.2	54.5	57.9	59.0
0-30 days	87.6	84.1	75.6	71.2	80.4	78.4
0-60 days	93.8	91.5	85.1	82.1	89.3	87.3
Serious Adverse Events						
0-7 days	0.6	0.8	0.2	0.2	0.2	0.3
0-30 days	3.9	3.4	0.9	1.1	2.1	1.6
0-60 days	5.2	5.2	1.5	1.6	4.1	2.7

[1] "Control" means Daptacel, IPOL, and ActHIB vaccines for Study P3T06., and HCPDT, Poliovax, and ActHIB components for Study 494-01.
'N' is the number of subjects from the Safety Population who received at least 1 dose during the Infant Series.

Table 17: 4th Dose: Percentage of Subjects with Immediate, Solicited Systemic Reactions, Non-Serious Unsolicited Adverse Events, and Serious Adverse Events of Any Severity Within the Specified Time Period

	P3T06		494-01		494-03	5A9908	All Studies Combined
	Pentacel N=431	Control [1] N=418	Pentacel N=1862	Control [1] N=739	Pentacel [2] N=958	Pentacel N=1782	Pentacel N=5033
	%	%	%	%	%	%	%
Immediate Reactions (within 30 minutes)	0.5	0.2	0.0	0.0	2.3	0.5	0.7
Solicited Systemic Reactions							
0-3 days	65.8	67.7	65.2	70.0	68.2	68.9	67.2
0-7 days	69.1	73.5	68.8	73.4	72.2	76.6	72.4
Non-serious Unsolicited Adverse Events							
0-7 days	36.7	37.3	30.9	29.1	34.1	26.4	30.4
0-30 days	57.1	52.9	45.8	42.2	54.4	40.5	46.5
0-60 days	66.8	63.9	57.6	56.0	68.1	51.4	58.2
Serious Adverse Events							
0-7 days	0.5	0.7	0.1	0.0	0.2	0.1	0.2
0-30 days	1.2	1.0	0.3	0.3	0.8	1.1	0.8
0-60 days	2.1	1.7	0.4	0.5	1.1	1.6	1.1
61-180 days	2.1	0.5	NA	NA	NA	NA	NA

[1] "Control" means Daptacel and ActHIB vaccines for Study P3T06 (Group 1), and HCPDT, Poliovax, and ActHIB components for Study 494-01.

[2] All groups in Study 494-03 are pooled for analysis.

'N' is the number of subjects from the Safety Population who received the 4th Dose.

NA = Not applicable.

2.2.5 Immediate Reactions

During the Infant Series, only 1 (<0.1%) subject in the Pentacel groups experienced an immediate reaction (see Table 16); 1 case of urticaria in study 494-01. Among the subjects who received Control vaccines, 1 (0.1%) subject in study 494-01 experienced diarrhea and 3 (0.2%) subjects in study P3T06 experienced 4 immediate adverse reactions (moderate allergic reaction, irritability, crying and erythema) within 30 minutes following any of the Daptacel vaccinations.

After the 4th Dose, a total of 33 (0.7%) of the 5033 subjects in the Pentacel groups experienced at least one immediate reaction (see Table 17); 2 (0.5%) in study P3T06, 0 (0.0%) in Study 494-01, 22 (2.3%) subjects in study 494-03 (mainly local injection site reactions categorized as immediate by some investigators), and 9 (0.5%) in study 5A9908. No life-threatening immediate reactions (i.e., anaphylaxis, angioedema, bronchospasm) were reported. Among Control subjects, 1 (0.2%) subject in study P3T06 experienced an immediate reaction (injection site induration).

2.2.6 Solicited Local Reactions

Table 18 and Table 19 show the percentage of subjects reporting solicited local reactions following any of the doses in the Infant Series and following Dose 4, respectively.

During the Infant Series, Pentacel vaccine subjects reported an overall frequency of 64.6% for solicited local reactions within 3 days of any vaccination, and of 64.7% within 7 days. The most common reaction within 3 days was tenderness, reported by 61.5 % of Infant Series subjects. The majority of local reactions were mild or moderate, occurred and resolved within 3 days of vaccination.

Following the 4th Dose, for all pivotal studies combined, Pentacel vaccine subjects reported an overall frequency of 64.2% for solicited local reactions within 3 days of vaccination and of 64.6% within 7 days. As for the Infant Series, the most common reaction within 3 days was tenderness, reported by 44.1% of subjects. The majority of local reactions occurred and resolved within 3 days of vaccination.

Pentacel Vaccine versus Control Vaccines

In the controlled studies P3T06 and 494-01, the percentage of Pentacel vaccine recipients who reported local reactions was compared against Controls in 2 ways: against the percentage who reported a reaction at the Diphtheria-Tetanus-Pertussis vaccine injection site (Daptacel vaccine in Study P3T06, HCPDT in Study 494-01), and against the percentage who reported a reaction at any of the injection sites (Daptacel, IPOL, and ActHIB vaccines for the Infant Series in Study P3T06; Daptacel, and ActHIB vaccines for the 4th Dose in Study P3T06 [Group 1]; and HCPDT, Poliovax, and ActHIB components in Study 494-01).

Table 18 shows the number of subjects reporting any type of solicited local reaction within 3 days following any of the doses in the Infant Series. In Study P3T06, the percentage of Pentacel vaccine recipients reporting a solicited local reaction within 3 days (71.8%) was similar to the rate reported for the Daptacel vaccine injection site alone (70.1%) (p value = 0.5218), and lower than the rate reported for any of the 3 Control vaccine injection sites (76.6%) (p value = 0.0417). In Study 494-01, the percentage of Pentacel vaccine recipients reporting a solicited local reaction within 3 days (60.0%) was lower than the rate for the Control subjects, whether the comparison was made to just the HCPDT injection site (67.6%) or to any of the 3 Control vaccine injection sites (73.8%) (p values <0.0001 for both comparisons).

Table 19 shows the number of subjects reporting any type of solicited local reaction within 3 days following the 4th Dose. In Study P3T06, the percentage of Pentacel vaccine recipients reporting a solicited local reaction within 3 days (69.8%) was comparable to the rates reported for the Daptacel injection site (64.3%) (p value = 0.1095) and for either of the Control vaccine injection sites (68.8%) (p value = 0.8156). In Study 494-01, the percentage of Pentacel vaccine recipients reporting a solicited local reaction within 3 days (60.3%) was comparable to the rate reported for the HCPDT injection site (63.1%) (p value = 0.2158) and lower than the rate reported for the 3 Control vaccine injection sites (68.1%) (p value = 0.0005).

Table 18: Infant Series: Percentage of Subjects with Any and Severe Solicited Local Reactions Within 3 Days of any Vaccination

		P3T06			494-01			494-03	All Studies Combined
		Pentacel N=484	Daptacel N=1455	Control [1] N=1455	Pentacel N=2506	HCPDT N=1032	Control [1] N=1032	Pentacel N=1207	Pentacel N=4197
		%	%	%	%	%	%	%	%
Any Solicited Local Reactions		71.8	70.1	76.6	60.0	67.6	73.8	71.6	64.6
Redness	**Any (>5 mm)**	14.6	14.8	23.0	10.0	8.5	14.1	10.9	10.8
	Severe (>50 mm)	0.8	0.4	0.7	0.2	0.2	0.5	1.3	0.6
Swelling	**Any (>5 mm)**	13.6	9.5	12.2	6.9	6.8	9.8	8.9	8.3
	Severe (>50 mm)	0.8	0.6	0.6	0.4	0.1	0.2	1.1	0.6
Tenderness [2]	**Any**	68.0	66.8	71.7	56.8	65.5	70.6	69.0	61.5
	Severe	7.8	6.8	8.4	5.2	10.3	12.4	11.5	7.3

[1] "Control" includes subjects who had a reaction at any of the 3 injection sites: Daptacel, IPOL, and ActHIB vaccines for Study P3T06, and HCPDT, Poliovax, and ActHIB components for Study 494-01. Each subject is counted only once, regardless of whether a reaction was experienced at 1, 2, or all 3 of the injection sites.

[2] Mild=subject whimpers when site is touched; Moderate=subject cries when site is touched; Severe=subject cries when leg or arm is moved.

'N' is the number of subjects from the Safety Population. '%' are based on the total number of subjects with available data from the Safety Population.

Table 19: 4th Dose: Percentage of Subjects with Solicited Any and Severe Local Reactions Within 3 Days of Vaccination

		P3T06			494-01			494-03	5A9908	All Studies Combined
		Pentacel N=431	Daptacel N=418	Control [1, 2] N=418	Pentacel N=1863	HCPDT N=739	Control [1] N=739	Pentacel [3] N=958	Pentacel N=1782	Pentacel N=5033
		%	%	%	%	%	%	%	%	%
Any Solicited Local Reactions		69.8	64.3	68.8	60.3	63.1	68.1	66.9	65.2	64.2
Redness	**Any (>5 mm)**	17.3	16.4	18.2	21.4	19.5	23.1	10.6	34.8	24.0
	Severe (>50 mm)	2.3	2.4	2.4	2.6	2.1	2.2	0.8	4.1	2.8
Swelling	**Any (>5 mm)**	9.7	10.3	11.6	11.7	11.4	13.9	7.0	20.6	14.0
	Severe (>50 mm)	0.8	1.3	1.3	1.3	1.3	1.3	0.2	2.3	1.4
Tenderness[4]	**Any**	56.1	51.1	53.7	45.9	49.9	56.3	55.9	33.7	44.1
	Severe	3.3	2.4	2.9	3.3	2.3	5.2	4.4	2.9	3.4
Change in Limb circumference	**Any (>5 mm)**	33.6	30.6	37.5	25.3	21.7	NA	27.8	37.7	31.2
	Severe (>40 mm)	0.5	0.8	1.1	0.2	0.0	NA	0.2	1.1	0.6

[1] In Study P3T06, each Control subject had 2 injection sites (Daptacel and ActHIB vaccines) and in Study 494-01, each Control subject had 3 injection sites (HCPDT, Poliovax, and ActHIB components).
"Control" includes subjects who had a reaction at any of the injection sites. Each subject is counted only once, regardless of whether a reaction was experienced at 1 or more sites.

[2] Only Group 1 from Study P3T06 4th Dose (Daptacel and ActHIB vaccines at 15 months of age) is being used for the safety comparisons with the 4th Dose of Pentacel.

[3] In Study 494-03, all groups are pooled for analysis.

[4] Mild=subject whimpers when site is touched; Moderate=subject cries when site is touched; Severe=subject cries when leg or arm is moved.

'N' is the number of subjects from the Safety Population. '%' are based on the total number of subjects with available data from the Safety Population.

NA = 'Not Applicable'; the circumference of the vaccinated limb for Poliovax and ActHIB components (Right Lower and Upper Thigh, respectively) was not measured.

Figure 1, Figure 2, Figure 3, and Figure 4 present the local reactions of redness, swelling, and tenderness after each dose of the Infant Series, and change in limb circumference only after Dose 4, respectively, by severity within 3 days after vaccination with Pentacel (all studies combined) as compared to vaccination with Daptacel, IPOL, and ActHIB vaccines (only Daptacel and ActHIB vaccines at Dose 4) or HCPDT, Poliovax, and ActHIB components.

Most local reactions observed after both Pentacel and Control vaccine immunizations were mild or moderate in severity.

After any dose, the mean duration for redness, swelling and tenderness was less than 3 days. After Dose 4, the mean duration for change in limb circumference was less than 4 days in the pooled Pentacel group. The duration of each local reaction was comparable between the Pentacel group and either of the Control groups.

After each dose of the Infant Series, lower percentages of local reactions were reported at the pooled Pentacel vaccine injection site when compared to any of the 3 Control vaccine injection sites (either Daptacel, IPOL, or ActHIB vaccines , and either HCPDT, Poliovax, or ActHIB components).

Post-Dose 4, higher rates of redness and swelling were reported at the Pentacel vaccine injection site (pooled studies) than at any of the Control vaccine injection sites (Figure 1 and Figure 2). However, this was due to higher rates of redness and swelling observed in the non-controlled study 5A9908 (see Table 19) as the rates observed in the Pentacel group of the individual controlled studies (P3T06 and 494-01) were lower than those reported at any of the 3 Control vaccine injection sites (either Daptacel, IPOL, or ActHIB vaccines, and either HCPDT, Poliovax, or ActHIB components). In addition, tenderness post-Dose 4 was reported by fewer Pentacel vaccine recipients than Controls (Figure 3).

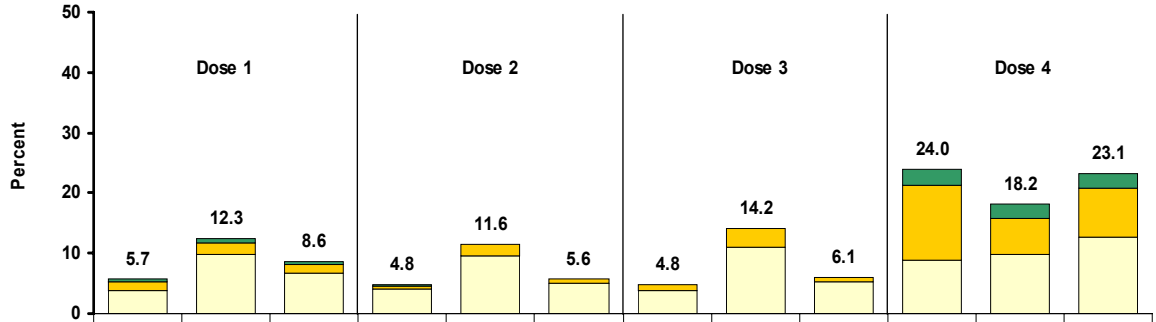
Changes in limb circumference (>5 mm increase over the pre-vaccination baseline measurement) were reported more frequently for subjects who received Pentacel vaccine than HCPDT, but when compared to the most severe changes in limb circumference reported at the Daptacel (left arm) and ActHIB (right arm) vaccination sites, more occurrences were reported in the Control group (Figure 4). No limb circumference measurements were performed for the limbs injected with Poliovax or ActHIB vaccines in Study 494-01.

A change in limb circumference that was rated as Severe (>40 mm increase over the baseline measurement) was reported by a total of 29 subjects: 25 (0.6%) Pentacel recipients (2 [0.5%] in Study P3T06, 3 [0.2%] in Study 494-01, 2 [0.2%] in Study 494-03, and 18 [1.1%] in Study 5A9908) and 4 [1.1%] Control vaccine recipients (all in Study P3T06).

Extensive or entire limb swelling is a recognized rare adverse event following administration of acellular pertussis vaccines, which is usually observed after Dose 4 or subsequent doses. The pivotal studies P3T06, 494-01, 494-03, and 5A9908 were not designed to specifically collect (i.e., as a solicited event) the presence and extent (i.e., limb segments and joints involved) of limb swelling. Instead, all of these pivotal trials collected daily measurements of limb circumference after Dose 4 as an intended marker for this adverse reaction. There were 11 cases of potential post-immunization limb swelling reported as unsolicited AEs by the parents and 3 additional cases in which data provided in the Comments section of the case report form denoted the appearance of limb swelling. No further information was available on these latter 3 events. Of the 11 events reported as unsolicited AEs, 7 were graded as mild and 4 as moderate, 5 resulted in a telephone call or visit to the doctor's office, and no action was taken on the other 6. The 11 events resolved without sequelae. Eight out of the 11 events occurred after Dose 4 and 6 of them returned a Diary Card with limb circumference data. None of these subjects experienced a

solicited severe (>40 mm) increase in limb circumference, as measured and reported by their parents.

Figure 1: Comparison of the Pooled Pentacel with Controls After Each Dose; Percentage of Subjects Experiencing Redness Within 3 Days After Vaccination by Severity



	PENTACEL	SC	FE	PENTACEL	SC	FE	PENTACEL	SC	FE	PENTACEL	SC	FE
Any	5.7	12.3	8.6	4.8	11.6	5.6	4.8	14.2	6.1	24.0	18.2	23.1
Severe	0.4	0.6	0.5	0.1	0.1	0.0	0.1	0.0	0.0	2.8	2.4	2.2
Moderate	1.4	1.9	1.4	0.6	1.8	0.6	0.9	3.2	0.8	12.3	6.1	8.2
Mild	3.9	9.9	6.7	4.0	9.6	5.1	3.9	11.0	5.3	8.9	9.8	12.7

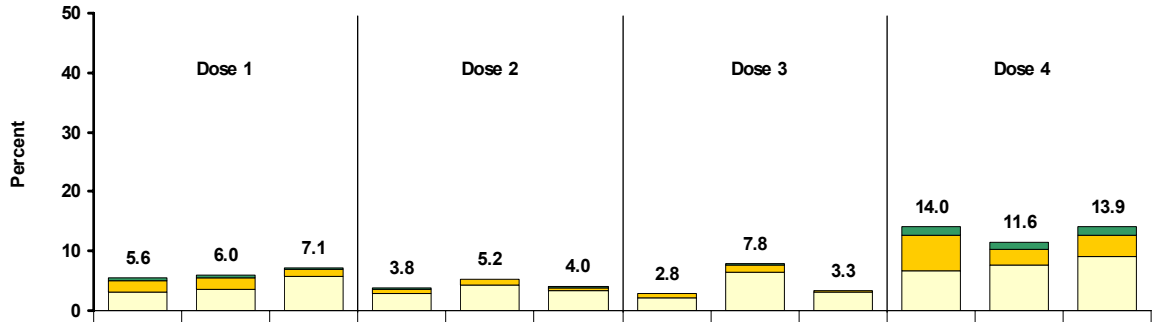
Notes: Percentages for solicited reactions are based on the number of subjects with available data from Safety Population.

SC=Standard of Care at the time of Study P3T06 and corresponds to Daptacel, ActHIB, and IPOL injection sites for Doses 1 through 3. Only Group 1 (Daptacel and ActHIB at 15 months of age) from Study P3T06 is being used for the safety comparisons with the 4th Dose of Pentacel.

FE=Formulation equivalent and corresponds to HCPDT, Poliovax, and ActHIB injection sites for Doses 1 through 4 in Study 494-01.

FE and SC include subjects who had a reaction at any of the injection sites. Each subject is counted only once, regardless of whether a reaction was experienced at 1 or more sites and is classified according to the highest recorded severity score.

Figure 2: Comparison of the Pooled Pentacel with Controls After Each Dose; Percentage of Subjects Experiencing Swelling Within 3 Days After Vaccination by Severity



	PENTACEL	SC	FE	PENTACEL	SC	FE	PENTACEL	SC	FE	PENTACEL	SC	FE
Any	5.6	6.0	7.1	3.8	5.2	4.0	2.8	7.8	3.3	14.0	11.6	13.9
Severe	0.5	0.4	0.1	0.2	0.1	0.1	0.0	0.1	0.0	1.4	1.3	1.3
Moderate	1.8	2.0	1.2	0.8	0.9	0.5	0.7	1.2	0.3	5.9	2.6	3.5
Mild	3.2	3.6	5.8	2.8	4.3	3.4	2.1	6.5	3.0	6.7	7.7	9.2

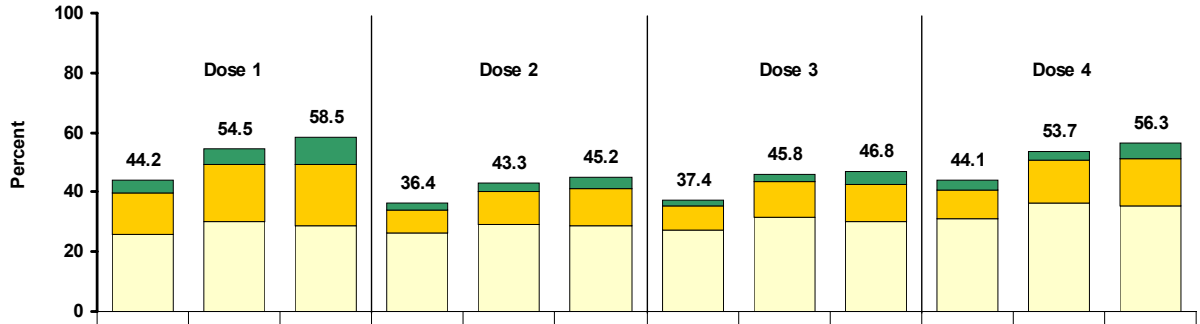
Notes: Percentages for solicited reactions are based on the number of subjects with available data from Safety Population.

SC=Standard of Care at the time of Study P3T06 and corresponds to Daptacel, ActHIB, and IPOL injection sites for Doses 1 through 3. Only Group 1 (Daptacel and ActHIB at 15 months of age) from Study P3T06 is being used for the safety comparisons with the 4th Dose of Pentacel.

FE=Formulation equivalent and corresponds to HCPDT, Poliovax, and ActHIB injection sites for Doses 1 through 4 in Study 494-01.

FE and SC include subjects who had a reaction at any of the injection sites. Each subject is counted only once, regardless of whether a reaction was experienced at 1 or more sites and is classified according to the highest recorded severity score.

Figure 3: Comparison of the Pooled Pentacel with Controls After Each Dose; Percentage of Subjects Experiencing Tenderness Within 3 Days After Vaccination by Severity



	PENTACEL	SC	FE	PENTACEL	SC	FE	PENTACEL	SC	FE	PENTACEL	SC	FE
Any	44.2	54.5	58.5	36.4	43.3	45.2	37.4	45.8	46.8	44.1	53.7	56.3
Severe	4.6	5.0	9.1	2.2	2.9	4.0	1.9	2.2	4.3	3.4	2.9	5.2
Moderate	14.0	19.5	20.7	7.9	11.0	12.6	8.3	11.9	12.1	9.6	14.5	15.9
Mild	25.6	30.0	28.7	26.2	29.4	28.6	27.3	31.7	30.3	31.2	36.3	35.2

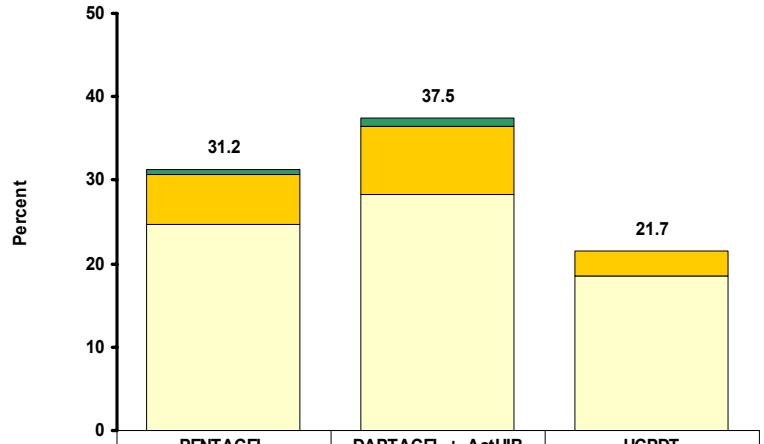
Notes: Percentages for solicited reactions are based on the number of subjects with available data from Safety Population.

SC=Standard of Care at the time of Study P3T06 and corresponds to Daptacel, ActHIB, and IPOL injection sites for Doses 1 through 3. Only Group 1 (Daptacel and ActHIB at 15 months of age) from Study P3T06 is being used for the safety comparisons with the 4th Dose of Pentacel.

FE=Formulation equivalent and corresponds to HCPDT, Poliovax, and ActHIB injection sites for Doses 1 through 4 in Study 494-01.

FE and SC include subjects who had a reaction at any of the injection sites. Each subject is counted only once, regardless of whether a reaction was experienced at 1 or more sites and is classified according to the highest recorded severity score.

Figure 4: Comparison of the Pooled Pentacel with Controls After Dose 4; Percentage of Subjects Experiencing Change in Limb Circumference Within 3 Days After Vaccination by Severity



	PENTACEL	DAPTACEL + ActHIB	HCPDT
Any	31.2	37.5	21.7
Severe	0.6	1.1	0.0
Moderate	5.9	8.2	3.1
Mild	24.7	28.2	18.5

Notes: Only Group 1 (Daptacel and ActHIB at 15 months of age) from Study P3T06 is being used for the safety comparisons with the 4th Dose of Pentacel.
Percentages for solicited reactions are based on the number of subjects with available data from Safety Population.
Each subject is counted once and is classified according to the highest recorded severity score.

2.2.7 Solicited Systemic Reactions

The percentages of subjects reporting solicited systemic reactions following any of the doses in the Infant Series and the 4th Dose are presented in Table 20 and Table 21.

In the Infant Series overall, solicited systemic reactions were reported by 93.8% of Pentacel subjects within 3 days post-vaccination, and by 94.6% within 7 days. The most common reaction within the first 3 days was fussiness, reported for 87.4% of subjects. Following the 4th Dose, solicited systemic reactions were reported by 67.2% of subjects within 3 days and by 72.4% within 7 days. The most common reaction within the first 3 days was fussiness, reported for 50.2% of subjects. For both the Infant Series and the 4th Dose, across studies, the majority of solicited reactions occurred and resolved within 3 days of vaccination.

Fever Rates

- **Comparison of the Safety of Pentacel to Control Vaccines**

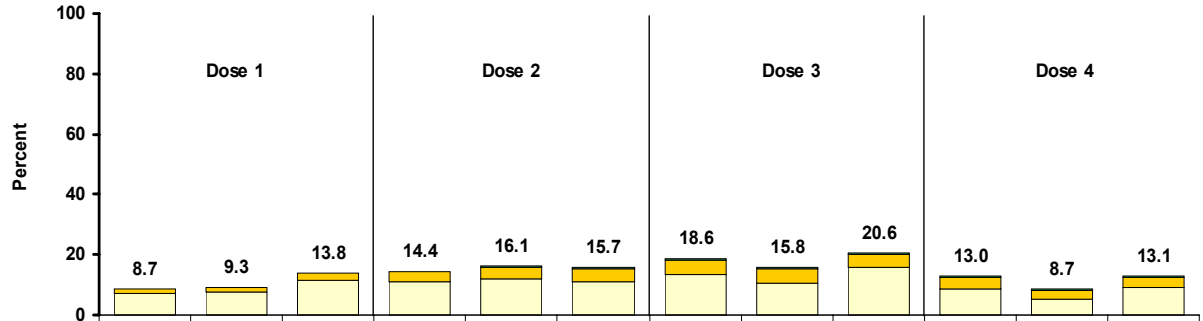
Table 20 and Table 21 summarize the percentages of subjects with fever (defined as temperature ≥38.0°C) and with severe fever (defined as temperature >39.5°C), within 3 days after any vaccination of the Infant Series and Dose 4, respectively.

During the Infant Series, after any of the 3 doses combined, subjects who received Pentacel were consistently less likely to report fever than were subjects who received Control vaccines, whether the comparison was to the licensed-equivalent vaccines (28.7% for the pooled Pentacel vaccine recipients versus 30.1% for Daptacel, IPOL, ActHIB vaccine separate injection recipients) or to the separately administered formulation-equivalent components (32.0% for HCPDT, Poliovax, ActHIB separate injection recipients).

After the 4th Dose, in Study P3T06, fever was reported more frequently for subjects receiving Pentacel (13.4%) than for those receiving Daptacel and ActHIB (8.7%), whereas in Study 494-01, fever was reported less frequently for subjects receiving Pentacel (10.7%) than for those receiving HCPDT, Poliovax, and ActHIB (13.1%).

Figure 5 displays fever by severity within 3 days of vaccination, for each Infant Series dose and Dose 4. During the Infant Series, Pentacel vaccine recipients had lower rates of fever than did Controls following each dose, with the exception of the 3rd dose in Study P3T06. In all groups with the exception of the Daptacel, IPOL, and ActHIB vaccine Control group after Dose 3, the percentage of subjects reporting fever increased following each dose of the Infant Series.

Figure 5: Comparison of the Pooled Pentacel with Controls After Each Dose; Percentage of Subjects Experiencing Fever Within 3 Days After Vaccination by Severity



	PENTACEL	SC	FE	PENTACEL	SC	FE	PENTACEL	SC	FE	PENTACEL	SC	FE
Any	8.7	9.3	13.8	14.4	16.1	15.7	18.6	15.8	20.6	13.0	8.7	13.1
Severe	0.3	0.1	0.1	0.3	0.4	0.6	0.7	0.3	0.7	0.7	0.8	0.5
Moderate	1.2	1.5	2.2	3.2	3.9	4.3	4.8	4.8	3.9	3.5	2.4	3.5
Mild	7.3	7.7	11.5	11.0	11.8	10.8	13.2	10.7	16.0	8.8	5.5	9.1

Notes: Percentages for solicited reactions are based on the number of subjects with available data from Safety Population. Each subject is counted once and is classified according to the highest recorded severity score. Fever is based upon actual temperatures recorded, with no adjustment for route measurements.

SC=Standard of Care at the time of Study P3T06 and means Daptacel, ActHIB, and IPOL vaccines for Doses 1 through 3. Only Group 1 (Daptacel and ActHIB vaccines at 15 months of age) from Study P3T06 is being used for the safety comparisons with the 4th Dose of Pentacel.

FE=Formulation equivalent and means HCPDT, Poliovax, and ActHIB components for Doses 1 through 4 in Study 494-01.

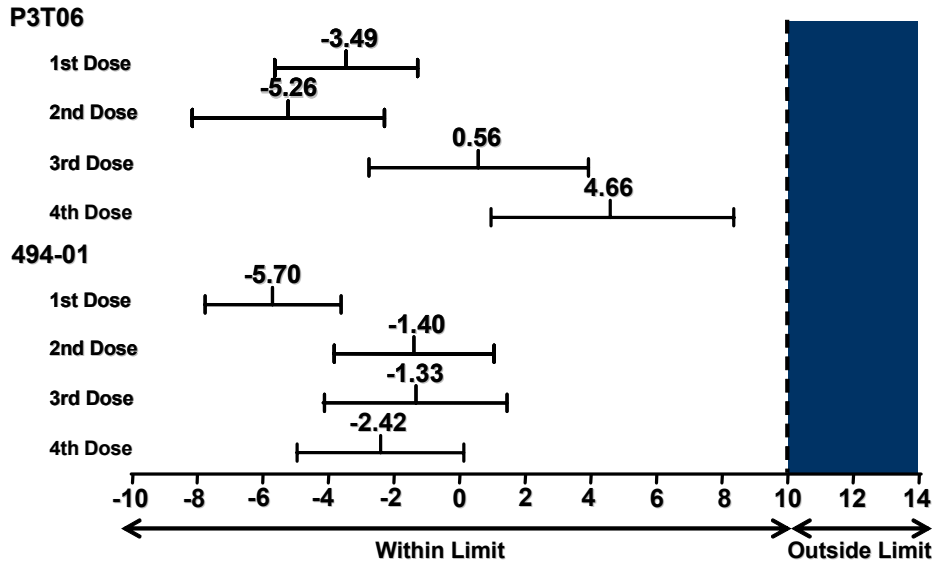
Most of the fever reactions were mild or moderate in severity; severe fever (>39.5°C) within 3 days was reported by similar percentages of Pentacel and Control vaccine recipients. There were no hospitalizations due to fever within 3 days of immunization.

In the controlled studies after each dose of the Infant Series and Dose 4, the maximum mean duration of fever in the Pentacel group was 2.4 days and 2.2 days in the Control groups.

For both the Pentacel and Control vaccine groups, temperature was measured more frequently by the rectal route and after each dose in the Infant Series and by the axillary route after Dose 4. The usage pattern of temperature measurement routes was very similar between groups in the same study, and was constant across studies.

Figure 6 graphically presents non-inferiority testing of the difference in fever rates in the 3-day period after any vaccination in Studies P3T06 and 494-01. Based on the statistical criteria established for Study 494-01 (not prospectively identified in Study P3T06), non-inferiority was demonstrated if the upper limit of the 90% confidence intervals of the difference in fever rates (0-3 days after each dose) was less than 10%. In both of the controlled studies, for most doses, subjects who received Pentacel vaccine tended to have lower fever rates (yielding negative differences) compared to those who received the Control vaccines. All comparisons of the fever rate difference between the Pentacel and Control vaccine groups fulfilled the statistical criterion for non-inferiority.

Figure 6: Comparison of Pentacel with Individual Components (Control Group) After Each Dose; Non-inferiority Testing of Difference in Fever Rates Within 3 Days After Vaccination (90% Confidence Intervals)



- **Lot Consistency**

All Pentacel vaccine lots were equivalent with respect to rates of any fever within 3 days of vaccination for the Infant Series. The results were similar within 7 days after each vaccination, and there were very few severe fevers associated with any lot (data not shown).

Solicited Systemic Reactions (Other than Fever)

Table 20 and Table 21 show the percentage of subjects reporting any type of solicited systemic reaction of any severity following any of the doses in the Infant Series and following Dose 4, respectively. In both controlled studies, similar rates of solicited systemic reactions of any category were reported within 3 days by Pentacel and Control vaccine recipients.

Most systemic reactions were mild or moderate in severity. The most common reactions within 3 days of vaccination were crying and fussiness. After any dose, crying and fussiness were reported slightly more frequently by the Control than the Pentacel vaccine recipients.

After any dose, the mean duration for every solicited systemic reaction was less than 3 days in the pooled Pentacel group and the duration was comparable between the Pentacel group and any of the Control groups.

As explained in Table 14, the event of "rash" was not rated by severity and was not collected consistently across studies (494-01, 494-03, intended to capture those subjects with an allergic reaction to the vaccine and Study P3T06 captured all rash events). In Study 494-01 (defined as the presence of welts) within 3 days, rash was reported present for 4.6% of Pentacel vaccine recipients compared to 5.3% of Controls during the Infant Series and for 3.7% of Pentacel vaccine recipients compared to 2.8% of Controls after Dose 4. In Study P3T06 (defined as any type of rash) rash was reported present for 12.9% of Pentacel vaccine recipients compared to 13.2% of Controls during the Infant Series and for 7.0% of Pentacel vaccine recipients compared to 10.2% of Controls after Dose 4. Among all the reported cases of rash occurring within 3 days of vaccinations in Study P3T06, 1 case of rash all over the body was reported following each of Doses 1 to 3 and 3 cases after Dose 4 in the Pentacel group and 6, 8, 10, and 10 cases were reported following Daptacel Doses 1, 2, 3, and 4 respectively.

Table 20: Infant Series: Percentage of Subjects with Any and Severe Solicited Systemic Reactions Within 3 Days of Any Vaccination

		P3T06		494-01		494-03	All Studies Combined
		Pentacel N=484	Control [1] N=1455	Pentacel N=2506	Control [1] N=1032	Pentacel N=1207	Pentacel N=4197
		%	%	%	%	%	%
Fever:	**Any (≥38.0°C)**	25.2	30.1	28.6	32.0	30.5	28.7
	Severe (>39.5°C)	1.1	0.7	1.1	1.2	0.7	1.0
Less Active:	**Any**	66.3	67.8	59.1	68.6	65.8	61.8
	Severe	3.0	2.8	3.1	5.5	4.5	3.5
Vomiting (per 24 hours):	**Any**	26.1	24.7	23.6	23.4	25.5	24.4
	Severe	1.7	2.6	2.7	3.3	3.2	2.7
Diarrhea (per 24 hours):	**Any**	36.7	35.3	30.2	31.3	30.8	31.1
	Severe	1.7	1.3	1.5	1.8	2.0	1.6
Crying:	**Any**	82.0	79.6	73.8	78.7	79.8	76.4
	Severe	3.6	6.3	4.7	6.6	8.8	5.7
Fussiness:	**Any**	93.4	91.7	84.9	88.1	90.4	87.4
	Severe	11.0	13.2	11.2	14.7	17.4	12.9
Anorexia:	**Any**	44.7	46.8	40.9	48.6	46.8	43.0
	Severe	2.1	2.4	1.8	2.4	2.3	2.0
Presence of Rash		12.9	13.2	4.6	5.3	2.9	NA

[1] "Control" means Daptacel, IPOL, and ActHIB vaccines for Study P3T06 and HCPDT, Poliovax, and ActHIB components for Study 494-01.
'N' is the number of subjects from the Safety Population. '%' are based on the total number of subjects with available data from the Safety Population.
For definition of Severe reactions, See Table 14.
NA= Not Applicable; the event of "rash" was not rated by severity and was not collected consistently across studies (494-01, 494-03, intended to capture those subjects with an allergic reaction to the vaccine and Study P3T06 captured all rash events).

Table 21: 4th Dose: Percentage of Subjects with Any and Severe Solicited Systemic Reactions Within 3 Days of Vaccination

		P3T06		494-01		494-03	5A9908	All Studies Combined
		Pentacel	Control [1,2]	Pentacel	Control [1]	Pentacel	Pentacel	Pentacel
		N=431	N=418	N=1862	N=739	N=958	N=1782	N=5033
Fever:	**Any (≥38.0°C)**	13.4	8.7	10.7	13.1	8.6	17.5	13.0
	Severe (>39.5°C)	0.3	0.8	0.7	0.5	0.7	0.9	0.7
Less Active:	**Any**	24.1	24.1	26.5	28.9	30.4	25.3	26.6
	Severe	2.5	0.3	1.3	0.9	2.7	0.7	1.5
Vomiting (per 24 hours):	**Any**	5.8	3.9	5.7	6.4	6.1	6.1	5.9
	Severe	0.8	0.8	0.5	0.2	1.7	0.4	0.7
Diarrhea (per 24 hours):	**Any**	15.6	16.5	14.5	15.6	15.7	23.7	18.2
	Severe	2.5	1.3	0.7	0.8	0.8	0.5	0.8
Crying:	**Any**	35.9	36.2	36.1	40.3	41.4	27.4	33.9
	Severe	2.3	1.8	1.6	2.0	2.4	0.9	1.5
Fussiness:	**Any**	53.5	53.8	53.3	59.1	58.6	42.1	50.2
	Severe	5.3	4.5	4.4	4.8	5.7	4.7	4.8
Anorexia:	**Any**	23.4	24.9	26.2	30.0	30.0	31.7	28.7
	Severe	2.3	1.3	1.5	2.0	3.2	2.9	2.4
Presence of Rash		7.0	10.2	3.7	2.8	1.4	4.7	NA

[1] "Control" means Daptacel and ActHIB vaccines for Study P3T06, and HCPDT, Poliovax, and ActHIB components for Study 494-01.
'N' is the number of subjects from the Safety Population who received the 4th Dose.

[2] Only Group 1 from Study P3T06 4th Dose (Daptacel and ActHIB vaccines at 15 months of age) is being used for the safety comparisons with the 4th Dose of Pentacel.

For definition of Severe reactions, See Table 14.
NA= Not Applicable; the event of "rash" was not rated by severity and was not collected consistently across studies (494-01, 494-03, intended to capture those subjects with an allergic reaction to the vaccine and Study P3T06 captured all rash events).

2.2.8 Non-Serious Unsolicited Adverse Events

All unsolicited AEs were collected for 7 days post-vaccination, and those that elicited contact with a health-care provider were collected for 60 days (180 days in Study P3T06 4th Dose). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v3.1 and were pooled for Pentacel groups across studies.

In the Infant Series, for all studies combined, 87.3% of Pentacel vaccine subjects reported non-serious unsolicited adverse events within 60 days post-vaccination, but only 7.5% of the subjects were assessed by the Investigators as experiencing an event that was related to vaccination. The majority of these events occurred within 7 days post-vaccination, and no trends or unexpected adverse events were identified. Across all Pentacel vaccine groups combined, the most common non-serious unsolicited adverse events deemed to be related to vaccination were pyrexia, reported by a total of 27 subjects (0.6%), somnolence, reported by 27 (0.6%), irritability and injection site bruising, each reported by 19 (0.5%), injection site pain, reported by 13 (0.3%), and nasal congestion, reported by 12 (0.3%) subjects.

Following the 4th Dose, for all studies combined, 58.2% of Pentacel vaccine subjects reported non-serious unsolicited adverse events within 60 days post-vaccination, but only 5.8% of the subjects were assessed by the Investigators as experiencing an event that was related to vaccination. The majority of the related events occurred within 7 days post-vaccination, and no trends or unexpected adverse events were identified. Across all Pentacel vaccine groups combined, the most common non-serious unsolicited adverse events deemed to be related to vaccination were nasopharyngitis, reported by a total of 47 subjects (0.9%), rhinorrhea, reported by 33 (0.7%), injection site erythema, reported by 28 (0.6%), dermatitis not otherwise specified (NOS), reported by 26 (0.5%), and cough, reported by 21 (0.4%) subjects.

Comparison of the Safety of Pentacel to Control Vaccines

No major differences were observed between the Pentacel and the Control vaccine groups in Studies P3T06 and 494-01.

Table 22 and Table 23 summarize the percentage of subjects with at least one of the most frequently reported non-serious unsolicited adverse events (by MedDRA Preferred Term) that occurred within 60 days of any vaccination of the Infant Series and of the 4th Dose, respectively. Upper respiratory tract infection NOS and otitis media NOS were the most commonly reported non-serious unsolicited adverse events after any injection. These events were experienced by comparable percentages of Pentacel and Control vaccine subjects and are typical of the infant and toddler populations.

Non-serious unsolicited AEs within 60 days of any dose that were deemed to be related to vaccination were experienced by comparable percentages of Pentacel and Control vaccine subjects in Study P3T06 and 494-01. The majority of these events were reported within 7 days of vaccination, and consisted mostly of nasopharyngitis, rhinorrhea, cough, dermatitis, and adverse events at the vaccine administration site (i.e., injection site bruising, erythema, dermatitis, induration, and non-specific reactions).

In Study P3T06 4th Dose, which continued to collect chronic events and events of possible autoimmune origin from Day 61 to Day 180 after the 4th Dose, no related non-serious unsolicited AEs were reported for this period.

Table 22: Infant Series: Percentage of Subjects with the Most Common Non-Serious Unsolicited Adverse Events Within 60 Days After Vaccination

	Pooled Pentacel N=4197	P3T06 Control [1] N=1455	494-01 Control [2] N=1032
	%	%	%
Any Unsolicited Adverse Event	**87.3**	**91.5**	**82.1**
Upper respiratory tract infection NOS	46.6	45.4	40.8
Otitis media NOS	33.8	36.0	26.3
Teething	12.5	14.1	10.8
Nasal congestion	10.4	14.8	7.2
Nasopharyngitis	11.2	12.2	8.1
Cough	10.2	14.2	7.1
Bronchiolitis	9.9	13.5	6.8
Conjunctivitis NEC [3]	10.7	11.3	7.8
Viral infection NOS	8.8	9.1	8.1
Candida NOS	8.3	10.2	7.4

[1] Control means Daptacel, IPOL, and ActHIB vaccines for the Infant Series of Study P3T06.
[2] Control means HCPDT, Poliovax, and ActHIB components for the Infant Series of Study 494-01.
[3] NEC = Not Elsewhere Classified.
'N' is the number of subjects from the Safety Population.

Table 23: 4th Dose: Percentage of Subjects with Most Common Non-Serious Unsolicited Adverse Events Within 60 Days After Vaccination

	Pooled Pentacel N=5033	P3T06 Control [1] N=418	494-01 Control [2] N=739
	%	%	%
Any Unsolicited Adverse Event	**58.2**	**63.9**	**56.0**
Otitis media NOS	13.2	21.1	12.2
Upper respiratory tract infection NOS	11.6	17.7	13.4
Teething	5.8	8.1	9.5
Nasopharyngitis	7.0	6.2	4.3
Cough	5.3	5.7	3.2
Pyrexia	4.4	3.1	4.3
Viral infection NOS	2.9	2.4	3.9
Rhinorrhoea	3.9	3.1	2.7
Nasal congestion	1.9	3.8	2.0
Conjunctivitis NEC [3]	3.0	4.1	1.6

[1] Only Group 1 from Study P3T06 4th Dose (Daptacel and ActHIB vaccines at 15 months of age) is included.
[2] Control means HCPDT, Poliovax, and ActHIB components for the 4th Dose of Study 494-01.
[3] NEC = Not Elsewhere Classified.
N' is the number of subjects from the Safety Population.

A post-hoc analysis was performed based on a list of categories of particular interest provided to sanofi pasteur by the FDA. Based upon this request, Table 24 presents the non-serious unsolicited adverse events occurring within 60 days of any vaccination of the Infant Series classified by FDA categories of particular interest and Table 25 presents the same analysis for the non-serious unsolicited adverse events occurring within 60 days of Dose 4. The most frequent category of interest for non-serious unsolicited AEs reported within 60 days of any vaccination of the Infant Series or Dose 4 was asthma and related diagnoses. In this category most commonly reported event was bronchiolitis during the Infant Series and bronchospasm after the 4th Dose.

As presented in Table 24, 0.1% of the subjects in each group experienced non-serious AEs that were classified in the pertussis category of interest. All 4 cases occurred after Dose 1 or Dose 2, recovered without sequelae and completed the trials.

Table 24: Infant Series: Incidence of Categories of Interest for Non-Serious Adverse Events Occurring Within 60 Days After Vaccination

	Pooled Pentacel	P3T06 Control [1]	494-01 Control [2]
	N=4197	N=1455	N=1032
Categories of Interest	%	%	%
Asthma and related diagnoses	16.2	21.6	11.8
Serious bacterial infections	1.3	2.0	1.4
Meningitis, not further specified	0.0	0.0	0.0
Viral meningitis	0.0	0.0	0.0
Encephalopathy, encephalitis	0.0	0.0	0.0
Fever, fever of unknown origin	7.1	10.9	3.7
Pertussis	<0.1	0.1	0.1
Hypotonic-hyporesponsive episode (HHE)	0.0	0.0	0.0
Hypotonia	0.1	0.1	0.0
Apnea	<0.1	0.0	0.4
Crying, irritability, restlessness	2.6	4.5	2.1
Somnolence, hypersomnia, lethargy	0.9	0.6	1.1
Febrile seizure	<0.1	0.1	0.0
Afebrile seizure	<0.1	0.1	0.2
Possible seizure	0.1	0.0	0.1
Infantile spasms	0.0	0.0	0.0
Other neurological events	0.3	0.3	0.0
Developmental delay	0.1	0.1	0.1
Autism	0.0	0.0	0.0
Injection site reactions	2.2	4.5	2.6
Petechiae, thrombocytopenia, purpura	<0.1	0.0	0.1

[1] Control means Daptacel, IPOL, and ActHIB vaccines for the Infant Series of Study P3T06.
[2] Control means HCPDT, Poliovax, and ActHIB components for the Infant Series of Study 494-01.
'N' is the number of subjects from the Safety Population.

Table 25: 4th Dose: Incidence of Categories of Interest for Non-Serious Adverse Events Occurring Within 60 Days After Vaccination

	Pooled Pentacel	P3T06 Control [1]	494-01 Control [2]
	N=5033	N=418	N=739
Categories of Interest	%	%	%
Asthma and related diagnoses	4.2	6.0	3.1
Serious bacterial infections	0.7	1.0	0.8
Meningitis, not further specified	0.0	0.0	0.0
Viral meningitis	0.0	0.0	0.0
Encephalopathy, encephalitis	0.0	0.0	0.0
Fever, fever of unknown origin	4.5	3.1	4.3
Pertussis	0.0	0.0	0.0
HHE	0.0	0.0	0.0
Hypotonia	0.0	0.0	0.0
Apnea	0.0	0.0	0.1
Crying, irritability, restlessness	0.4	0.2	1.4
Somnolence, hypersomnia, lethargy	0.1	0.2	0.1
Febrile seizure	0.2	0.0	0.3
Afebrile seizure	<0.1	0.0	0.0
Possible seizure	0.0	0.0	0.0
Infantile spasms	0.0	0.0	0.0
Other neurological events	0.1	0.0	0.0
Developmental delay	0.1	0.5	0.1
Autism	0.0	0.0	0.0
Injection site reactions	1.4	1.0	0.8
Petechiae, thrombocytopenia, purpura	0.0	0.0	0.0

[1] Control means Daptacel and ActHIB vaccines for the 4th Dose of Study P3T06; only data from Group 1 are presented.
[2] Control means HCPDT, Poliovax, and ActHIB components in Study 494-01.

Percentages are based on the number of subjects in the Safety Population.

Chronic Adverse Events and Events of Possible Autoimmune Origin Collected from Day 61 to Day 180 after Dose 4 in Study P3T06

Only 2 Pentacel vaccine subjects and 3 Control subjects experienced unsolicited events which were considered "chronic" based on duration (defined for the purposes of this report as ≥30 days) or that were specified as "chronic" by the Investigator. These events were cellulitis, congestive cardiac failure, congenital aortic valve incompetence (the last 2 events were experienced by the same subject) in the Pentacel group and otitis media chronic NOS, oral candidiasis, and failure to thrive in the Control Group. Four Pentacel vaccine subjects and 1 Control subjects experienced an event which was considered of possible auto-immune origin: asthma NOS, asthma aggravated (experienced by the subject with the congestive cardiac failure and the congenital aortic valve incompetence), serum sickness, leucopenia NOS, and thrombocytopenia (the last 2 events were

experienced by the same subject) in the Pentacel group and bronchospasm NOS in the Control Group. None of these events were considered related to vaccination by the investigators.

2.2.9 Events of Special Interest

The adverse events of hypotonic-hyporesponsive episode (HHE), hypotonia, non-febrile seizure, febrile seizure, and possible seizure were considered of special interest. The following parameters were used in the identification of these AEs:

- HHE: Investigators were asked to report as HHEs those events that fulfilled the Health and Human Services criteria published by Braun et al. (6): "events of sudden onset occurring within 48 hours of immunization, consisting of hypotonia, hyporesponsiveness and cyanosis (or failure to observe or to recall skin coloration), with duration of the episode ranging from 1 minute to 48 hours, in children younger than 10 years of age."
- Hypotonia: Investigators reported cases of hypotonia for which the association with other HHE criteria was not observed by the reporting parent or legally authorized representative.
- Non-febrile seizure: Events under this category were reported as seizures, convulsions, or epilepsy without the association of fever.
- Febrile seizure: Events were reported as "febrile seizures" or synonymous.
- Possible seizure: Events that elicited a suspicion of seizure but, in the opinion of the Principal Investigator, were not justified to be reported as such. Includes diagnoses of infantile spasms which, following FDA's request, are presented in this section as a separate category (post-hoc analysis).

The overall incidence of any of these events that occurred within 7 days are presented across all the pivotal trials in Table 26 for the Infant Series and in Table 27 for the 4th Dose.

Table 26: Infant Series; Number (Percentage) and Rates per 1000 Doses of Subjects With HHE, Hypotonia, Non-Febrile Seizure, Febrile Seizure and Possible Seizure Occurring Within 7 Days After Vaccination

	Pentacel N=4197		P3T06 Control [1] N=1455		494-01 Control [2] N=1032	
	n (%)	Rate/1000 Doses	n (%)	Rate/1000 Doses	n (%)	Rate/1000 Doses
HHE	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Hypotonia	4 (0.1)	1.0	1 (0.1)	0.7	0 (0.0)	0.0
Non-Febrile Seizure	1 (<0.1)	0.2	1 (0.1)	0.7	1 (0.1)	1.0
Febrile Seizure	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Possible seizure	1 (<0.1)	0.2	0 (0.0)	0.0	0 (0.0)	0.0

[1] Control means Daptacel, IPOL, and ActHIB vaccines for Infant Series of Study P3T06.

[2] Control means HCPDT, Poliovax, and ActHIB components for Infant Series of Study 494-01.

Percentages are based on the number of subjects in the Safety Population.

Table 27: 4th Dose: Number (Percentage) and Rates per 1000 Doses of Subjects With HHE, Hypotonia, Non-Febrile Seizure, Febrile Seizure and Possible Seizure Occurring Within 7 Days After Vaccination

	Pentacel N=5033		P3T06 Control [1] N=418		494-01 Control [2] N=739	
	n (%)	Rate/1000 Doses	n (%)	Rate/1000 Doses	n (%)	Rate/1000 Doses
HHE	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Hypotonia	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Non-Febrile Seizure	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Febrile Seizure	2 (<0.1)	0.4	0 (0.0)	0.0	2 (0.3)	2.7
Possible seizure	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0

[1] Control means Daptacel and ActHIB vaccines for the 4th Dose of Study P3T06; only data from Group 1 are presented.

[2] Control means HCPDT, Poliovax, and ActHIB components in Study 494-01.

Note: Percentages are based on the number of subjects in the Safety Population.

Hypotonic-Hyporesponsive Episode and Hypotonia

There were no reports of HHEs in subjects who were vaccinated with Pentacel vaccine after any of the Infant Series doses. Among the Control groups, no HHEs occurred within 7 days of vaccination; 1 subject in Study P3T06 experienced an event 16 days after the 2nd dose, which, although it occurred past the period during which it could have been classified as an HHE, was classified as such by the Investigator.

All cases of hypotonia occurred during the Infant Series. Five cases occurred within 7 days of vaccination (4 in subjects who received Pentacel and 1 in subject who received Control vaccines). Two additional cases were reported more than 7 days after vaccination: 1 in subject who received Pentacel vaccine (55 days post-Dose 2) and 1 in subject who received Control vaccines (91 days post-Dose 3). In several cases, given the reportedly mild nature of the event, the subject's parent or legally authorized representative did not contact a physician.

No cases of HHEs or Hypotonia were reported after Dose 4.

Non-Febrile Seizure

During the Infant Series, a total of 3 cases of non-febrile seizure occurred within 7 days of vaccination (1 in a subject who received Pentacel and 2 in subjects who received Control vaccines). A total of 12 additional cases occurred more than 7 days after vaccination: 10 in subjects who received Pentacel vaccine (4 within 60 days of any dose, 6 more than 60 days after the 3rd dose) and 2 in subjects who received Control vaccines (within 60 days of any dose).

In the 4th Dose studies, no cases of non-febrile seizure occurred within 7 days of Dose 4. A total of 7 cases (6 subjects) occurred more than 7 days after vaccination: 6 cases in 5 subjects who received Pentacel vaccine (5 within 60 days of Dose 4 and 1 had an event occurring more than 60 days after vaccination) and 1 in subject who received Control vaccines (14 days after Dose 4).

Febrile Seizure

During the Infant Series, no cases of febrile seizure occurred within 7 days of vaccination. A total of 19 subjects (21 cases) experienced a febrile seizure(s) more than 7 days after vaccination: 14 subjects who received Pentacel vaccine (1 within 60 days of any dose and 15 cases reported for 13 subjects occurred more than 60 days after the 3rd dose) and 5 subjects who received Control vaccines (2 within 60 days of any dose, and 3 more than 60 days after the 3rd dose).

In the 4th Dose studies, 4 cases occurred within 7 days of vaccination (2 in subjects who received Pentacel and 2 in subjects who received Control vaccines). A total of 14 additional cases of febrile seizure were reported more than 7 days after Dose 4: 12 in subjects who received Pentacel vaccine (11 subjects and 12 events occurred within 60 days, and an additional subject reported an event more than 60 days after vaccination) and 1 in subject who received Control vaccines (49 days after Dose 4).

Possible seizure

During the Infant Series, 1 case of possible seizure occurred within 7 days of Pentacel vaccination. A total of 8 additional cases occurred more than 7 days after vaccination: 6 in subjects who received Pentacel (4 within 60 days of any dose and 2 more than 60 days after the 3rd dose) and 2 in subjects who received Control vaccines (1 within 60 days of any dose, and 1 more than 60 days after the 2nd dose).

After the 4th Dose, no possible seizures were reported.

2.2.10 Serious Adverse Events

The numbers of SAEs that occurred within 60 days of vaccination after each dose of the Infant Series and within 60 days of Dose 4 (180 days for Study P3T06 4th Dose) are summarized in Table 28 and in Table 29, respectively.

For Pentacel vaccine recipients overall, 112 out of 4197 (2.7%) subjects in the Infant Series experienced 174 SAEs and 56 of 5033 (1.1%) subjects in the 4th Dose studies experienced 77 SAEs. In the controlled studies, within 60 days following any vaccination, SAEs were experienced by comparable percentages of Pentacel and Control vaccine subjects. The rate of SAEs was lower in the Infant Series and Dose 4 of Study 494-01 than it was for Study P3T06. In Study P3T06 4th Dose, which collected SAEs for 180 days, SAEs were reported for 2.1% of Pentacel vaccine recipients and 0.5% of Control subjects in the 61 to 180 days after the 4th Dose.

Table 28: Infant Series: Number (Percentage) of Subjects with Serious Adverse Events and Related Serious Adverse Events of Any Severity Within 60 Days After Vaccination

	P3T06		494-01		494-03	All Studies Combined
	Pentacel N=484	Control [1] N=1455	Pentacel N=2506	Control [1] N=1032	Pentacel N=1207	Pentacel N=4197
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Serious Adverse Events	25 (5.2)	75 (5.2)	38 (1.5)	17 (1.6)	49 (4.1)	112 (2.7)
Related Serious Adverse Events	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[1] "Control" means Daptacel, IPOL, and ActHIB vaccines for Study P3T06 and HCPDT, Poliovax, and ActHIB components for Study 494-01.

Notes: 'n' is the number of subjects experiencing the specified unsolicited event within the specified time period; 'N' is the number of subjects from the Safety Population who received at least 1 dose during the Infant Series.

Table 29: 4th Dose: Number (Percentage) of Subjects with Serious Adverse Events and Related Serious Adverse Events of Any Severity Within the Specified Time Period (Safety Population)

	P3T06		494-01		494-03	5A9908	All Studies Combined
	Pentacel N=431	Control [1, 2] N=418	Pentacel N=1862	Control [1] N=739	Pentacel [3] N=958	Pentacel N=1782	Pentacel N=5033
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Serious Adverse Events							
0-60 days	9 (2.1)	7 (1.7)	7 (0.4)	4 (0.5)	11 (1.1)	29 (1.6)	56 (1.1)
61-180 days	9 (2.1)	2 (0.5)	NA	NA	NA	NA	9 (2.1)
Related Serious Adverse Events							
0-60 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
61-180 days	0 (0.0)	0 (0.0)	NA	NA	NA	NA	0 (0.0)

[1] "Control" means Daptacel and ActHIB vaccines for Study P3T06 and HCPDT, Poliovax, and ActHIB component for Study 494-01.

[2] Only Group 1 from Study P3T06 4th Dose (Daptacel and ActHIB vaccines at 15 months of age) is included.

[3] All groups in Study 494-03 are pooled for analysis.

Notes: 'n' is the number of subjects experiencing the specified unsolicited event within the specified time period.; 'N' is the number of subjects from the Safety Population who received the 4th Dose.

NA = Not Applicable; events were captured between days 61 and 180 post-Dose 4 for study P3T06, only.

A post-hoc analysis was performed based on a list of categories of particular interest provided to sanofi pasteur by the FDA. Based upon this request, Table 30 presents the SAEs occurring with 60 days of any vaccination of the Infant Series classified by FDA categories of particular interest and Table 31 presents the same analysis for the SAEs occurring within 60 days of Dose 4. The most frequent category of interest was asthma and related diagnoses for SAEs reported within 60 days of any vaccination of the Infant Series and serious bacterial infection for SAEs reported within 60 days of Dose 4.

Non-febrile and febrile seizures (convulsions) have been specifically described in Section 2.2.9.

There were 5 cases of hospitalization in the category “fever, fever of unknown origin”, 2 after any dose of the Infant Series both in Control subjects in Study 494-01 (17 and 54 days after Dose 1) and 3 after the 4th Dose of Pentacel: 1 in Study 494-01 (14 days after Dose 4) and 2 in Study 5A9908 (16 and 21 days after Dose 4). None of these hospitalizations occurred within 3 days of immunization, which is the period when most vaccine-associated fevers occur. There were 2 reported cases of bronchospasm (both in Pentacel vaccine subjects) during the Infant Series and 7 cases (6 in Pentacel vaccine subjects and 1 in a Control vaccine subject) after the 4th Dose, none of which occurred within 3 days of immunization and only 1 case occurred within 7 days (Study 494-01). Three cases of pertussis were reported: one after the 1st dose of Pentacel vaccine, one (possible pertussis) after the 2nd dose of Pentacel vaccine, and one after the 1st dose of Daptacel vaccine. Only 1 case was confirmed by culture. All these subjects recovered without sequelae and completed the respective trials.

Table 30: Infant Series: Incidence of Categories of Interest for SAEs Occurring Within 60 Days After Vaccination

	Pentacel N=4197	P3T06 Control [1] N=1455	494-01 Control [2] N=1032
Categories of Interest	**%**	**%**	**%**
Asthma and related diagnoses	1.0	2.9	0.8
Serious bacterial infections	0.7	0.7	0.3
Meningitis, not further specified	0.0	0.1	0.0
Viral meningitis	0.1	0.1	0.0
Encephalopathy, encephalitis	<0.1	0.0	0.0
Fever, fever of unknown origin	0.0	0.0	0.2
Pertussis	<0.1	0.1	0.0
HHE	0.0	0.1	0.0
Hypotonia	0.0	0.0	0.0
Apnea	<0.1	0.1	0.0
Crying, irritability, restlessness	0.0	0.1	0.0
Somnolence, hypersomnia, lethargy	0.0	0.0	0.0
Febrile seizure	0.0	0.0	0.1
Afebrile seizure	0.1	0.1	0.0
Possible seizure	<0.1	0.0	0.0
Infantile spasms	0.0	0.0	0.0
Other neurological events	<0.1	0.0	0.0
Developmental delay	<0.1	0.0	0.0
Autism	0.0	0.0	0.0
Injection site reactions	0.0	0.0	0.0
Petechiae, thrombocytopenia, purpura	<0.1	0.0	0.0

[2] Control means Daptacel, IPOL, and ActHIB vaccines for the Infant Series of Study P3T06.

[1] Control means HCPDT, Poliovax, and ActHIB components for the Infant Series of Study 494-01.

'N' is the number of subjects from the Safety Population.

Table 31: 4th Dose: Incidence of Categories of Interest for SAEs Occurring Within 60 Days After Vaccination

	Pentacel N=5033	P3T06 Control [1,2] N=418	494-01 Control [1] N=739
Categories of Interest	**%**	**%**	**%**
Asthma and related diagnoses	0.2	0.0	0.1
Serious bacterial infections	0.3	0.0	0.1
Meningitis, not further specified	0.0	0.0	0.0
Viral meningitis	0.0	0.0	0.0
Encephalopathy, encephalitis	0.0	0.0	0.0
Fever, fever of unknown origin	0.1	0.0	0.0
Pertussis	0.0	0.0	0.0
HHE	0.0	0.0	0.0
Hypotonia	0.0	0.0	0.0
Apnea	0.0	0.0	0.0
Crying, irritability, restlessness	0.0	0.0	0.0
Somnolence, hypersomnia, lethargy	0.0	0.0	0.0
Febrile seizure	0.1	0.2	0.0
Afebrile seizure	<0.1	0.0	0.1
Possible seizure	0.0	0.0	0.0
Infantile spasms	0.0	0.0	0.0
Other neurological events	0.0	0.0	0.0
Developmental delay	0.0	0.0	0.0
Autism	0.0	0.0	0.0
Injection site reactions	0.0	0.0	0.0
Petechiae, thrombocytopenia, purpura	0.0	0.0	0.0

[1] "Control" means Daptacel and ActHIB vaccines for Study P3T06, and HCPDT, Poliovax, and ActHIB components for Study 494-01.
[2] Only Group 1 from Study P3T06 4th Dose (Daptacel and ActHIB vaccines at 15 months of age) is included.
'N' is the number of subjects from the Safety Population.

In Study P3T06, there were 9 SAEs reported by Pentacel vaccine recipients and 2 reported by Daptacel vaccine recipients between Day 61 and Day 180. None of these events were deemed by the Investigators as being related to vaccination.

No SAEs were reported as related to Pentacel vaccine in any of the pivotal trials. A 7-week-old female Study P3T06 participant experienced [non-febrile] seizure with apnea 12 hours post-Dose 1 of Daptacel, ActHIB, and IPOL vaccine administration, as well as Recombivax and Prevnar vaccine immunization. The events were considered probably related to vaccination.

In summary, the overall frequency of SAEs was similar between Pentacel and Control vaccine recipients, and no clustering of SAEs traditionally associated with acellular pertussis-based combination vaccines was identified.

Deaths reported in any of the pivotal trials

A total of 5 deaths were reported in the pivotal trials. Among these, 3 deaths occurred during the Infant Series, 2 of them in subjects who had received Pentacel vaccine and 1 in a subject who had received Control vaccines.

- A 2-month-old female Study 494-03 participant died following an automobile accident, 22 days post-Dose 1 of Pentacel vaccine.
- A 4-month-old male Study 494-03 participant died 52 days post-Dose 1 of Pentacel vaccine. The cause of death was reported as Sudden Infant Death Syndrome.
- An 8-month-old female Study P3T06 participant developed symptoms and was diagnosed with ependymoma, 54 days post-Dose 3 of Control vaccines. Death occurred 222 days post-Dose 3, and was due to aspiration.

One death occurred after Day 60 of the Infant Series and before the administration of the toddler dose:

- A 9-month-old male Study 494-01 participant developed symptoms, 95 days post-Dose 3 of Pentacel, and was later diagnosed with neuroblastoma, which eventually led to death, 256 days post-Dose 3.

One death occurred after administration of the toddler dose:

- A 15-month-old male Study P3T06 participant died from suffocation 9 days post-Dose 4 of Pentacel vaccine (the subjects was sleeping in a box covered by a sheet of Plexiglas).

All deaths were considered unrelated to vaccination by both the investigator and the Sponsor.

2.2.11 Safety of Pentacel Given at Different Ages at the 4th Dose

Study 5A9908 compared the safety of a 4th Dose of Pentacel vaccine when administered to subjects at different ages within the age range of 15 to 18 months. Fever rates were compared between the combined group of subjects who received the 4th Dose of Pentacel vaccine at 15 or 16 months and the combined group who received it at 17 or 18 months. The difference in the percentage of subjects reporting fever between the 2 groups was small (16.2% in the 15- and 16-month group versus 18.8 % in the 17- and 18-month group) and met the criteria of equivalence. During Day 0 to 3 post-vaccination, there were 2.59% fewer subjects (90% CI [-5.61, 0.42]) with fever in the 15- and 16-month group than in the 17-and 18-month group. Other solicited and unsolicited adverse events were also reported in very similar frequencies across age groups. The majority of local and systemic reactions were of mild or moderate intensity and were reported by similar numbers of subjects in each age group up to 3 days post-immunization. None of the reported SAEs was considered to be related to the study vaccine.

2.2.12 Safety of Pentacel With or Without Concomitant Vaccines

This section discusses the pivotal studies that compared safety findings on subjects who received Pentacel vaccine alone with those who received it concomitantly with other routine pediatric vaccines.

When Study 494-01 Infant Series was originally designed, Pneumococcal Conjugate vaccine (Prevnar) was not part of the standard infant vaccination schedule. However, shortly after the study began, the schedule changed; consequently, those subjects who were among the earlier participants received Pentacel vaccine alone at 2 months, while the majority received Pentacel

vaccine concomitantly with Prevnar vaccine at 2, 4, and 6 months of age. The data comparing subjects who received Pentacel vaccine with or without Prevnar vaccine are presented using descriptive methods only. After Dose 1, fever within 3 days was reported in 163 out of 1836 subjects (8.9%) who received the 2 vaccines concomitantly, compared to 23 out of 460 subjects (5.0%) who received Pentacel vaccine alone. After Dose 2, the difference in fever rates was reduced: 293/2044 (14.3%) compared to 11/86 (12.8%), and after Dose 3, fever rates were 377/1961 (19.2%) in the concomitant group compared to 6/27 (22.2%) subjects who received Pentacel alone.

In contrast, Study 494-03 4th Dose was designed from the onset to compare the safety results of 15-month-old subjects who received the 4th Dose of Pentacel vaccine alone (Group 1) to those of subjects who received Pentacel co-administered with measles, mumps and rubella (MMR) vaccine and varicella vaccine (Group 2) or co-administered with Prevnar vaccine (Group 3). The rates of severe solicited local and systemic reactions that occurred within 3 days were compared between groups using non-inferiority testing. Results showed that the percentage of subjects experiencing at least 1 severe local or systemic reaction in Groups 2 and 3 was statistically non-inferior to Group 1: that is, co-administration of MMR and varicella or Prevnar with Pentacel did not adversely affect the reactogenicity of Pentacel vaccine. The proportion of subjects experiencing at least 1 episode of fever within 7 days ranged from 10.3% in Group 1 to 17.3% in Group 3. Subjects in Group 4, who received Prevnar, MMR, and varicella vaccines at 15 months and Pentacel vaccine alone at 16 months, had almost identical rates of fever to Group 3 (17.2%), indicating that the co-administration of Prevnar with Pentacel vaccines did not induce more fever than the co-administration of Prevnar vaccine with MMR vaccine and varicella vaccines.

2.2.13 Safety Conclusions

The data presented in this document support the following conclusions with regard to the Pentacel vaccine trials:

- The safety profile of Pentacel vaccine compares favorably to that of the separate administration of its licensed-equivalent component vaccines (Daptacel, IPOL, and ActHIB vaccines) or formulation-equivalent components (HCPDT, Poliovax, and ActHIB). Subjects who received Pentacel vaccine were equally or less likely to experience vaccine reactions (i.e., solicited local and systemic) than were subjects who received the separate administration of its licensed-equivalent vaccines or formulation-equivalent components. There were no SAEs or seizures that the Investigators considered to be related to Pentacel vaccine, and no HHEs were reported.
- Pentacel vaccine is safe when administered alone or concomitantly with other age-recommended vaccines.
- The safety profile of Pentacel vaccine is consistent across different manufacturing lots.

The overall reactogenicity profile of Pentacel vaccine indicates that it is a well-tolerated vaccine with a safety profile that is adequate to support its licensure.

2.3 Immunogenicity Results

All results presented for the immunogenicity analyses are for the PP Immunogenicity Population, which was the population defined for use in the primary analyses. In all cases, results were similar in the Intent-to-Treat Immunogenicity Population. The clinical studies included in this section are P3T06, which compared Pentacel to the US-licensed standard-of-care vaccines; 494-01, which was a Pentacel lot-consistency study and a comparison to the formulation-equivalent components; 494-03 and M5A07, which assessed the concomitant administration of Pentacel with other recommended vaccines; and 5A9908, which assessed the immunogenicity of a 4th Dose of Pentacel administered at 15-18 months of age.

2.3.1 Immunogenicity Endpoints

The clinical limits defining non-inferiority are presented in Table 32.

Table 32: Clinical Limits Defining Non-Inferiority or Equivalence

Endpoint	Non-inferiority or Equivalency Criteria Using 90% or 95% CI
4-fold Rise Rates (Pertussis), Seroprotection Rates (Diphtheria, Tetanus, and PRP), and Vaccine Response Rates [1] (Pertussis)	Difference in rates between groups at 10% margin
Polio Seroprotection Rates	5% margin and rates >90%
Geometric Means Titers (GMTs) (All Antigens)	Ratio between groups at 1.5 margin

[1] Not predefined in the protocols.

2.3.2 Immunologic Outcomes

The endpoints defining the immunologic outcomes are presented in Table 33.

Table 33: Endpoints for Immunologic Outcomes

Antibody to	Infant Series Endpoints	4th Dose Endpoints
Diphtheria, Tetanus	**Seroprotection:** ≥0.01 IU/mL, ≥0.1 IU/mL **GMT**	**Seroprotection:** ≥0.1 IU/mL, ≥1.0 IU/mL **GMT**
PT, FHA, PRN, FIM	**4-fold Rise:** ≥4-fold rise (post-Dose 3/pre-Dose 1) **Vaccine Response [1]:** ≥4x LOQ [2] if pre- Dose 1 <4x LOQ EU/mL, or ≥pre-Dose 1 if pre-Dose 1 ≥4x LOQ **GMT**	**4-fold Rise:** ≥4-fold rise (post-Dose 4/pre-Dose 1) **Vaccine Response [1]:** ≥4x LOQ [2] if pre- Dose 1 <4x LOQ EU/mL, or ≥pre-Dose 1 if pre- Dose 1 ≥4x LOQ **GMT**
PRP	**Seroprotection:** ≥0.15 µg/mL, ≥1.0 µg/mL **GMT**	**Seroprotection:** ≥1.0 µg/mL **GMT**
Poliovirus Types 1, 2, 3	**Seroprotection**: ≥8 (1/dil) **GMT**	**Seroprotection**: ≥8 (1/dil) **GMT**

[1] Not predefined in the protocols.
[2] Limit of Quantitation (LOQ) is defined as 5 EU/mL for PT, 3 EU/mL for PRN and FHA, and 17 EU/mL for FIM.

2.3.3 Efficacy Assessment

Defined immunologic correlates of protection exist for diphtheria, tetanus, Hib, and poliovirus, therefore evidence of efficacy is provided by demonstrating that the immune responses to these antigens attain levels previously established as protective (7) (8) (9).

Efficacy of Pentacel vaccine against diphtheria and tetanus was assessed in study P3T06 by evaluating the percentage of subjects achieving short term and long term protective thresholds of 0.01 IU/mL and 0.1 IU/mL respectively and by demonstrating that the anti-diphtheria and anti-tetanus toxin seroprotective rates for Pentacel vaccine were non-inferior to the US-licensed standard-of-care (Daptacel, IPOL, and ActHIB) vaccines.

Efficacy of Pentacel vaccine against Hib was assessed in study P3T06 by evaluating the percentage of subjects achieving the protective thresholds ≥0.15 µg/mL and ≥1.0 µg/mL and by demonstrating that the anti-PRP seroprotective rates for Pentacel vaccine were non-inferior to the rates achieved with the current standard of care (Daptacel, IPOL, and ActHIB) vaccines.

Efficacy of Pentacel vaccine against polio was assessed in Study P3T06 by evaluating the percentage of subjects achieving neutralizing antibodies to a titer of at least 1:8 (1/dil) and by demonstrating that the anti-polio seroprotective rates for Pentacel vaccine were non-inferior to the current standard of care (Daptacel, IPOL, and ActHIB) vaccines.

There are no universally accepted correlates of protection for pertussis; accordingly, consistent with the FDA Guidelines for the Evaluation of Combination Vaccines for Preventable Diseases, April 1997 (10), efficacy is inferred through immunogenicity comparison to the current standard of care and to the underlying efficacy trial. The efficacy for Pentacel vaccine in infants and toddlers was established based on post-Dose 3 and post-Dose 4 non-inferiority comparisons of anti-pertussis 4-fold rise rates and antibody geometric mean titers (GMTs) achieved by Pentacel vaccine as compared to the standard-of-care (Daptacel, IPOL, and ActHIB vaccines in Study P3T06, and by non-inferiority comparisons of anti-pertussis 4-fold rise rates and antibody GMTs achieved by 4 doses of Pentacel vaccine in Studies P3T06 and 494-01 as compared to a cohort of sera obtained from infants given Daptacel vaccine in the Sweden I Efficacy Trial (see Sections 2.3.4.1.1 and 2.3.4.3.1).

2.3.4 Pertussis

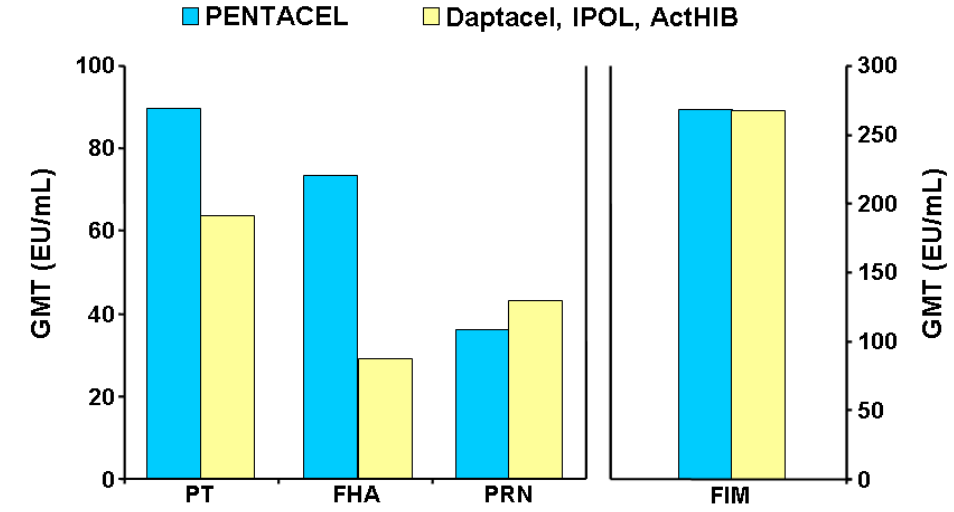
2.3.4.1 Comparison to Standard of Care Vaccines

Geometric Mean Titers

Figure 7 and Figure 8 present the antibody GMTs for the Pertussis antigens after the 3rd and 4th Dose, respectively, for Study P3T06. For all Pertussis antigens, the comparisons based on the GMT ratios for the PT, FHA, PRN, and FIM antigens fulfilled the statistical criteria supporting the non-inferiority of Pentacel to the separately administered US-licensed standard of care vaccines Daptacel, IPOL, and ActHIB (the Control vaccines) after the 3rd dose (see Figure 11). Similarly, the comparisons based on the GMT ratios of the PT, FHA, and FIM antigens fulfilled the statistical criteria supporting the non-inferiority of Pentacel to Daptacel vaccine after the 4th Dose (see Figure 12). Of the 8 non-inferiority comparisons, the only one that did not meet the statistical criteria of non-inferiority was that based on the GMT ratio of the antibodies to PRN after the 4th Dose; the GMT elicited by Pentacel vaccine for PRN was lower than that elicited by the Control vaccines. As shown in Figure 11, in a post-hoc analysis PT and FHA post-Dose 3 GMTs for Pentacel vaccine were found to be significantly superior to those of Daptacel vaccine in

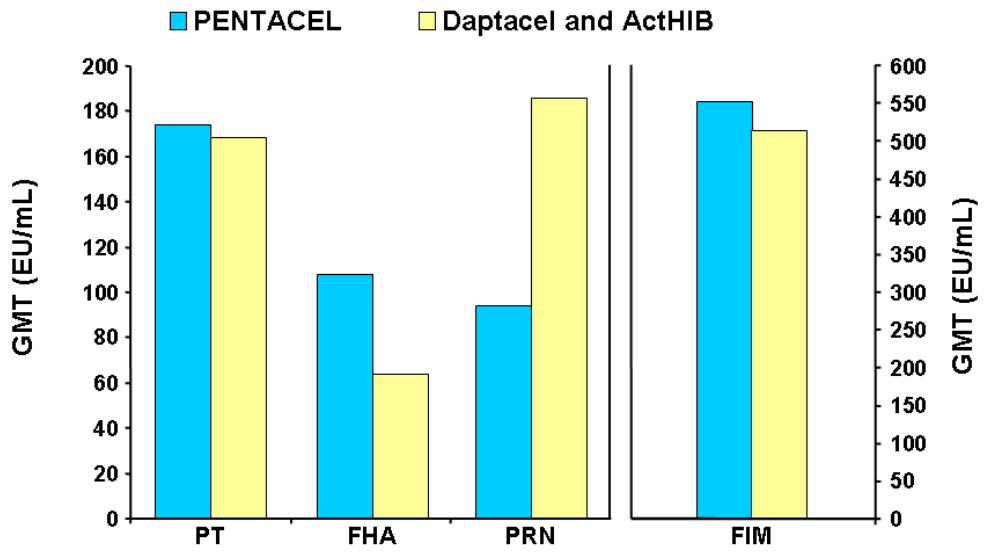
Study P3T06, as assessed by the upper bound of the confidence interval being below 1. In addition, following the 4th Dose, the FHA GMT for Pentacel vaccine was found to be significantly superior to that of Daptacel vaccine (see Figure 12).

Figure 7: Study P3T06: Pentacel vs. Standard of Care - Post-Dose 3 Pertussis GMTs



PENTACEL	90.0	73.7	36.1	268.2
Control	63.8	29.2	43.3	267.2

Figure 8: Study P3T06: Pentacel vs. Standard of Care - Post-Dose 4 Pertussis GMTs



PENTACEL	174.0	107.9	93.6	553.4
Control	168.5	64.0	186.1	513.5

Four-fold Rise Rates

Table 34 and Table 35 summarize, respectively, the post-Dose 3 and post-Dose 4 Pentacel vaccine 4-fold rise rates for the pertussis antigens as compared to the separate administration of Daptacel vaccine in Study P3T06.

Pentacel vaccine elicited 4-fold rise rates to each of the pertussis antigens that fulfilled the pre-established criteria demonstrating the non-inferiority of Pentacel vaccine to Daptacel vaccine after 3 doses and after 4 doses (see Figure 11 and Figure 12, respectively). As shown in Figure 11, in a post-hoc analysis PT, FHA, and FIM post-Dose 3 4-fold rise rates for Pentacel vaccine were found to be significantly superior to those of Daptacel vaccine in Study P3T06, as assessed by the upper bound of the confidence interval being below 0. In addition, following the 4th Dose, the FHA 4-fold rise rate for Pentacel vaccine was found to be significantly superior to that of Daptacel vaccine (see Figure 12).

Table 34: Study P3T06: Post-Dose 3 Four-fold Rise Rates for Pertussis Antigens and Non-inferiority Testing Results for Pentacel vs. Daptacel

Antigen	Criteria	Pooled Daptacel Lots n/N % (95%CI)	Pentacel n/N % (95%CI)	Non-inferiority Comparison Daptacel-Pentacel (90%CI)	Non-inferiority Yes/No [1]
PT (EU/mL)	**≥4-fold rise [2]**	613/712 86.1 (83.3, 88.6)	205/219 93.6 (89.5, 96.5)	-7.51 (-10.97, -4.06)	Yes
FHA (EU/mL)	**≥4-fold rise [2]**	441/724 60.9 (57.2, 64.5)	181/221 81.9 (76.2, 86.7)	-20.99 (-26.19, -15.79)	Yes
PRN (EU/mL)	**≥4-fold rise [2]**	540/716 75.4 (72.1, 78.5)	164/221 74.2 (67.9, 79.8)	1.21 (-4.31, 6.73)	Yes
FIM (EU/mL)	**≥4-fold rise [2]**	616/714 86.3 (83.5, 88.7)	200/218 91.7 (87.3, 95.0)	-5.47 (-9.19, -1.74)	Yes

[1] Non-Inferiority is achieved when the upper limit of the 90% CI of the rate difference (Daptacel-Pentacel) is <10%.

[2] The fold-rise is calculated by Post-Dose 3/Pre-Dose 1.

Note: 'n' is the number of subjects who achieved the criteria specified.
'N' is the number of subjects with a valid serology result post-Dose 3 and pre-Dose 1.

Table 35: Study P3T06: Post-Dose 4 Four-fold Rise Rates for Pertussis Antigens and Non-inferiority Testing Results for Daptacel+ActHIB (Group 1) vs. Pentacel (Group 4)

Antigens	Criteria	Group 1 n/N % (95% CI)	Group 4 n/N % (95% CI)	Non-inferiority Comparison Group 1-Group 4 (90% CI)	Non-inferiority Yes/No [1]
PT (EU/mL)	**≥4-fold rise [2]**	231/238 97.1 (94.0, 98.8)	225/231 97.4 (94.4, 99.0)	-0.34 (-2.84, 2.15)	Yes
FHA (EU/mL)	**≥4-fold rise [2]**	192/242 79.3 (73.7, 84.3)	205/232 88.4 (83.5, 92.2)	-9.02 (-14.53, -3.52)	Yes
PRN (EU/mL)	**≥4-fold rise [2]**	237/241 98.3 (95.8, 99.5)	215/232 92.7 (88.5, 95.7)	5.67 (2.55, 8.79)	Yes
FIM (EU/mL)	**≥4-fold rise [2]**	217/237 91.6 (87.3, 94.8)	215/230 93.5 (89.5, 96.3)	-1.92 (-5.92, 2.08)	Yes

[1] Non-inferiority: Upper limit of the 2-sided 90% CI of Group 1–Group 4 <10%.

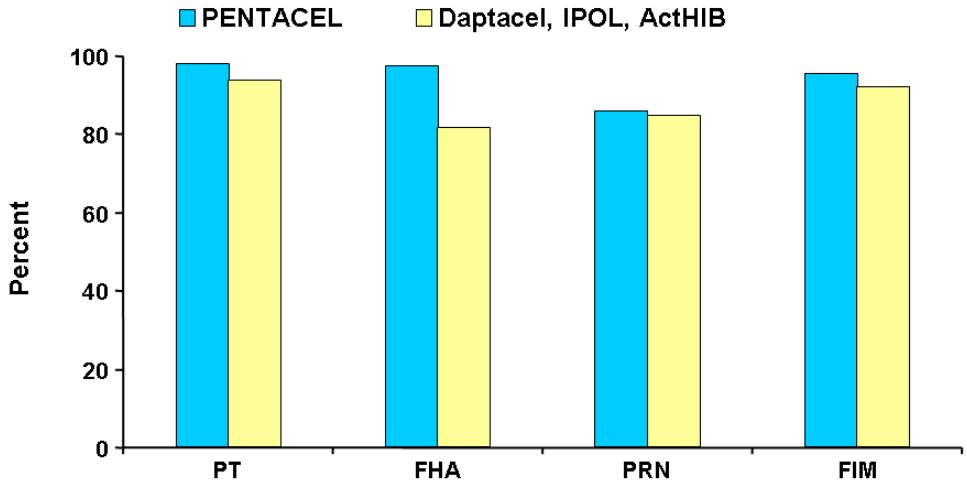
[2] The fold-rise is calculated by Post-Dose 4/Pre-Dose 1.

Note: Group is defined as per randomization. Group 1 received the 4th Dose of Daptacel concomitantly with the 4th Dose of ActHIB at 15-16 months of age. The 1st dose of MMR and varicella vaccines, and the 4th Dose of Prevnar were given at 12 months. Group 4 received the 4th Dose of Pentacel at 15-16 months of age. The 1st dose of MMR and varicella vaccines, and the 4th Dose of Prevnar were given at 12 months.
'n' is the number of subjects who met the criteria of the test indicated.
'N' is the total number of subjects with available serology data from the PP Immunogenicity Population.

Vaccine Response Rates

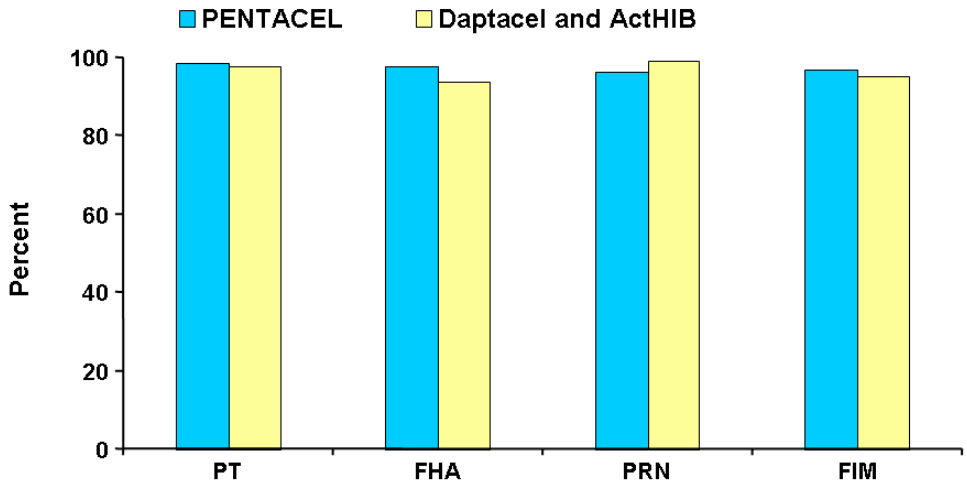
Figure 9 and Figure 10 summarize, respectively, the post-Dose 3 and post-Dose 4 Pentacel vaccine response rates for the pertussis antigens as compared to the separate administration of Daptacel, IPOL, and ActHIB vaccines in Study P3T06. The estimate of vaccine response rates was performed as a post-hoc analysis designed to control for high pre-immunization titers that may interfere with the assessment of 4-fold rise as a parameter of vaccine response. In this analysis, Pentacel vaccine elicited vaccine response rates to each of the pertussis antigens that fulfilled the criteria demonstrating the non-inferiority of Pentacel vaccine to Daptacel vaccine after 3 doses and after 4 doses (see Figure 11 and Figure 12, respectively). Although not part of the pre-specified criteria, we believe that these exploratory data reflect the ability to measure how individuals receiving Pentacel respond to the Pertussis antigens. After Dose 4, ≥97% of Pentacel recipients and ≥94% of Daptacel recipients responded to the Pertussis antigens in these vaccines.

Figure 9: Study P3T06: Pentacel vs. US Standard of Care Vaccines - Post-Dose 3 Pertussis Vaccine Response Rates



PENTACEL	98.2	97.7	86.4	95.9
Control	93.8	81.9	84.9	92.2

Figure 10: Study P3T06: Pentacel vs. US Standard of Care Vaccines - Post-Dose 4 Pertussis Vaccine Response Rates



PENTACEL	99.1	98.3	97.0	97.4
Control	98.3	94.2	99.6	95.8

Figure 11: Study P3T06: Pentacel vs. US Standard of Care Vaccines - Post-Dose 3 Pertussis Non-Inferiority Comparisons

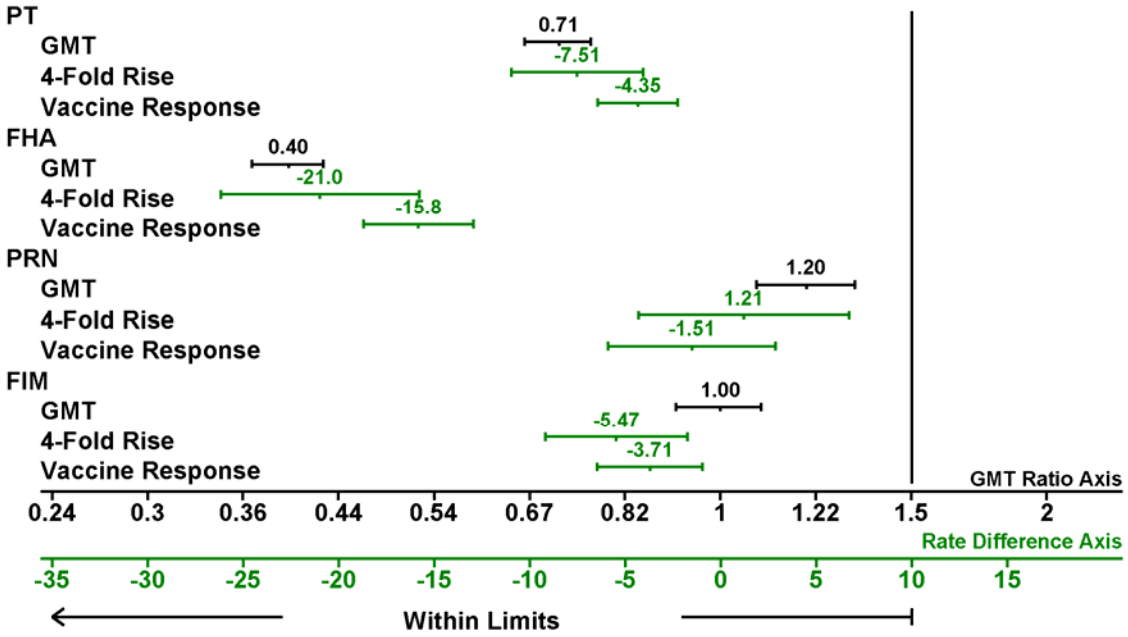
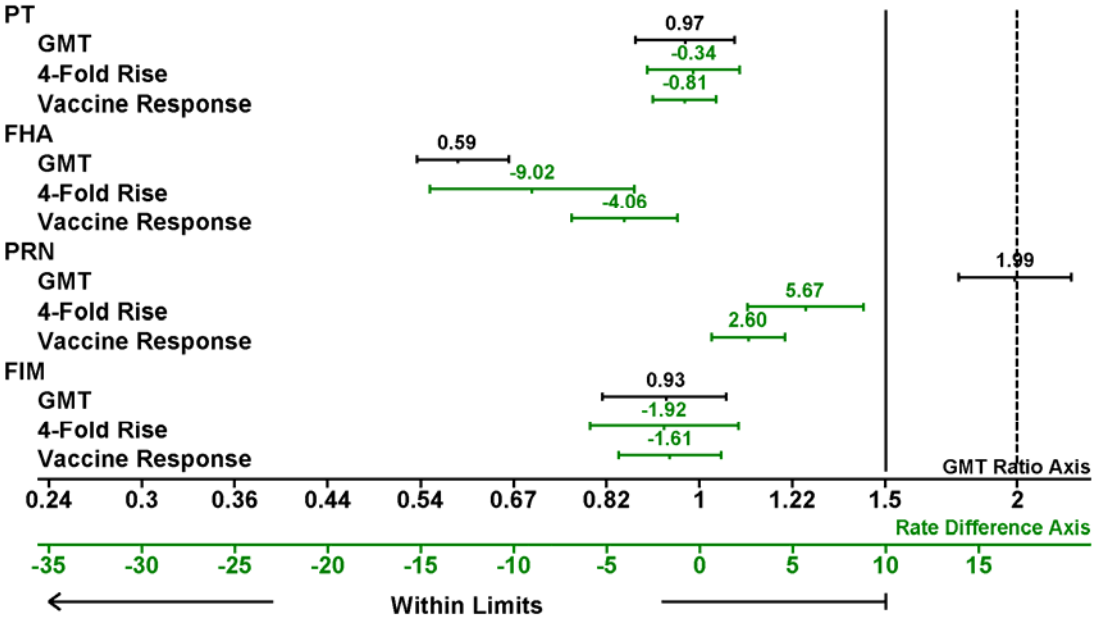


Figure 12: Study P3T06: Pentacel vs. US Standard of Care Vaccines - Post-Dose 4 Pertussis Non-Inferiority Comparisons



2.3.4.1.1 Bridge to Efficacy: Comparison to Sweden I

In the Sweden I Efficacy trial a total of 9,829 infants received 1 of 4 vaccines at 2, 4, and 6 months of age: Daptacel (called CPDT in that study); a 2 component acellular pertussis vaccine (DTaP2) (SmithKline Beecham); a whole-cell pertussis vaccine (DTwP, Connaught Laboratories); or DT vaccine as placebo. In this study, it was demonstrated that the protective efficacy of Daptacel using the World Health Organization case definition of pertussis (i.e., ≥21

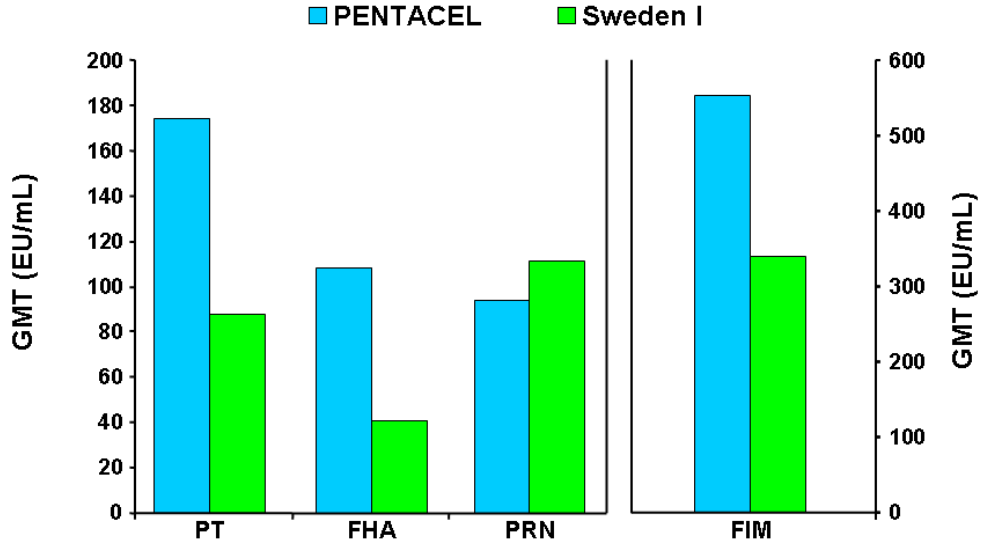
consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiologic link to a confirmed case) was 84.9% (95% CI 80.1 to 88.6%). The protective efficacy of Daptacel vaccine against mild pertussis (defined as ≥1 day of cough with laboratory confirmation of pertussis) was 77.9% (95% CI 72.6 to 82.2%). While the efficacy of the DTwP vaccine tended to decline over time, the efficacy of Daptacel vaccine remained at 80% or higher during the 2 years of follow-up (11).

The pertussis antigens in Pentacel vaccine are identical to those in Daptacel vaccine with the exception that Pentacel contains higher quantities of PT and FHA. In order to compare the immunogenicity of Daptacel vaccine in Sweden I to trials with Pentacel vaccine in the US, a panel of representative sera from the infants immunized with Daptacel vaccine in the Sweden I Efficacy trial and sera from Pentacel vaccine recipients were contemporaneously tested in the same sanofi pasteur laboratory using a validated assay and identical methodology. Non-inferiority of antibody levels was assessed using the 2-sided 90% CI around the antibody GMT ratios derived from US subjects who received 4 doses of Pentacel vaccine in Study P3T06 and Sweden subjects who received 3 doses of Daptacel vaccine in the Sweden I Efficacy Trial. This approach provided a direct link between the clinical performance of Pentacel vaccine and the vaccine efficacy demonstrated in the Sweden I Efficacy Trial.

Geometric Mean Titers

Figure 13 presents the anti-Pertussis GMTs of subjects given Pentacel in Study P3T06 as compared to those of children given Daptacel in the Sweden I efficacy study. Statistical comparisons based on the antibody GMT ratios for the PT, FHA, PRN, and FIM antigens fulfilled the statistical criteria supporting the non-inferiority of antibodies following Pentacel vaccine to those following Daptacel vaccine in the Sweden I efficacy trial (see Figure 16). As shown in Figure 16, in a post-hoc analysis PT, FHA, and FIM GMTs for Pentacel vaccine were found to be significantly superior to Daptacel vaccine GMTs from Sweden I, as assessed by the upper bound of the confidence interval being below 1.

Figure 13: Study P3T06: Pentacel vs. Sweden I (Bridge to Efficacy) - GMTs

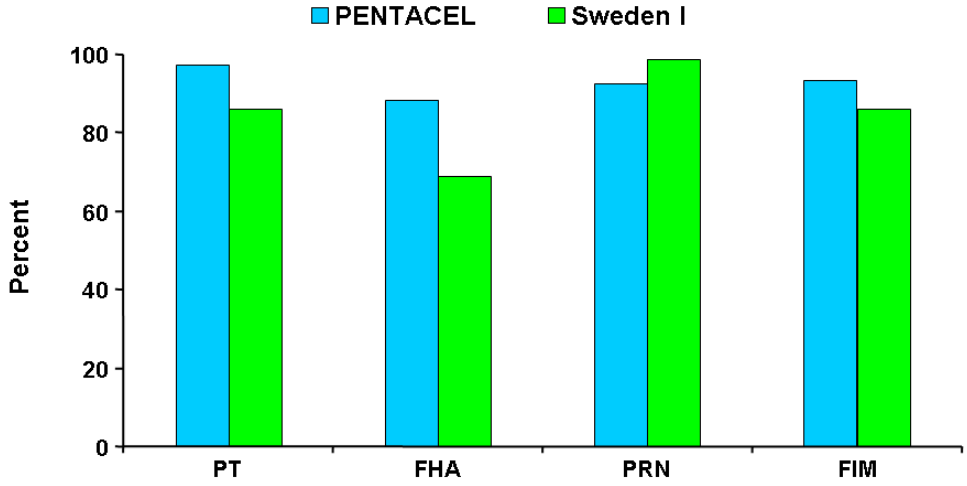


PENTACEL	174.0	107.9	93.6	553.4
Sweden I	87.5	40.7	111.3	339.3

Four-fold Rise Rates

Figure 14 presents the 4-fold rise rates for Pentacel recipients from Study P3T06 with those for Daptacel recipients in the Sweden I Efficacy Trial. The comparisons based on the 4-fold rise rates (post/pre ≥4-fold rise) of PT, FHA, and FIM fulfilled the statistical criteria supporting the non-inferiority of Pentacel vaccine in Study P3T06 to Daptacel vaccine in the Sweden I Efficacy Trial (see Figure 16). The only comparison that did not meet the statistical criterion of non-inferiority was that based on the difference in the 4-fold rates to PRN. The upper bound of the 95% CI of the difference in the 4-fold rise rate to PRN was 10.2% as compared to a non-inferiority limit of 10%. As shown in Figure 16, in a post-hoc analysis PT and FHA 4-fold rise rates for Pentacel vaccine were found to be significantly superior to the 4-fold rise rates for Daptacel vaccine from Sweden I, as assessed by the upper bound of the confidence interval being below 0.

Figure 14: Study P3T06: Pentacel vs. Sweden I (Bridge to Efficacy) - 4-Fold Rise Rates



PENTACEL	97.4	88.4	92.7	93.5
Sweden I	86.3	68.8	98.8	86.3

Analysis of PRN Pre-vaccination Titers in P3T06 and Sweden I

Additional (post-hoc) analysis of the anti-Pertussis GMTs in the PP Population showed that subjects participating in Study P3T06 had a significantly higher mean anti-PRN pre-immunization (2 months of age) antibody level than did subjects who participated in the Sweden I Efficacy Trial (GMT 3.09 EU/mL in Study P3T06 versus 2.17 EU/mL in Sweden I; $p<0.001$ by t-test based on log-titers). Based on this finding, an exploratory matching analysis was performed (12),(13) in order to assess whether subjects with equivalent anti-PRN pre-immunization antibody levels in P3T06 and Sweden I had similar post-immunization outcomes. Sweden I subjects were sorted according to their pre-Dose 1 PRN antibody levels, and a subset of Study P3T06 subjects was identified by matching their pre-immunization antibody levels to the subjects in Sweden I. A 95% CI for the difference in 4-fold rise rates between Sweden I and Study P3T06 (4th Dose) was calculated. As shown in Table 36, the difference in seroconversion rates between Sweden I and Study P3T06 was 2.8% with an upper limit of the 95% CI of 6.7%, thus fulfilling the non-inferiority criteria of an upper limit of the 95% CI of <10%. Accordingly, the previously noted failure of non-inferiority appears primarily to be due to a mismatch in pre-vaccination titers rather than a difference in response to vaccine.

Table 36: Serology Bridge Data: Seroconversion Analysis of Antibody Levels for PRN (2:1 Matched Data Analysis)

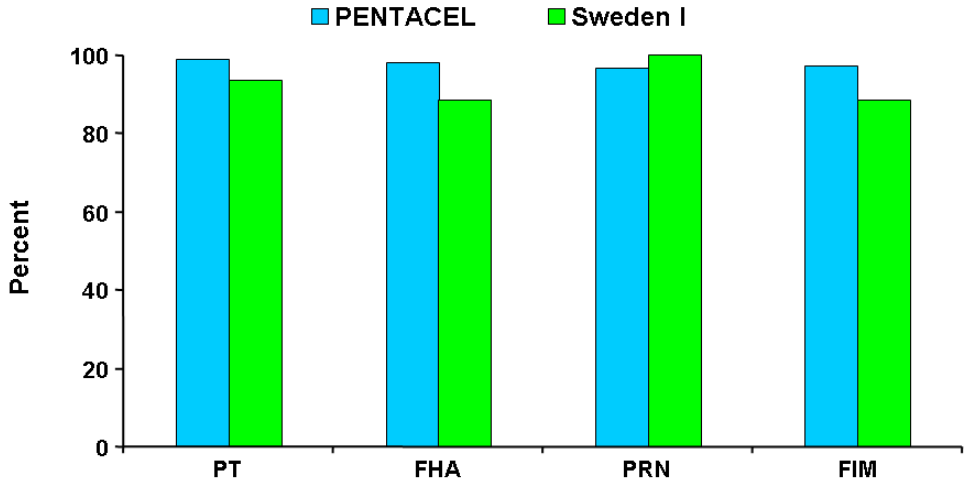
Probability of a ≥4-fold Rise		Non-Inferiority Comparison		
Sweden I Daptacel (N=80)	P3T06 4th Dose Pentacel (N=160)	Daptacel-Pentacel	95% CI	Non-Inferiority Yes/No [1]
98.8%	96.0%	2.8%	(-1.1, 6.7)	Yes

[1] Non-inferiority was achieved if the upper limit of the 2-sided 95% CI of Daptacel-Pentacel is <10%.

Vaccine Response Rates

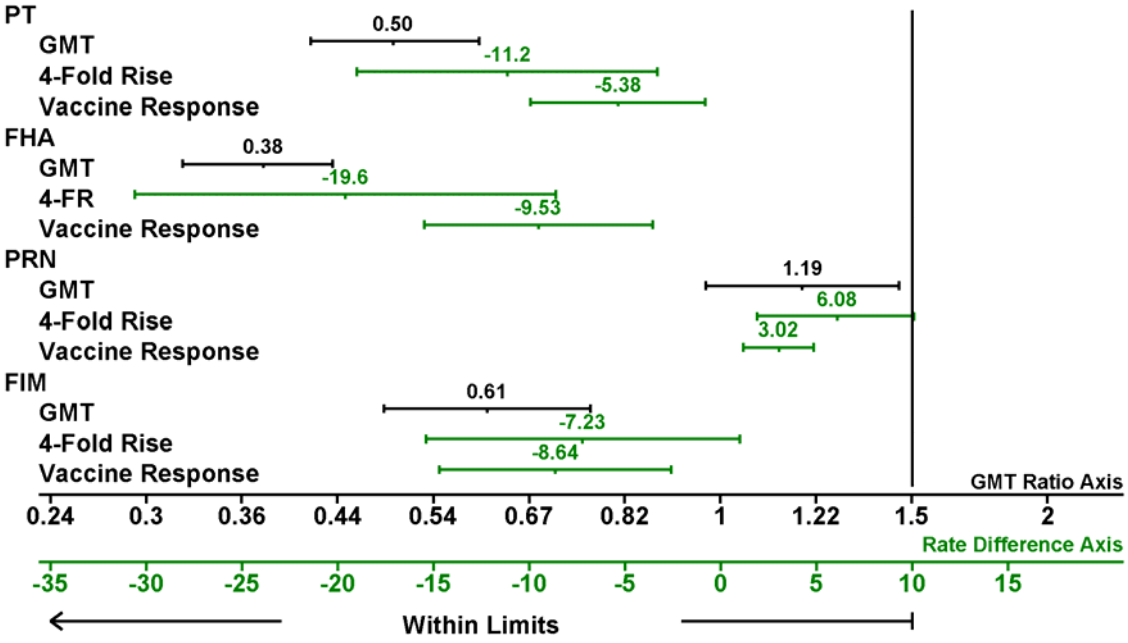
Figure 15 summarizes the post-Dose 4 vaccine response rates for the pertussis antigens for Pentacel recipients from Study P3T06 as compared to the separate administration of Daptacel vaccine in the Sweden I Efficacy Trial. In this post-hoc analysis, Pentacel vaccine elicited vaccine response rates to each of the pertussis antigens that would fulfill the statistical criteria demonstrating the non-inferiority of Pentacel vaccine in the US cohorts to Daptacel vaccine in the Sweden I trial (see Figure 16).

Figure 15: Study P3T06: Pentacel vs. Sweden I (Bridge to Efficacy) - Vaccine Response Rates



PENTACEL	99.1	98.3	97.0	97.4
Sweden I	93.8	88.8	100.0	88.8

Figure 16: Study P3T06: Pentacel vs. Sweden I (Bridge to Efficacy) - Non-Inferiority Analyses

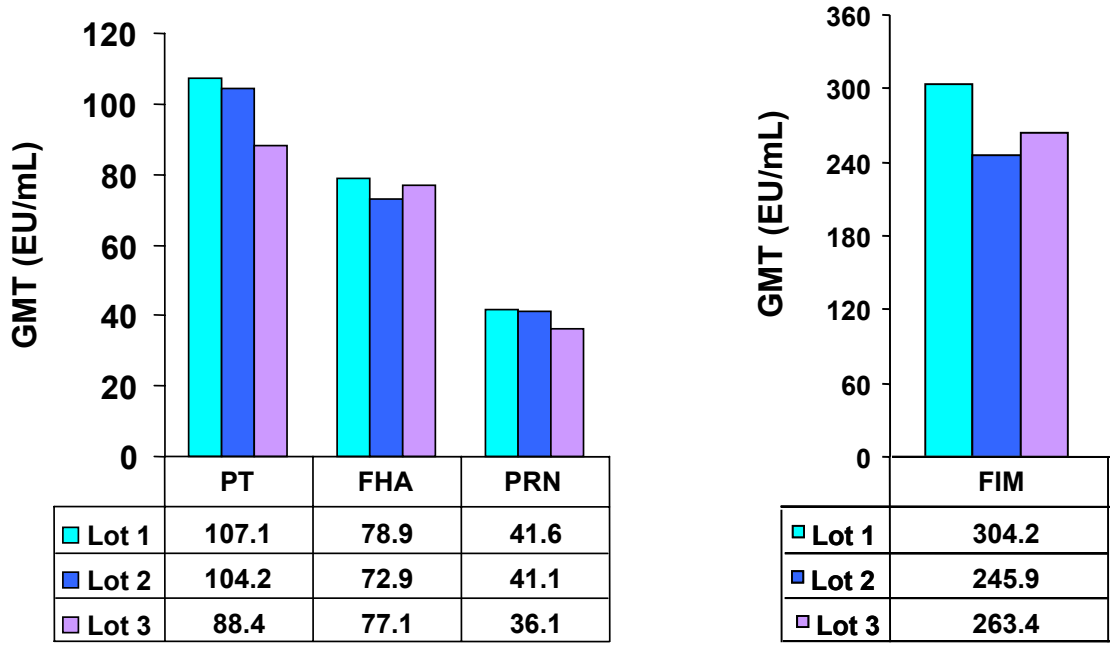


2.3.4.2 Lot Consistency

Geometric Mean Titers

Figure 17 presents the GMTs for all pertussis antigens after the 3rd dose of each lot of Pentacel vaccine in Study 494-01. The GMTs for each of the pertussis antigens fulfilled the statistical criteria for equivalence (see Figure 20).

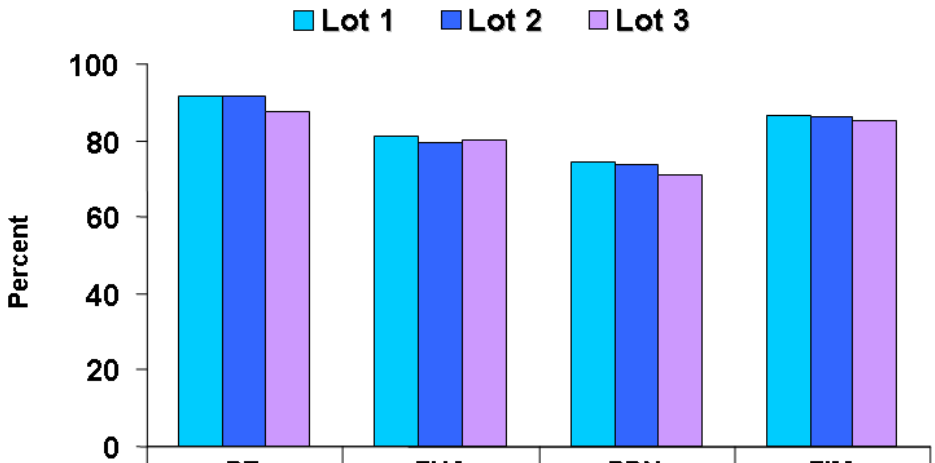
Figure 17: Study 494-01: Lot Consistency - Post-Dose 3 Pertussis GMTs



Four-fold Rise Rates

Figure 18 shows the 4-fold rise rates for the pertussis antigens across the 3 lots of Pentacel. The 4-fold rise rates to all the antigens contained in Pentacel vaccine fulfilled the statistical criteria for equivalence among the 3 lots of Pentacel vaccine (see Figure 20).

Figure 18: Study 494-01: Lot Consistency - Post-Dose 3 Pertussis 4-Fold Rise Rates

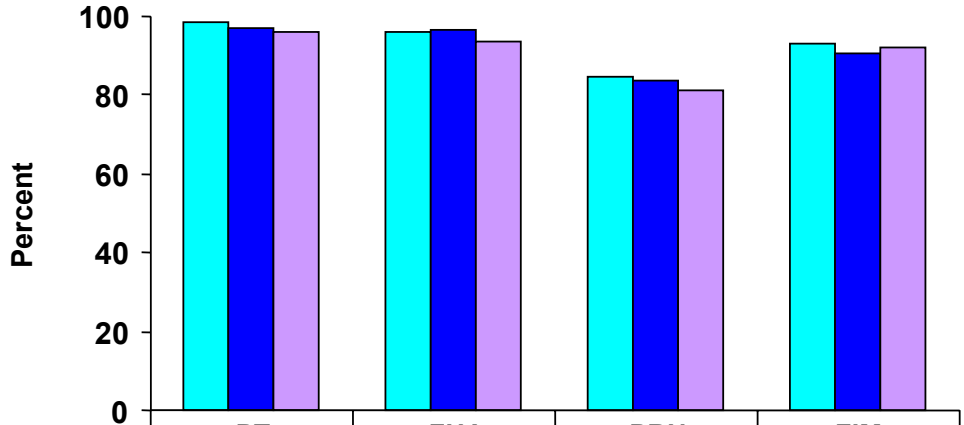


	PT	FHA	PRN	FIM
Lot 1	91.7	81.3	74.4	86.9
Lot 2	91.9	79.3	74.0	86.1
Lot 3	87.4	80.3	71.1	85.5

Vaccine Response Rates

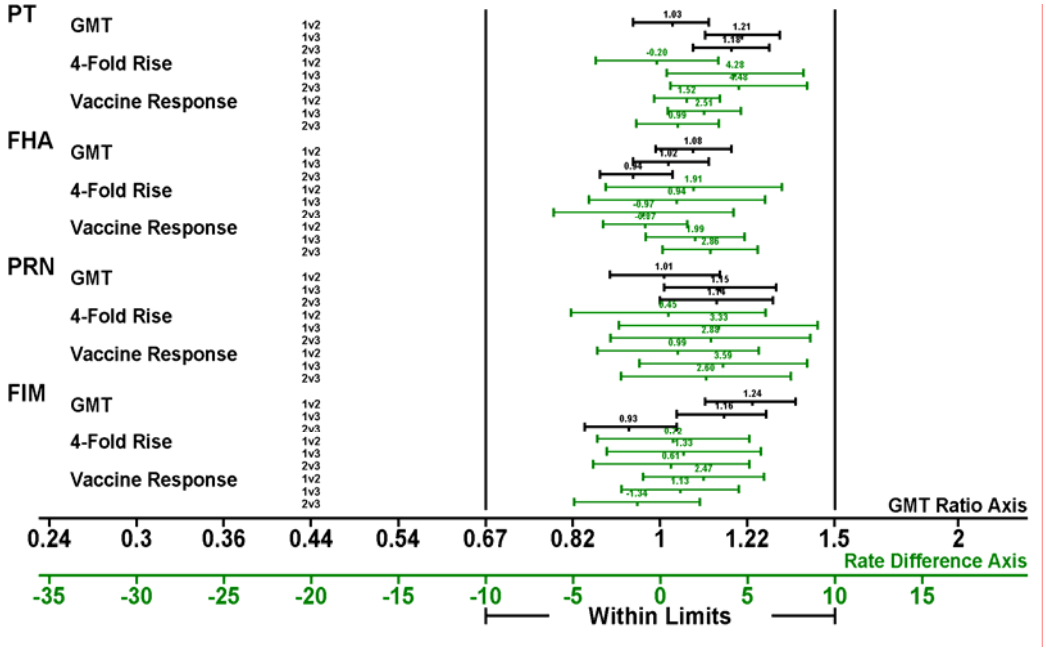
Figure 19 shows the vaccine response rates (post-hoc) for the pertussis antigens across the 3 lots of Pentacel. The vaccine response rates to all the antigens contained in Pentacel vaccine fulfilled the statistical criteria for equivalence among the 3 lots of Pentacel vaccine (see Figure 20).

Figure 19: Study 494-01: Lot Consistency – Post-Dose 3 Pertussis Vaccine Response Rates



	PT	FHA	PRN	FIM
Lot 1	98.5	95.8	84.8	93.1
Lot 2	97.0	96.7	83.8	90.7
Lot 3	96.0	93.8	81.2	92.0

Figure 20: Study 494-01: Lot Consistency - Post-Dose 3 Pertussis



In summary, all 36 (24 primary and 12 post-hoc) comparisons designed to demonstrate the immunogenicity lot consistency for the pertussis antigens in Pentacel fulfilled the statistical criteria of equivalence.

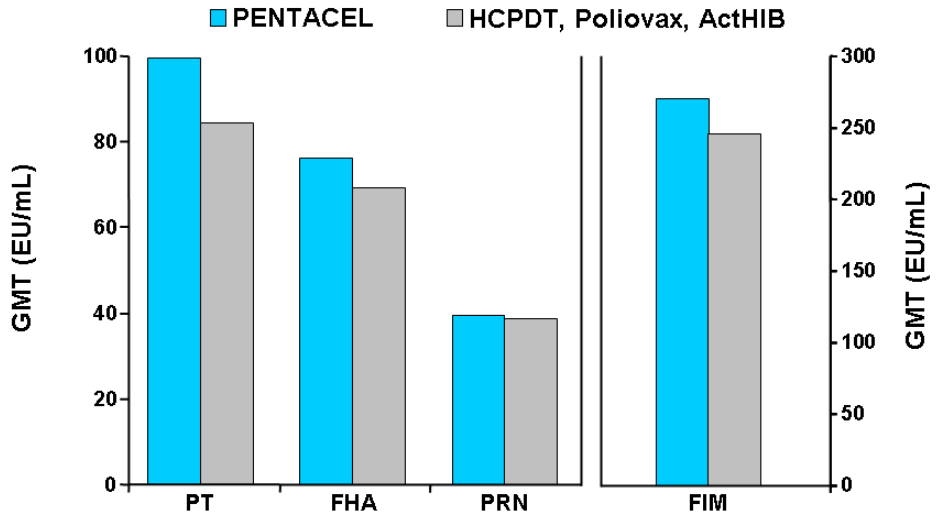
2.3.4.3 Comparison to HCPDT, Poliovax, ActHIB

Geometric Mean Titers

Figure 21 and Figure 22 summarize the GMTs for the Pertussis antigens after the 3rd and 4th Doses, respectively, for Study 494-01. The comparisons based on the GMT ratios of the PT, FHA, PRN, and FIM antigens fulfilled the statistical criteria supporting the non-inferiority of Pentacel vaccine compared to separate administration of the formulation-equivalent components (HCPDT, Poliovax, ActHIB) after the 3rd dose (see Figure 27).

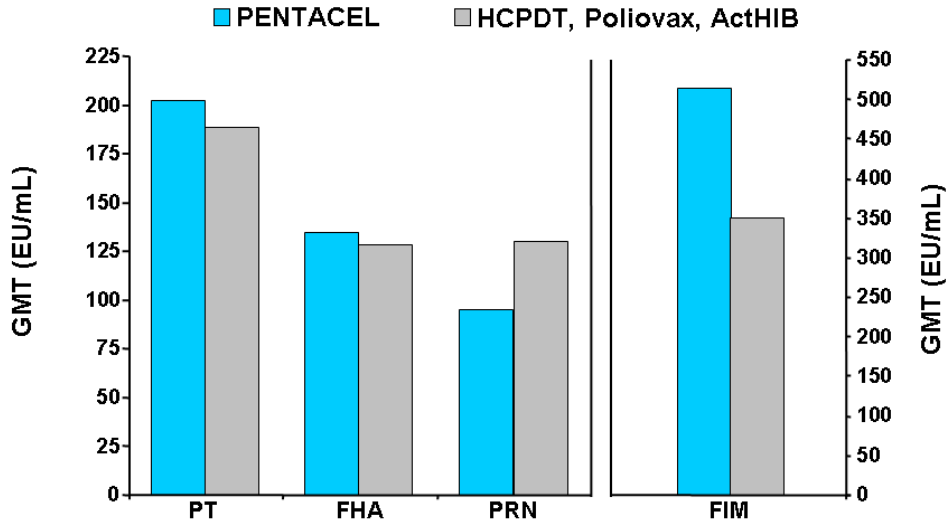
Similarly, the comparisons based on the GMT ratios of the PT, FHA, and FIM antigens fulfilled the statistical criteria supporting the non-inferiority of Pentacel to Control vaccines after the 4th Dose. The only comparison that did not meet the statistical criteria of non-inferiority was that based on the GMT ratio of the antibodies to PRN after the 4th Dose, for which the anti-PRN GMT elicited by Pentacel was lower than that elicited by the Control. As shown in Figure 27, in the post-hoc analyses, PT, FHA, and FIM post-Dose 3 GMTs for Pentacel vaccine were found to be significantly superior to Daptacel vaccine in Study 494-01, as assessed by the upper bound of the confidence interval falling below 1. Following the 4th Dose, the FIM GMT for Pentacel vaccine was found to be significantly superior to Daptacel vaccine (see Figure 28).

Figure 21: Study 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 3 Pertussis GMTs



PENTACEL	99.7	76.2	39.6	270.3
Control	84.5	69.2	38.6	246.0

Figure 22: Study 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 4 Pertussis GMTs



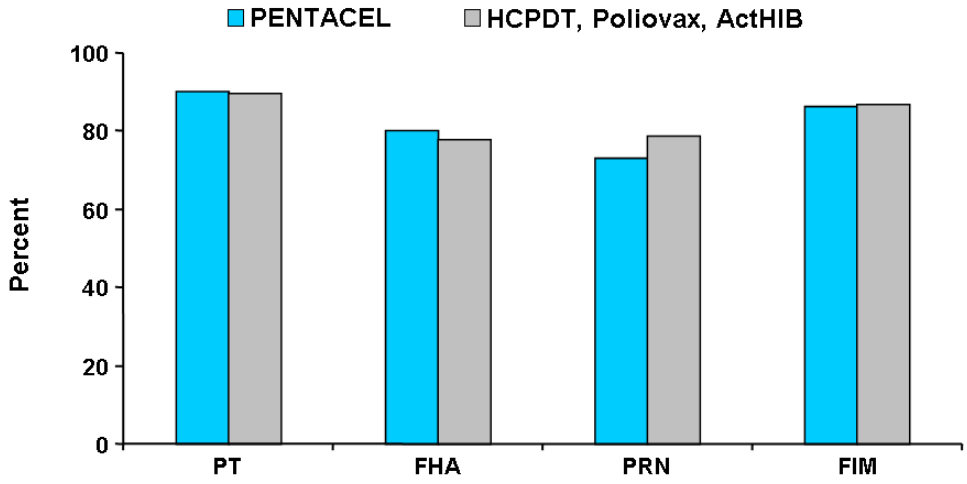
PENTACEL	202.2	134.6	94.9	514.2
Control	188.6	128.3	129.9	350.3

Four-fold Rise Rates

Figure 23 and Figure 24 summarize the post-Dose 3 and post-Dose 4 Pentacel vaccine 4-fold rise rates, respectively, for the pertussis antigens as compared to the separate administration of the formulation-equivalent components (HCPDT, Poliovax, ActHib) in Study 494-01.

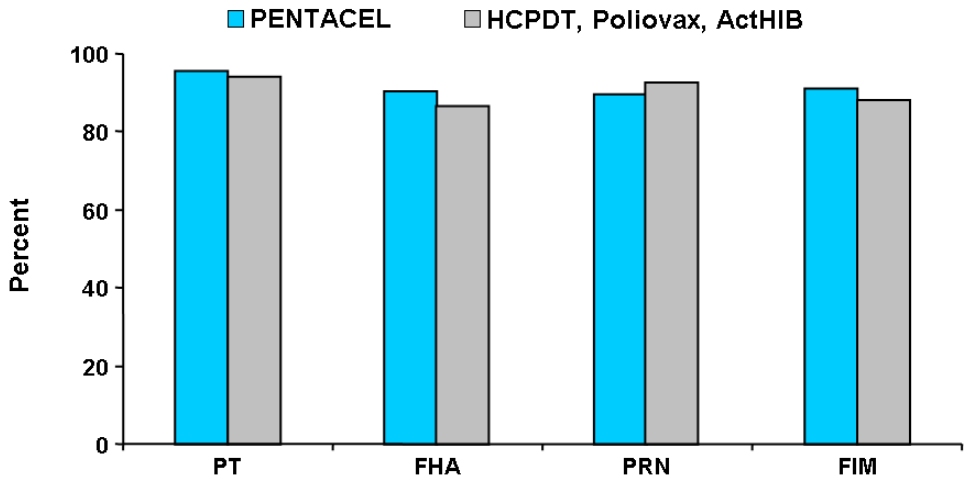
Pentacel vaccine elicited 4-fold rise rates to each of the pertussis antigens that fulfilled the pre-established criteria demonstrating the non-inferiority of Pentacel vaccine after 3 doses and after 4 doses (see Figure 27 and Figure 28, respectively).

Figure 23: Study 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 3 Pertussis 4-Fold Rise Rates



PENTACEL	90.3	80.3	73.2	86.2
Control	89.7	78.0	78.6	87.0

Figure 24: Study 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 4 Pertussis 4-Fold Rise Rates

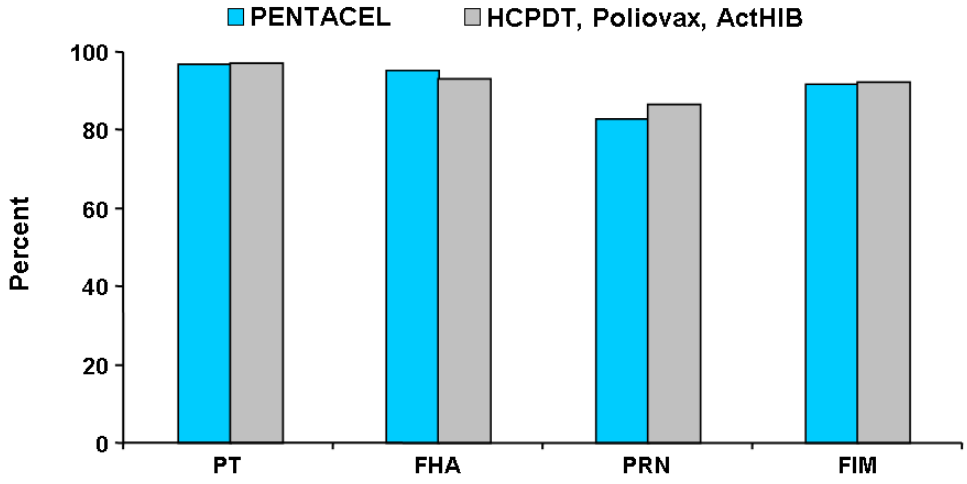


PENTACEL	95.4	90.2	89.3	91.3
Control	94.4	86.3	92.8	87.9

Vaccine Response Rates

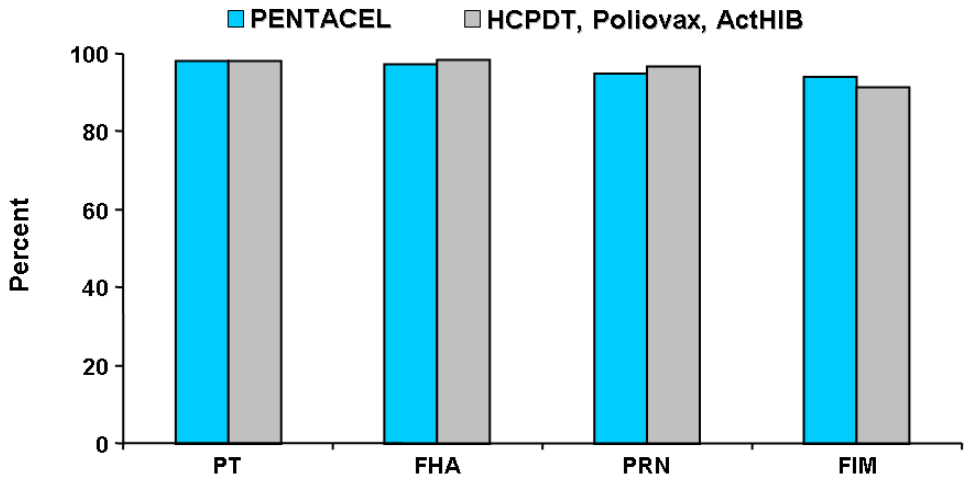
Figure 25 and Figure 26 summarize, respectively, the post-Dose 3 and post-Dose 4 Pentacel vaccine response rates for the pertussis antigens as compared to the separate administration of the formulation-equivalent components in Study 494-01. In this post-hoc analysis, Pentacel vaccine elicited vaccine response rates to each of the pertussis antigens that fulfilled the criteria demonstrating the non-inferiority of Pentacel vaccine after 3 doses and after 4 doses (see Figure 27 and Figure 28, respectively).

Figure 25: Study 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 3 Pertussis Vaccine Response Rates



PENTACEL	97.2	95.5	83.2	91.9
Control	97.4	93.3	86.8	92.6

Figure 26: Study 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 4 Pertussis Vaccine Response Rates



PENTACEL	98.5	97.8	95.3	94.5
Control	98.4	98.8	97.2	91.1

Figure 27: Study 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 3 Pertussis Non-Inferiority Analyses

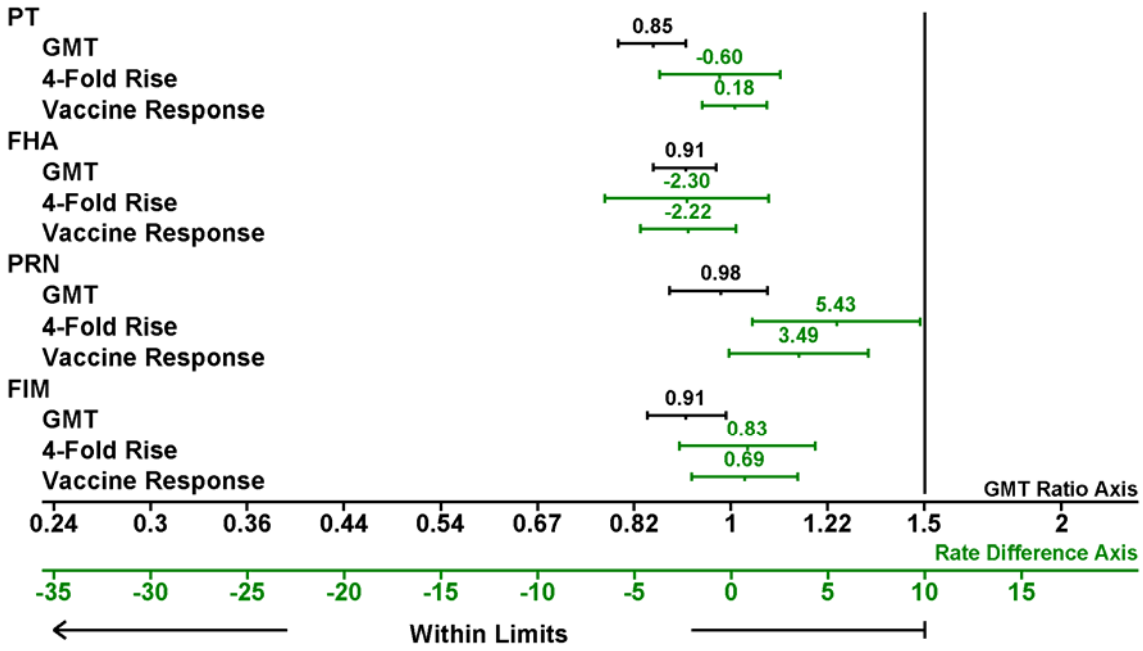
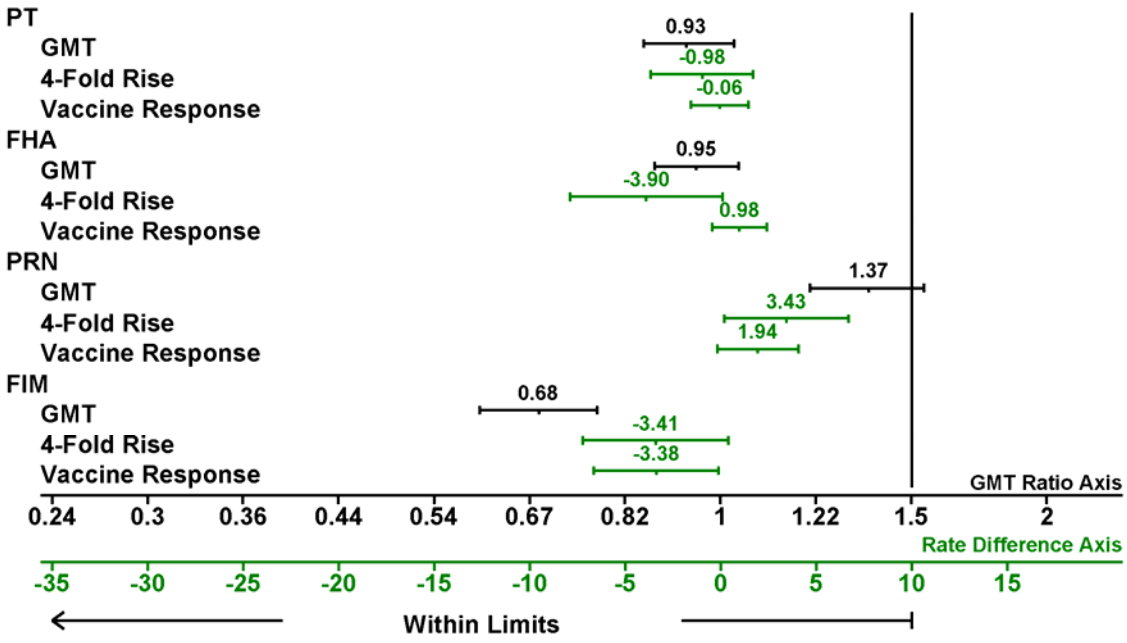


Figure 28: Study 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 4 Pertussis Non-Inferiority Analyses



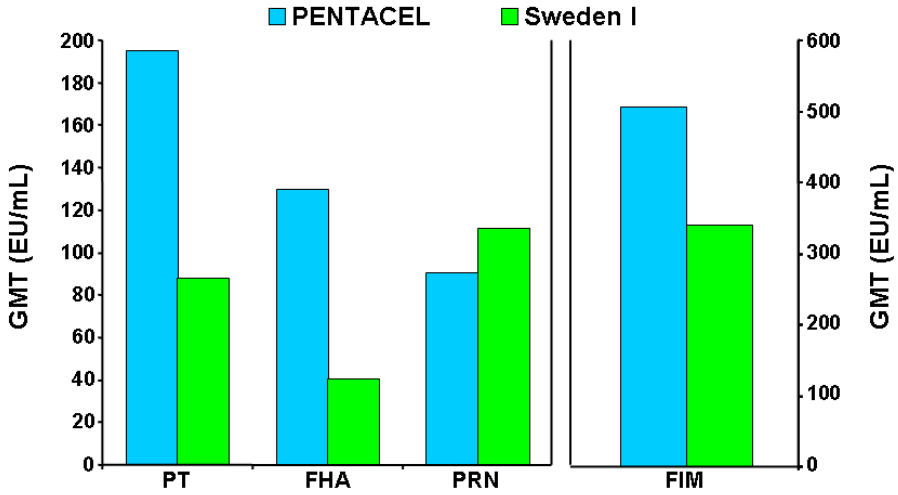
In summary, 23 out of 24 (16 primary and 8 post-hoc) comparisons fulfilled the statistical criteria established to demonstrate the non-inferiority of the immunogenicity responses for the pertussis antigens in Pentacel as compared to Daptacel.

2.3.4.3.1 Bridge to Efficacy: Comparison to Sweden I

Geometric Mean Titers

Figure 29 presents the anti-Pertussis GMTs elicited by Pentacel in US subjects participating in Study 494-01 as compared to those elicited by Daptacel in the Sweden I efficacy study. For all Pertussis antigens, the comparisons based on the antibody GMT ratios for the PT, FHA, PRN, and FIM antigens fulfilled the statistical criteria supporting the non-inferiority of Pentacel vaccine to Daptacel vaccine. As shown in Figure 32, in a post-hoc analysis PT, FHA, and FIM GMTs for Pentacel vaccine were found to be significantly superior to the Daptacel vaccine GMTs from Sweden I, as assessed by the upper bound of the confidence interval being below 1.

Figure 29: Study 494-01: Pentacel vs. Sweden I (Bridge to Efficacy) - GMTs



PENTACEL	195.1	129.9	90.8	506.6
Sweden I	87.5	40.7	111.3	339.3

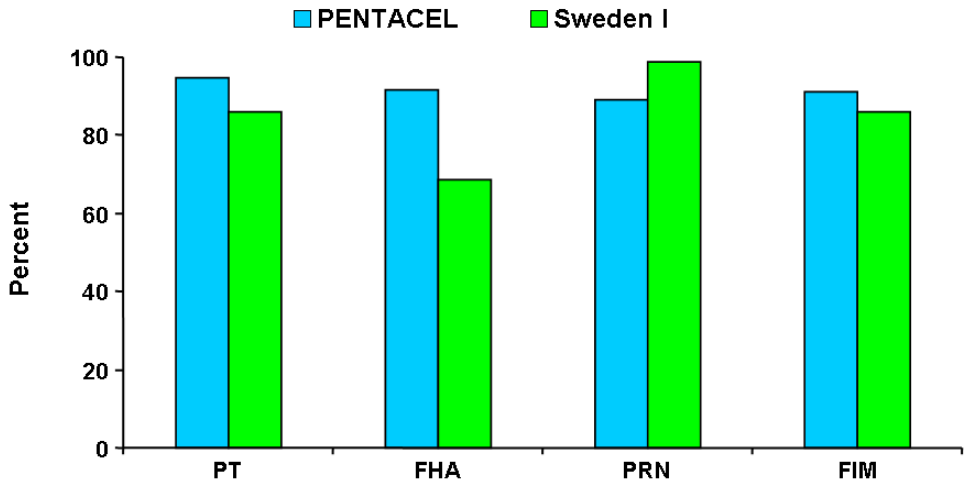
Four-fold Rise Rates

Figure 30 presents the 4-fold rise rates for Pentacel (Study 494-01) and Daptacel (Sweden I efficacy trial) vaccines from the 494-01 Serology Bridging Study. The comparisons based on the 4-fold rates of PT, FHA, and FIM fulfilled the statistical criteria supporting the non-inferiority of Pentacel vaccine in Study 494-01 to Daptacel vaccine in the Sweden I Efficacy Trial.

The only comparison that did not meet the statistical criterion of non-inferiority was that based on the difference in the 4-fold rise rates to PRN. Four-fold-rise rates to PRN were higher in subjects from Sweden I than in subjects from Study 494-01. As shown in Figure 32, in a post-hoc analysis PT and FHA 4-fold rise rates for Pentacel vaccine were found to be significantly superior to Daptacel vaccine in Sweden I, as assessed by the upper bound of the confidence interval being below 0.

Additional supportive analyses (post-hoc) of the anti-PRN responses in this study showed that the anti-PRN 4-fold rise rate, and consequently the comparison, was influenced by an uneven distribution of high anti-PRN pre-vaccination antibody levels in the 2 study populations, as previously discussed and detailed below.

Figure 30: Study 494-01: Pentacel vs. Sweden I (Bridge to Efficacy) - 4-Fold Rise Rates



PENTACEL	94.9	91.7	89.2	91.5
Sweden I	86.3	68.8	98.8	86.3

2.3.4.3.1.1 Matching Analysis

Additional (post-hoc) analysis of the anti-Pertussis GMTs in the PP population showed that subjects participating in Study 494-01 had a significantly higher mean anti-PRN pre-immunization (2 months of age) antibody level than did subjects who participated in the Sweden I Efficacy Trial (GMT 3.12 EU/mL in Study P3T06 versus 2.17 EU/mL in Sweden I; p=0.001 by t-test based upon log-titers). In contrast, pre-immunization antibody levels did not significantly differ for PT, FHA, or FIM. Based on this finding, an exploratory matching analysis was performed (12),(13) in order to assess whether subjects with equivalent anti-PRN pre-immunization antibody levels would have similar post-immunization outcomes after immunization with 4 doses of Pentacel in the United States or 3 doses of Daptacel in Sweden. Sweden I subjects were sorted according to their pre-Dose 1 PRN antibody levels, and a subset of Study 494-01 subjects was identified by matching their pre-immunization antibody levels to those of the subjects in Sweden I. Non-inferiority criteria were used to calculate and evaluate a 95% CI for the difference in 4-fold rise rates between Sweden I and Study 494-01 4th Dose. As shown in Table 37, the difference in 4-fold seroconversion rates between Sweden I and Study 494-01 was 5.55% with an upper limit of the 95% CI of 9.56%, thus fulfilling the non-inferiority criteria.

Table 37: Serology Bridge Data: Seroconversion Analysis of Antibody Levels for PRN (3:1 Matched Data Analysis)

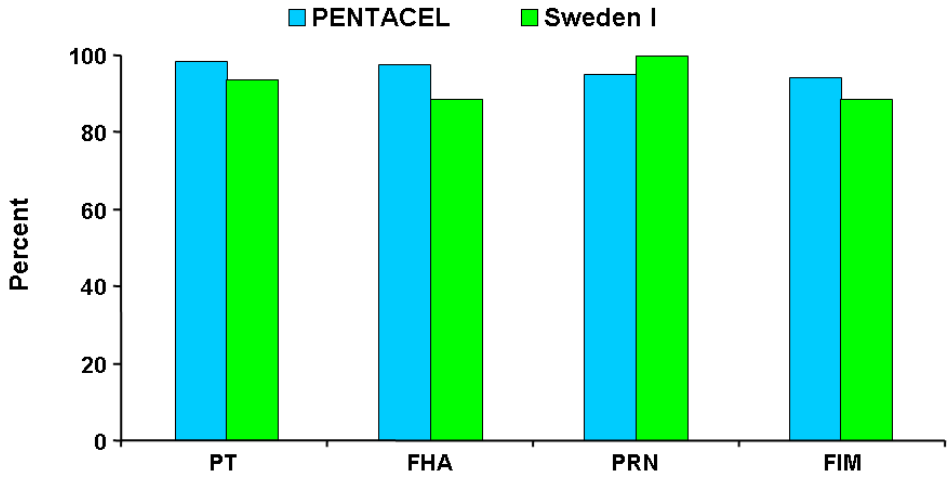
Probability of a ≥4-fold Rise		Non-Inferiority Comparison		
Sweden I Daptacel (N=80)	494-01 4th Dose Pentacel (N=240)	Daptacel-Pentacel	95% CI	Non-Inferiority Yes/No [1]
98.8%	93.2%	5.55%	(1.54, 9.56)	Yes

[1] Non-inferiority was achieved if the upper limit of the 2-sided 95% CI of Daptacel-Pentacel is <10%.

Vaccine Response Rates

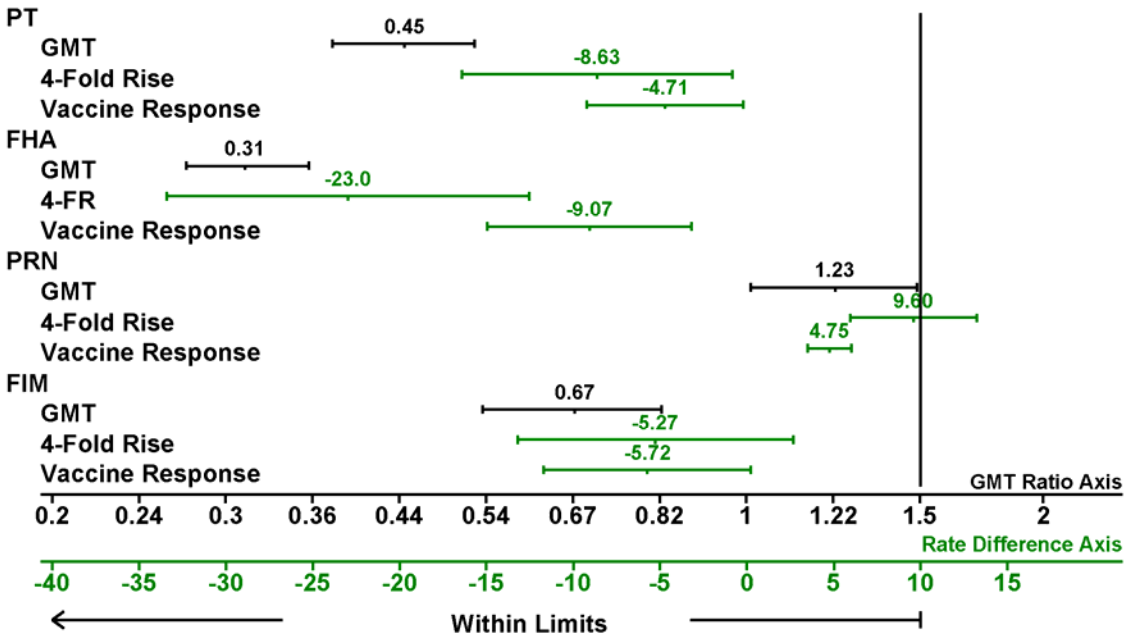
Figure 31 summarizes the post-Dose 4 Pentacel vaccine (Study 494-01) response rates for the pertussis antigens as compared to the separate administration of Daptacel vaccine in the Sweden I Efficacy Trial. In this post-hoc analysis Pentacel vaccine elicited vaccine response rates to each of the pertussis antigens that fulfilled the criteria demonstrating the non-inferiority of Pentacel vaccine in the US cohort to Daptacel vaccine in the Sweden I cohort (see Figure 32).

Figure 31: Study 494-01: Pentacel vs. Sweden I (Bridge to Efficacy) - Vaccine Response Rates



PENTACEL	98.5	97.8	95.3	94.5
Sweden I	93.8	88.8	100.0	88.8

Figure 32: Study 494-01: Pentacel vs. Sweden I (Bridge to Efficacy) - Non-Inferiority Analyses



2.3.4.4 Exploratory Aggregative Analysis of Anti-Pertussis Immune Responses

Pentacel was designed to contain all 5 of the recognized important acellular Pertussis antigens. The immune response to the 5 antigens in Pentacel and Controls (Daptacel vaccine in Study P3T06 and HCPDT component in Study 494-01) were evaluated by 4 enzyme-linked immunosorbent (ELISA) assays determining the antibodies to PT, FHA, PRN, and FIM (co-determining antibodies to FIM 2 and 3). Because these are distinct antigens, recipients may respond to one antigen and not another. This post-hoc analysis was designed to assess the proportion of subjects in the Pentacel versus control groups of studies P3T06 and 494-01 who achieved a ≥4-fold rise to any 1 antigen, 2 antigens, 3 antigens, or all 4 distinct antigens.

As shown in Table 38, the percentages of subjects in whom Pentacel elicited a ≥4-fold rise in antibody responses to at least 1, 2, 3, or all 4 of the acellular Pertussis antigens post-Dose 4 were very similar to the percentages of subjects achieving a ≥4-fold rise after immunization with Control vaccines in Studies P3T06 and 494-01. Only a few subjects in Study P3T06 (Pentacel: 0.9%; Control: 0.4%) and Study 494-01 (Pentacel: 1.0%; Control: 0.8%) did not achieve a 4-fold rise seroconversion to any of the antigens contained in the 5-component acellular Pertussis vaccines.

Table 38: Studies P3T06 and 494-01: Aggregate 4-Fold Rise Rates of Pertussis Antibody Levels by Study, Pentacel vs. Control, Post-Dose 4

≥4-Fold Rise for Pertussis Antigens [1]	P3T06				494-01			
	Control [2]		Pentacel		Control [3]		Pentacel	
	n/N	%	n/N	%	n/N	%	n/N	%
None	1/232	0.4	2/228	0.9	2/246	0.8	8/776	1.0
Any 1 of 4	231/232	99.6	226/228	99.1	244/246	99.2	768/776	99.0
Any 2 of 4	229/232	98.7	224/228	98.2	237/246	96.3	752/776	96.9
Any 3 of 4	220/232	94.8	215/228	94.3	225/246	91.5	725/776	93.4
All 4	170/232	73.3	182/228	79.8	184/246	74.8	599/776	77.2

[1] The fold-rise is calculated by post-Dose 4/pre-Dose 1 antibody level; pre-Dose 1 antibody levels were measured in the Infant Series study.

[2] Only Group 1 from Study P3T06 4th Dose (Daptacel and ActHIB vaccines at 15 months of age) is used in the non-inferiority analysis.

[3] Control means HCPDT, Poliovax, and ActHIB components for the 4th Dose of Study 494-01.

Notes: Subjects must have a valid test result pre-Dose 1, post-Dose 4 for all Pertussis antigens.
'n' is the number of subjects satisfying the criterion.
'N' is the number of subjects with available pre-Dose 1 and post-Dose 4 data for all Pertussis antigens from the PP Immunogenicity Population.

2.3.4.5 Post-Dose 4 Reverse Cumulative Distribution Curves

Figure 33, Figure 34, Figure 35, and Figure 36 present the post-Dose 4 comparisons from the various Pentacel study groups to the Sweden I efficacy trial for PT, FHA, PRN, and FIM, respectively. For PT, FHA, and FIM, the curves for each of the Pentacel arms dominate the curves representing the Daptacel recipients (labeled CPDT, Sweden I) in the Sweden Trial I. For PRN, the Pentacel and Sweden I curves overlap.

Figure 33: Pentacel Post-Dose 4 vs. Sweden I: PT

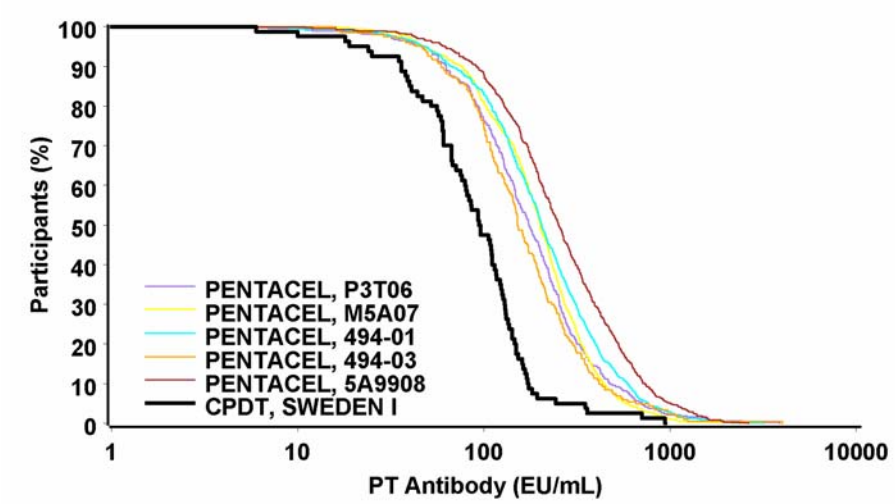


Figure 34: Pentacel Post-Dose 4 vs. Sweden I: FHA

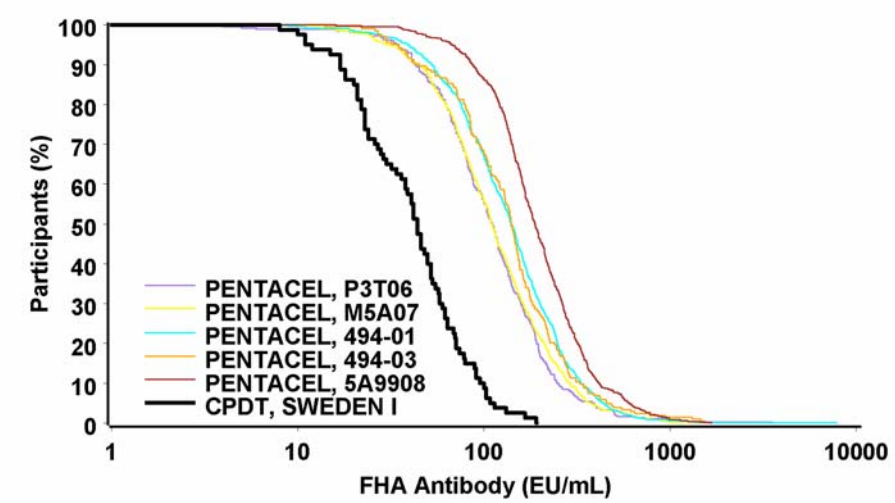


Figure 35: Pentacel Post-Dose 4 vs. Sweden I: PRN

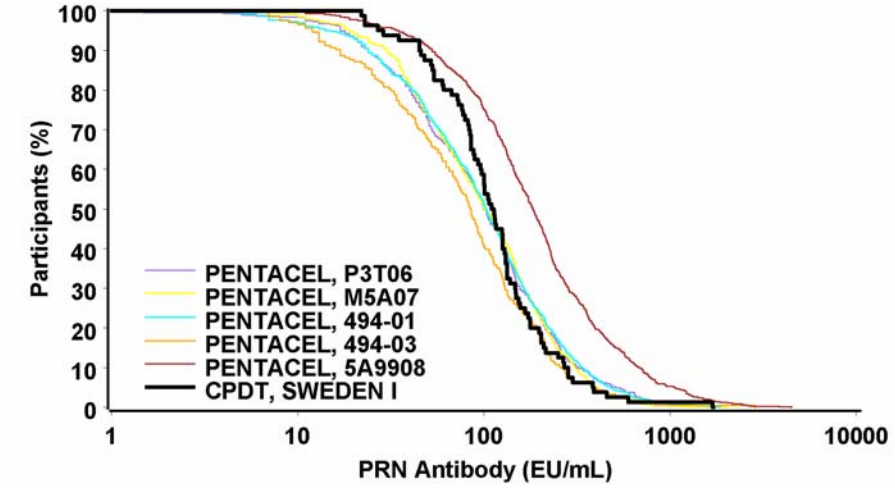
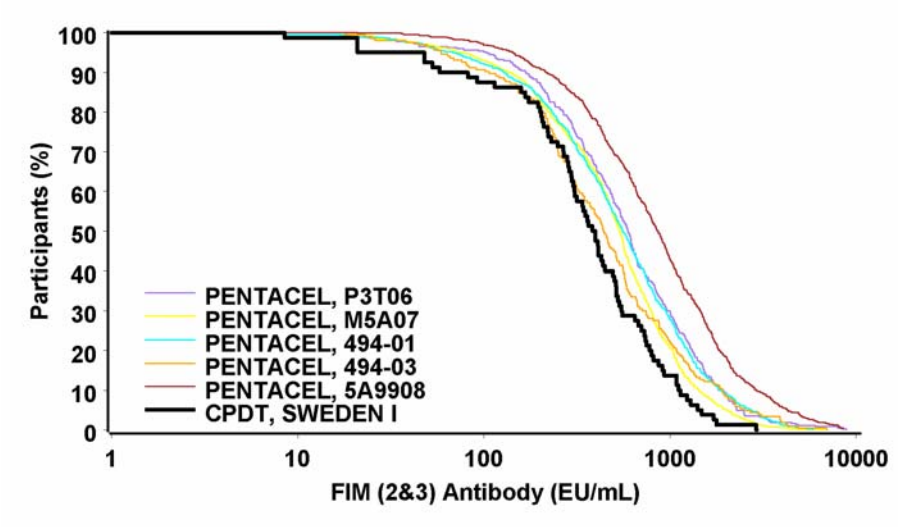


Figure 36: Pentacel Post-Dose 4 vs. Sweden I: FIM



2.3.4.6 Pertussis Responses in the Context of US Standard of Care

Typically, the efficacy of a vaccine is determined directly, either by an efficacy trial or by assessment of the proportion of recipients achieving antibody levels that meet or exceed a recognized seroprotective level. However, neither option is available for pertussis vaccines; no seroprotective levels have been defined and it is considered no longer possible to conduct efficacy trials (because the many efficacy trials conducted in the early 1990s were so successful, use of pertussis vaccine is the standard around the world).

In the clinical trials presented herein, the performance of Pentacel vaccine has been assessed against one of three distinct comparators:

1) the performance of its constituent components HCPDT, Poliovax, and ActHIB in Study 494-01;
2) the performance of the US-licensed standard-of-care vaccines Daptacel, IPOL, and ActHIB in Study P3T06; and
3) the performance of Daptacel in the Sweden I Efficacy Trial, as assessed by its comparison to the immunogenicity of Pentacel in Studies P3T06 and 494-01.

Comparison 3 is, we believe, the most important because it provides a direct linkage to efficacy data. Pertussis vaccines licensed based on a serological bridge to efficacy include Daptacel, Pediarix, Adacel, and Boostrix vaccines. Comparison 2 is also of particular importance in that Daptacel, IPOL, and ActHIB vaccines are widely used in the US; if Pentacel vaccine is licensed, it is likely to largely supplant use of these stand-alone vaccines. Although Comparison 1 represents a classical approach, its practical utility is not as clear as that of the other two criteria, given that HCPDT, Poliovax, and ActHIB are not given together as stand-alone vaccines; indeed, HCPDT is not licensed or used, except as a component of combination vaccines.

These 3 comparisons were based on prospectively established criteria that assessed the statistical non-inferiority of each of the acellular Pertussis vaccine components in Pentacel. Two co-primary outcomes per antigen were considered, the difference between groups in rates of seroconversion (defined as post-immunization antibody level/pre-immunization antibody level ≥4-fold rise) and the ratios of GMTs, for a total of 48 statistical non-inferiority comparisons for Pertussis alone.

The following table presents an overview of the results of these key comparisons. As shown in Table 39, of the 48 Pertussis statistical comparisons between Pentacel and Control vaccines, 44 satisfied the statistical criteria for non-inferiority. Pentacel immune responses were statistically superior to those elicited by the Control vaccines (i.e., the upper limit of the difference or ratio confidence interval being below 0 or 1, respectively) in 21 comparisons (exploratory observation).

Table 39: Studies 494-01 and P3T06: Overview of Statistical Outcomes

	Post-Dose 3				Post-Dose 4				Serology Bridge			
	P3T06		494-01		P3T06		494-01		P3T06		494-01	
Antigen	**≥4-fold**	**GMT**	**≥4-fold**	**GMT**	**≥4-fold**	**GMT**	**≥4-fold**	**GMT**	**≥4-fold**	**GMT**	**≥4-fold**	**GMT**
PT	>	>	=	>	=	=	=	=	>	>	>	>
FHA	>	>	=	>	>	>	=	=	>	>	>	>
FIM	>	=	=	>	=	=	=	>	=	>	=	>
PRN	=	=	=	=	=	<	=	<	<	=	<	=

Notes: "<" indicates that Pentacel results did not meet non-inferiority criteria; ">" indicates that non-inferiority was demonstrated and that Pentacel results were significantly higher than that of Control; "=" indicates that non-inferiority was demonstrated, and that Pentacel results were not significantly higher than that of Control.

Four-fold Rise Rates

Although 4-fold-rise rates may not be as predictive of protection as are GMTs, they are a traditional measure of vaccine response and were predefined as primary objectives of studies P3T06 and 494-01. All of the 16 comparisons based on the ≥4-fold rise seroconversion rates elicited by the PT, FHA, FIM, and PRN antigens after 3 and 4 doses fulfilled the statistical criteria demonstrating the non-inferiority of Pentacel to the Control vaccines in the 2 controlled pivotal studies (Studies P3T06 and 494-01) conducted in the United States. Furthermore, although these controlled studies were not designed to establish the superiority of the immune responses elicited by Pentacel, in Study P3T06, Pentacel elicited significantly higher 4-fold-rise rates than did Daptacel for PT, FHA, and FIM at post-Dose 3 and for FHA at post-Dose 4, as demonstrated by the upper limit of the 90% CI of the rate difference being <0%. Moreover, an additional (post-hoc) analysis of the seroconversion outcomes in these 2 studies showed a remarkable similarity in the proportion of the Pentacel and Control populations that had a ≥4-fold rise over the pre-immunization antibody levels to at least 1, 2, 3, or all 4 antigens tested at post-Dose 4, with very few subjects not achieving seroconversion to at least one of the Pertussis antigens.

Also pivotal to support the licensure of Pentacel are the serology bridging comparisons, designed to provide assurance that efficacy of the vaccine can be extrapolated to US children. Supporting the conclusions drawn for the 4-fold rise comparisons performed in the controlled pivotal studies, the comparisons based on the 4-fold rise to PT, FHA, and FIM also fulfilled the statistical criteria supporting the non-inferiority of Pentacel (see Sections 2.3.4.3.1 and 2.3.4.1.1). Furthermore, in a post-hoc analysis, Pentacel vaccine was significantly superior to Daptacel vaccine for PT and FHA. An exception to this observation was the 4-fold rise to PRN, which did not fulfill the statistical non-inferiority criteria due to differing pre-vaccination antibody levels. Although randomization will usually control for such a factor when comparisons are made within a study, the bridging comparisons, by definition, bridge results across differing populations evaluated in separate clinical studies. Given that the P3T06, 494-01, and Sweden I trials were performed at different times in different countries with different populations, the statistically significant difference in anti-PRN pre-immunization antibody levels is not surprising (see Sections 2.3.4.3.1 and 2.3.4.1.1). It is reassuring that matching analyses demonstrated that, when controlled for equal pre-immunization antibody levels, 4-fold rise rates with Pentacel were non-inferior to those found in the Sweden I population.

One of the difficulties in defining a seroresponse to the Pertussis antigens is the fact that a very wide range of pre-immunization anti-Pertussis antibody levels is observed at 2 months of age. Furthermore, based on 4-fold-rise criteria, those subjects with high pre-immunization antibody concentrations may mistakenly be identified as post-immunization non-vaccine responders. However, using a (post-hoc) criterion for vaccine response (see Sections 2.3.4.3.1 and 2.3.4.1.1), Pentacel recipients had vaccine responses to each of the Pertussis antigens that were comparable or superior to those shown by recipients of Daptacel vaccine in Study P3T06 or of the HCPDT component in Study 494-01.

Geometric Mean Titers

In both pivotal controlled clinical trials, all of the 8 comparisons based on the post-Dose 3 antibody GMTs elicited by the PT, FHA, PRN, and FIM antigens fulfilled the statistical criteria demonstrating the non-inferiority of Pentacel to Control vaccines in Studies P3T06 and 494-01. Furthermore, although these controlled studies were not designed to establish the superiority of the immune responses elicited by Pentacel, in Study P3T06, Pentacel elicited significantly higher GMTs than did Daptacel for PT and FHA, as demonstrated by the upper limit of the 90% CI of

the GMT ratio being <1. The post-Dose 3 anti-Pertussis responses seen in the Pentacel and Daptacel groups in Study P3T06 are in the range of anti-Pertussis responses elicited by Pentacel in the other pivotal (Studies 494-01 and 494-03) and the supportive Study M5A07, and by Daptacel in an additional clinical trial, Study P3T07. (5)

Following the 4th Dose, all of the comparisons based on the antibody GMTs to PT, FHA, and FIM fulfilled the statistical criteria demonstrating the non-inferiority of Pentacel to Control vaccines in Studies P3T06 and 494-01. Furthermore, although these studies were not designed to demonstrate superiority, in Study P3T06, Pentacel elicited a higher GMT than did Daptacel vaccine to FHA, and, in Study 494-01, Pentacel elicited a higher GMT than did the HCPDT component for FIM as demonstrated by the upper limit of the 90% CI of the GMT ratio being <1. The only comparison that did not meet the statistical criteria of non-inferiority was that based on the GMT ratio of the antibodies to PRN after the 4th Dose.

Similar to the seroconversion-based comparisons, the non-inferiority of Pentacel was also assessed by comparing the post-Dose 4 anti-Pertussis GMTs elicited by Pentacel with those elicited by 3 doses of Daptacel in the Sweden I Efficacy Trial. All of the comparisons based on the GMTs to PT, FHA, FIM, and PRN fulfilled the statistical criteria demonstrating the non-inferiority of Pentacel to Daptacel in the Sweden I Efficacy Trial. In a post-hoc analysis, Pentacel vaccine was significantly superior to Daptacel vaccine for PT, FHA, and FIM.

Summary

Of the 48 statistical comparisons designed to assess the anti-Pertussis immune responses elicited by Pentacel in the pivotal studies, 44 demonstrated the non-inferiority of Pentacel to either the the licensed-equivalent components, formulation-equivalent components, or to the trial that established the efficacy of the 5-component Pertussis vaccine. In post-hoc analyses, 21 of the 48 comparisons demonstrated superiority of Pentacel against those same controls. Most importantly, both of the serological bridge to efficacy comparisons demonstrated the non-inferiority of Pentacel GMTs to those seen in the Sweden I trial.

Furthermore, the high comparability of Pentacel to its formulation and licensed-equivalent components was also demonstrated by the remarkably similar manner in which Pentacel was able to elicit a ≥4-fold rise seroconversion response to the acellular Pertussis antigens, either by antigen, as demonstrated by each of the 16 prospectively planned seroconversion comparisons (see Table 35 and Figure 24), or cumulatively, as demonstrated by the proportion of those vaccinated achieving ≥4-fold rises to at least 1, at least 2, at least 3, or all 4 of the distinct pertussis antigens contained in Pentacel, Daptacel, and HCPDT. This multiplicity of anti-Pertussis immune responses elicited by the 5-component acellular Pertussis vaccine contained in Pentacel is believed to be an important contributor to the high degree of enduring efficacy against classic and mild Pertussis conferred by this vaccine, as compared to vaccines with a less rich antigenic repertoire. (2) (14)

2.3.5 *Haemophilus influenzae* type b (Hib)

The performance of conjugate Hib vaccines typically is evaluated by determining the proportion of subjects who achieve post-immunization titers ≥0.15 µg/mL and ≥1.0 µg/mL. Although some consider these thresholds arbitrary, it has conventionally been considered that 0.15 µg/mL represents the level of antibody needed for protection from invasive Hib disease and that 1.0 µg/mL represents the level of antibody needed following the Infant Series to assure that levels will not drop below 0.15 µg/mL before the toddler booster dose is administered. The GMT of Hib antibody following vaccination provides another assessment of vaccine performance; high GMTs

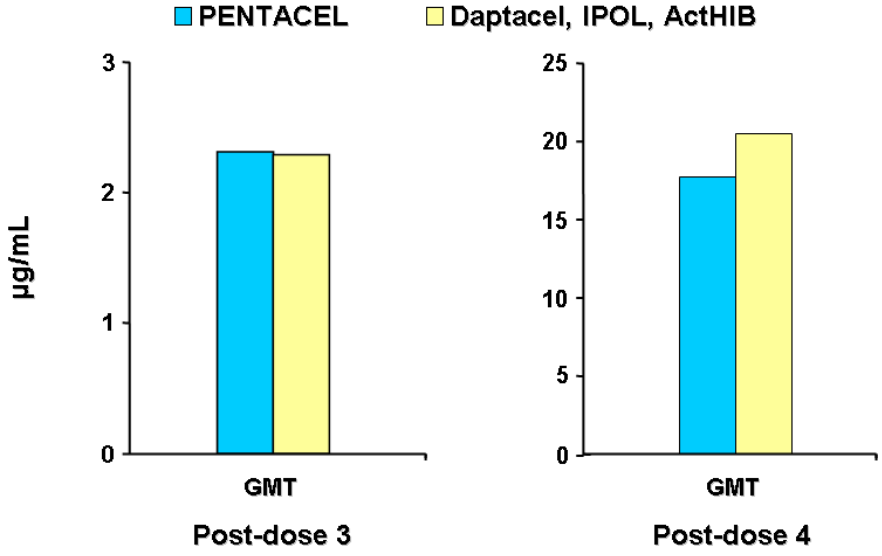
following the toddler booster give reassurance that antibody levels will persist above protective levels through the next few years, until immune system maturation by age 4-5 years eliminates the elevated susceptibility to Hib disease that characterizes the immature immune system.

2.3.5.1 Comparison to Standard of Care Vaccines (Daptacel, IPOL, ActHIB)

Geometric Mean Titers

Figure 37 summarizes the anti-PRP GMTs for Study P3T06 at post-Dose 3 and post-Dose 4. GMTs were essentially identical following the Infant Series and were similar and high following the toddler booster. As shown in Figure 39, Hib GMTs in Study P3T06 Pentacel recipients were non-inferior to those in the group receiving the US-licensed standard of care vaccines Daptacel, IPOL, and ActHIB.

Figure 37: Study P3T06: Pentacel vs. US Standard of Care Vaccines - Post-Dose 3 and Post-Dose 4 Hib GMTs

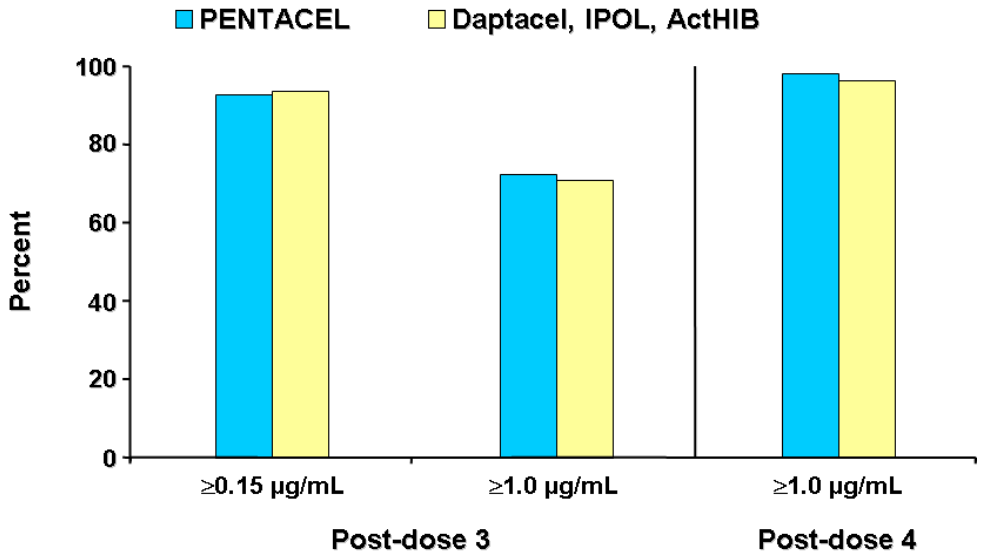


PENTACEL	2.31		17.71
Control	2.29		20.49

Seroprotection Rates

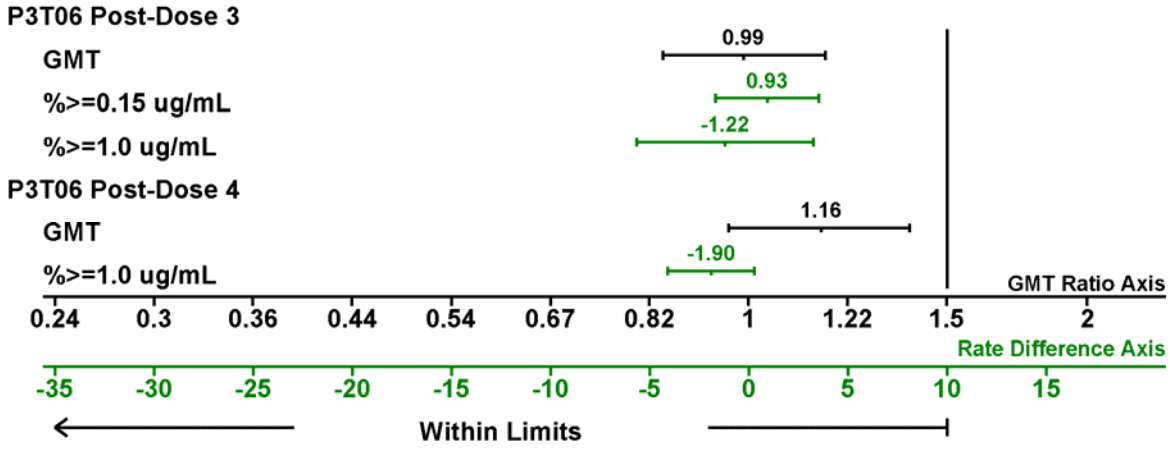
As shown in Figure 38, the proportions of children in Study P3T06 achieving seroprotective antibody levels following the Infant Series (post-Dose 3) and following the toddler dose (post-Dose 4) were essentially identical for the groups receiving Pentacel vaccine or the US-licensed standard of care vaccines Daptacel, IPOL, and ActHIB. As shown in Figure 39, Hib seroresponse rates in Study P3T06 Pentacel recipients were non-inferior to those in the group receiving the US-licensed standard of care vaccines Daptacel, IPOL, and ActHIB.

Figure 38: Study P3T06: Pentacel vs. US Standard of Care Vaccines - Post-Dose 3 and Post-Dose 4: Hib Seroprotection Rates



PENTACEL	92.3	72.1	97.8
Control	93.3	70.8	95.9

Figure 39: Study P3T06: Non-Inferiority Testing of Hib Seroprotection Rates (Control-Pentacel) and GMT Ratios (Control/Pentacel)



2.3.5.2 Lot Consistency

Lot consistency was assessed in clinical trial 494-01. Figure 40 presents the PRP seroprotection rates and GMTs for the 3 Pentacel lots after the 3rd dose of Pentacel vaccine in study 494-01. As shown in Figure 41, 8 of the 9 lot-consistency comparisons met the statistical criteria for equivalence and 1 did not (the GMT for PRP was statistically higher in Lot 3 than in Lot 2). Importantly, equivalence was demonstrated for all the seroprotection measures.

Figure 40: Study 494-01: Pentacel Lot Consistency - Post-Dose 3 Hib GMTs and Seroprotection Rates

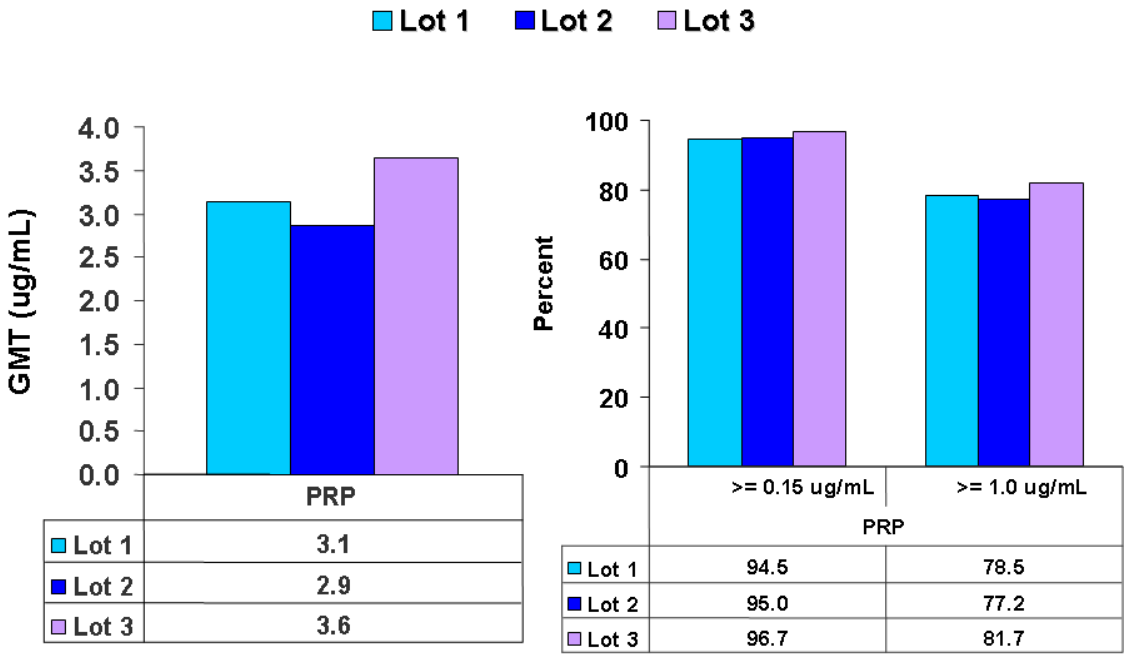
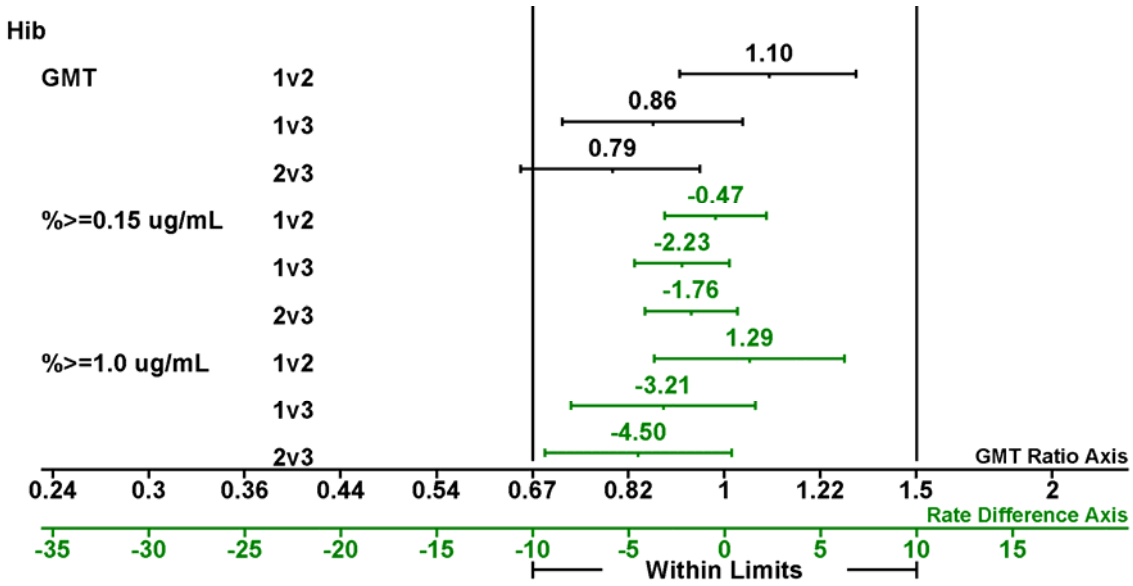


Figure 41: Study 494-01: Pentacel Lot Consistency - Post-Dose 3 Hib

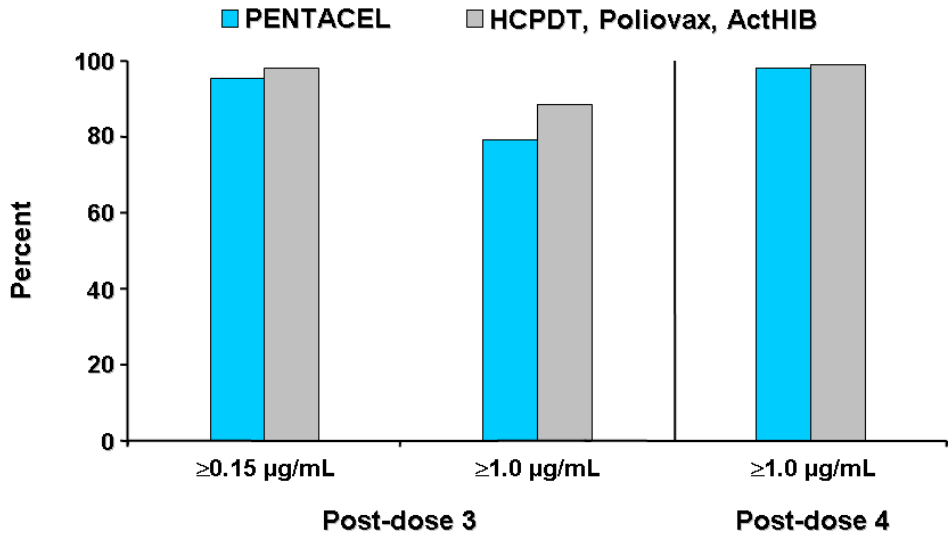


2.3.5.3 Comparison to HCPDT, Poliovax, ActHIB Given Separately

Seroprotection Rates

As shown in Figure 42, the proportions of children in Study P3T06 achieving seroprotective antibody levels ≥0.15 µg/mL following the Infant Series (post-Dose 3) and achieving ≥1.0 µg/mL following the toddler booster (post-Dose 4) were essentially identical for the groups receiving Pentacel vaccine or separately administered HCPDT, Poliovax, and ActHIB. The proportion achieving ≥1.0 µg/mL following the 3rd dose was somewhat higher in the separate-components group.

Figure 42: 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 3 and Post-Dose 4 Hib Seroprotection Rates

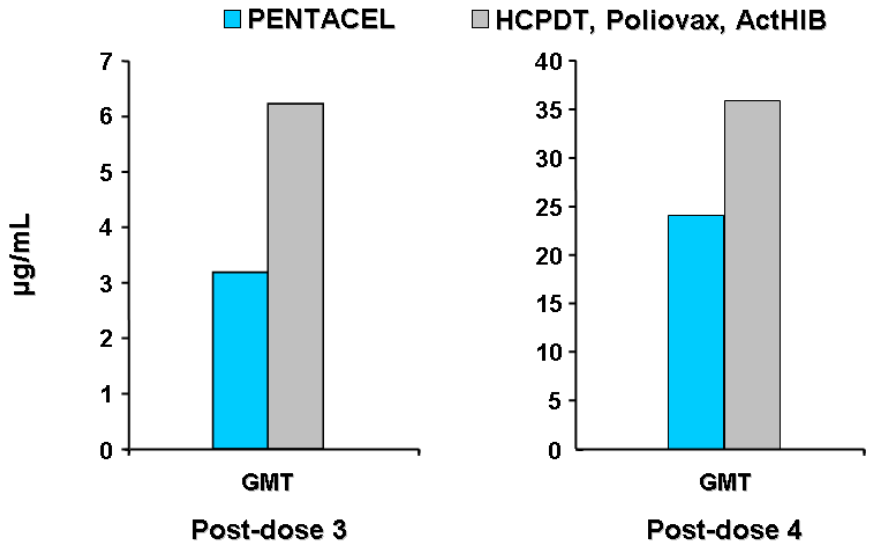


PENTACEL	95.4	79.1	98.2
Control	98.3	88.8	99.0

Geometric Mean Titers

Figure 43 summarizes the anti-PRP GMTs for Study 494-01 at post-Dose 3 and post-Dose 4 in Study 494-01. Although the Pentacel group in Study 494-01 achieved GMTs somewhat higher than seen in either group in Study P3T06, the 494-01 group receiving the HCPDT, Poliovax, and ActHIB components given separately had anti-PRP GMTs that exceeded those in the Pentacel vaccine group at both post-Dose 3 and post-Dose 4.

Figure 43: 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 3 and Post-Dose 4 Hib GMTs

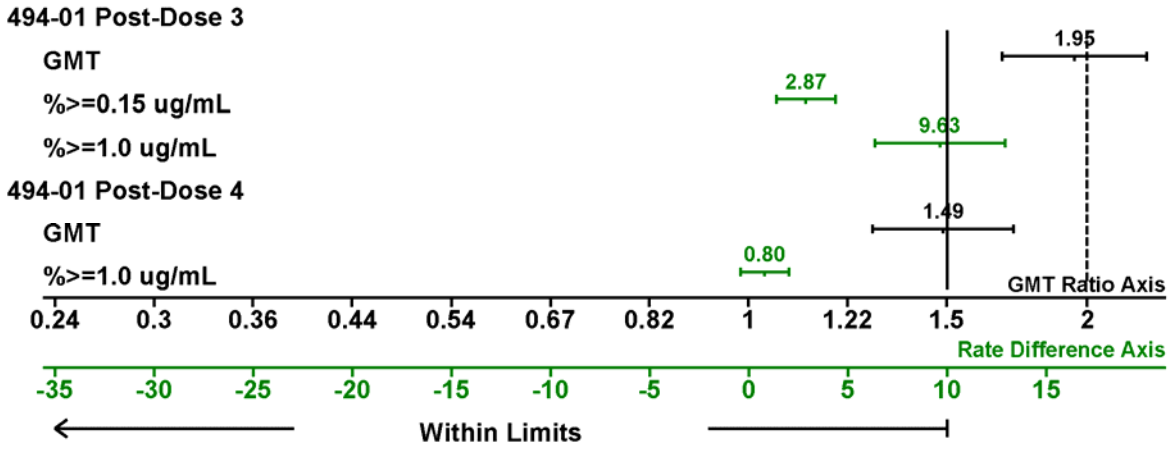


PENTACEL	3.19		24.1
Control	6.23		35.9

Non-inferiority comparisons

As shown in Figure 44, the Hib antibody statistical non-inferiority comparisons for Pentacel vs the separately administered HCPDT, Poliovax, and ActHIB components succeeded for the proportions achieving antibody levels ≥0.15 µg/mL following Dose 3 and achieving ≥1.0 µg/mL following Dose 4, and failed for the other 3 comparisons.

Figure 44: Study 494-01: Non-Inferiority Testing of Hib Seroprotection Rates (Control-Pentacel) and GMT Ratios (Control/Pentacel)



2.3.5.4 Post-Dose 3 and Post-Dose 4 Hib Antibody Reverse Cumulative Distribution Curves

Figure 45 and Figure 46 present the post-Dose 3 and post-Dose 4 Hib responses, respectively for the Pentacel groups in the four licensure trials compared to the US standard-of-care (Control group from Study P3T06). In both cases, the curves for the Pentacel vaccine groups are closely aligned and overly or exceed the curve for the US Standard of Care group.

Figure 45: Post-Dose 3 Hib Responses, Pentacel vs. Standard of Care

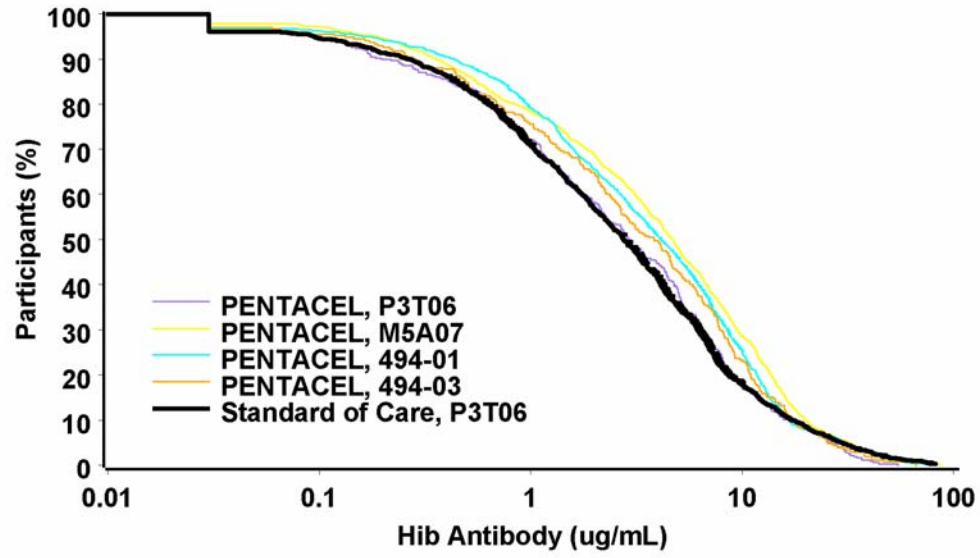
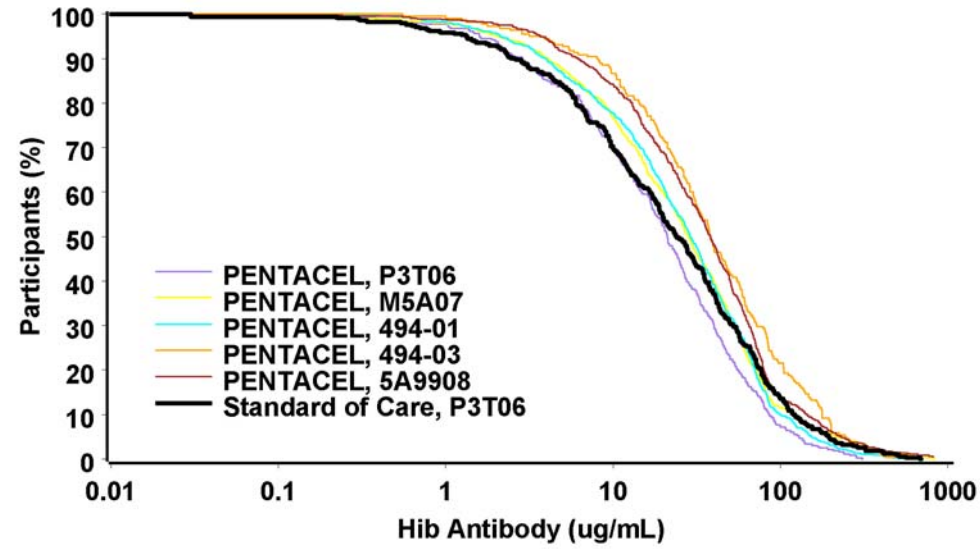


Figure 46: Post-Dose 4 Hib Responses, Pentacel vs. Standard of Care



2.3.5.5 Hib Responses in the Context of US Standard of Care

As discussed in Section 2.3.4.6 with respect to Pertussis vaccines, the most direct measure of the performance of a Hib vaccine would be an efficacy trial, but it is generally accepted that such trials are no longer practicable given the widespread use of effective Hib vaccines. However, unlike the situation with Pertussis vaccines, for Hib vaccines there are generally accepted seroprotective levels and vaccines can be evaluated with respect to the proportions of recipients achieving those levels. In addition, a candidate vaccine's performance can be compared to the performance of the existing standard of care. Finally, if a candidate vaccine is in widespread use in another jurisdiction, its performance there can be monitored through national or targeted surveillance. We address the first two approaches here, and the third later in this document.

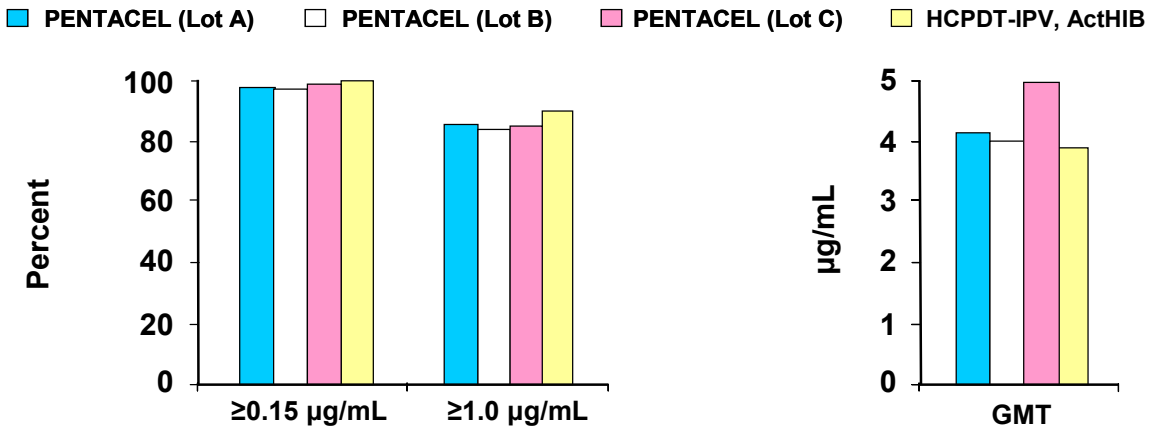
The clinical development plan of Pentacel included 2 studies designed to assess the non-inferiority of the immune responses elicited by Pentacel, Studies P3T06 and 494-01. Each clinical trial evaluated the non-inferiority of Pentacel after 3 Infant Series doses and after the 4th (toddler) Dose. Study P3T06 compared Pentacel to the separate but concurrent administration of the equivalent US-licensed standard of care vaccines Daptacel, IPOL, and ActHIB (which Pentacel, if licensed, would tend to replace). In contrast, Study 494-01 compared the immune responses elicited by Pentacel to those obtained after the separate but concurrent administration of its constituent components HCPDT, Poliovax, and ActHIB. Interpreting this comparison is limited, however, by the fact that the HCPDT and Poliovax components have not been administered concurrently as separate vaccines in any other studies, nor is HCPDT used as a stand-alone vaccine.

In both studies P3T06 and 494-01, Pentacel recipients achieved GMTs and seroprotection rates that equaled or exceeded those achieved by children given the US-licensed standard-of-care vaccines Daptacel, IPOL, and ActHIB. However, those receiving separately administered HCPDT, Poliovax, and ActHIB achieved even higher GMTs and seroprotection rates. Unfortunately, there is no context for this result, given that no other study has evaluated the simultaneous administration of these separate components. This result might merely reflect the variability that is inherent to Hib vaccine studies (see below), or might indicate that the separate administration of these components truly is more immunogenic. The latter possibility is, however, of little utility, given that HCPDT is not licensed or used as a stand-alone vaccine.

Study 494-01 is the only clinical trial in which we have observed material differences in Hib responses between the investigational and control groups (but as noted, it is the only study in which the control group received separately the constituent components of Pentacel rather than receiving actual licensed vaccines).

In contrast to Study 494-01, a similar study performed during the licensing process of Pentacel in Canada yielded different results. In that Study PB9502 (15), 3 lots of Pentacel (including 3 different lots of ActHIB) were compared to the separate administration of one lot of HCPDT-IPV (licensed and distributed in Canada as Quadracel) and separately administered ActHIB. The 3 Pentacel groups in Study PB9502 elicited anti-PRP GMTs of 5.0 µg/mL (this group received the same PRP-T lot as the group given separately administered ActHIB), 4.0 µg/mL, and 4.2 µg/mL following 3 doses compared to 3.8 µg/mL in the ActHIB group (see Figure 47). The seroprotection rates at the ≥0.15 µg/mL and ≥1.0 µg/mL thresholds were similar among the 3 Pentacel groups and between the Pentacel and ActHIB groups (see Figure 47). Therefore, Study PB9502 provides another example of a randomized study with a design similar to Study 494-01 (albeit with a different control group) but in which Pentacel elicited Hib responses that were the same or better than those seen with the separately administered ActHIB control.

Figure 47: Study PB9502: Pentacel vs. Control - Post-Dose 3 Hib Seroprotection Rates and GMTs



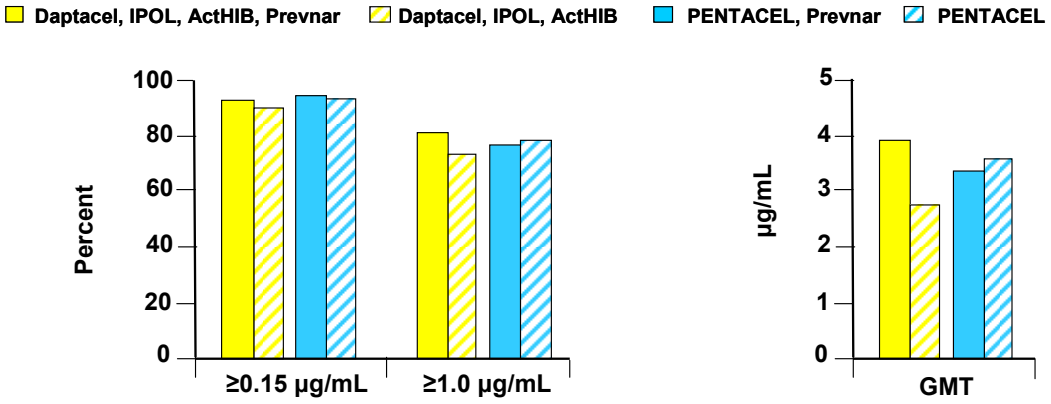
PENTACEL (Lot A)	98.2	85.3
PENTACEL (Lot B)	98.1	84.0
PENTACEL (Lot C)	99.1	84.9
HCPDT-IPV, ActHIB	100.0	88.9

PENTACEL (Lot A)	4.2
PENTACEL (Lot B)	4.0
PENTACEL (Lot C)	5.0
HCPDT-IPV, ActHIB	3.8

In the pivotal Study P3T06, which compared Pentacel to the separate US-licensed standard-of-care vaccines Daptacel, IPOL, and ActHIB, all comparisons based on the anti-PRP GMTs and seroprotection rates after the Infant Series and the 4th Dose fulfilled the statistical criteria for the non-inferiority of Pentacel.

Another pair of US studies can give further insight into the comparative performance of Pentacel vs separately administered Daptacel, IPOL, and ActHib vaccines. Study P3T07 was conducted following Daptacel licensure to evaluate the administration of Daptacel, IPOL, and ActHIB at 2, 4, and 6 months with Prevnar vaccine given either concurrently or at 3, 5, and 7 months; Study M5A07 used a similar design to compare the administration of Pentacel at 2, 4, and 6 months with Prevnar vaccine given either concurrently or at 3, 5, and 7 months. The two studies were conducted during the same time period at a variety of US sites. As shown in Figure 48 (5), Pentacel with concomitant Prevnar produced Hib responses similar to those of Daptacel with concomitant Prevnar; Pentacel without Prevnar produced Hib responses similar to those of Daptacel without Prevnar. In both studies, the non-inferiority criteria were met.

Figure 48: P3T07 & M5A07: Daptacel, IPOL, ActHIB and Pentacel with Prevnar vs. without Prevnar - Post-Dose 3 Hib Seroprotection Rates and GMTs



Daptacel, IPOL, ActHIB, Prevnar	94.4	80.3
Daptacel, IPOL, ActHIB	93.5	73.2
PENTACEL, Prevnar	95.8	77.1
PENTACEL	95.3	79.6

Daptacel, IPOL, ActHIB, Prevnar	3.8
Daptacel, IPOL, ActHIB	2.7
PENTACEL,Prevnar	3.3
PENTACEL	3.6

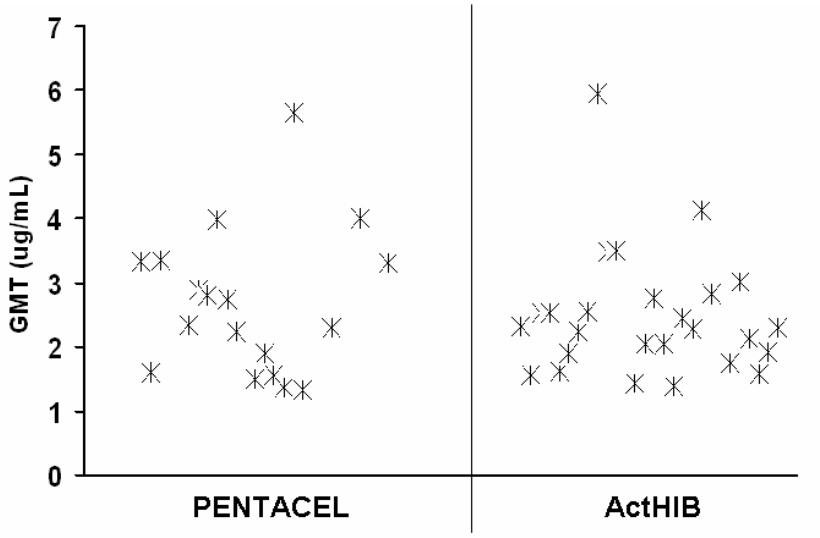
Hib Results in the Context of the Package Insert

Early studies on the performance of ActHIB in the US may be found in the package insert (PI) of this product. However, it is difficult to reliably compare those data to modern study results, because both the assays and the circumstances have changed. For example, the ActHIB PI describes 2 studies conducted in 1990-1991. In a clinical trial performed at Vanderbilt University in Tennessee, 65 infants were immunized with 3 doses of ActHIB. The anti-PRP GMT was 3.64 µg/mL and 83% of those subjects achieved an antibody level of ≥1.0 µg/mL. The anti-PRP testing for this study was performed at Vanderbilt University. In a second multi-center clinical trial performed in Minnesota, Missouri and Texas, 142 infants immunized with 3 doses of ActHIB yielded a GMT 6.37 µg/mL and 97% of those subjects achieved an antibody level of ≥1.0 µg/mL. The testing for this study was performed at Washington University. There are at least 3 factors that make comparing such data to each other or to modern trials problematic:

- The trials described in the package insert were performed more than 15 years ago, when the immunization schedule consisted of whole-cell DTP (DTwP) and oral Polio vaccine; no hepatitis B or Prevnar immunizations were required. In general, higher anti-PRP titers were documented during the DTwP era (perhaps due to an adjuvant effect).
- The sample sizes in these trials were typical of studies of that period, but small for studies using current statistical criteria. Because of the small sample size design, these trials typically were conducted in a single or few study centers, thus lim iting study population diversity and failing to balance for variation across a broad range of study sites. The statistically significant variance found across ethnic groups and study sites in larger sample size trials (i.e., P3T06) demonstrates that caution should be exercised when trying to generalize results generated from small sample size trials with limited diversity. In contrast, the anti-PRP results elicited by 3 doses of separately administered ActHIB in Study P3T06 were generated from 1128 infants enrolled in 31 study sites across the US, making the P3T06 data set not only considerably larger but more diverse and representative of the US population than all the

ActHIB studies contained in the package insert, combined. Figure 49 shows a graphic representation of the variability of anti-PRP responses elicited by either ActHIB or Pentacel in study sites participating in Study P3T06. Although the overall results were almost identical for the Pentacel and control groups in Study P3T06, results at individual sites varied nearly 6-fold. Clearly, Hib studies conducted at only a few (or even single) sites, common in the past, are highly susceptible to variability in results.

Figure 49: Study P3T06: Post-Dose 3 Hib GMTs by Study Site (≥10 Subjects)



- The anti-PRP antibodies reported in the PI studies were assayed by local investigators at the universities where the trials were conducted. Especially in those early years, Hib assays were not well standardized and the variability of the anti-PRP assay has been well documented (16). In comparing the anti-PRP assays in use at 6 study centers, Ward and coworkers found mean differences >6-fold and individual differences of 600-fold, with the assay performed at University of Rochester yielding the highest titers and the assay performed at sanofi pasteur laboratories some of the lowest. Even after standardization of low values (where most variance exists), the individual differences were as much as 64-fold (16). Several assay parameters and reagents have been found to affect the sensitivity of these assays. The uncertainty of inter-laboratory comparisons (17) makes comparison of the current studies to the early ActHIB studies in the PI virtually meaningless.

Summary Statement

For these reasons, we consider Study P3T06 to provide the most relevant assessment of the immunogenicity performance of Pentacel compared to separately administered vaccines. Study P3T06 appropriately compared the performance of Pentacel against the 3 separately administered licensed vaccines that represent the current standard of care, and which it would tend to replace. The results presented in the Study P3T06 Infant Series and 4th Dose clinical study reports and summarized in this document demonstrate that:

- Pentacel elicited post-Dose 3 GMTs and seroprotection rates at the ≥0.15 µg/mL and ≥1.0 µg/mL levels that were non-inferior to those achieved by the US-licensed standard-of-care vaccines Daptacel, IPOL, and ActHIB given separately.
- Pentacel subjects had anti-Hib pre-Dose 4 GMTs and seroprotection rates that were non-inferior to those achieved by the separate-vaccines group.

- Pentacel elicited post-Dose 4 GMTs and seroprotection rates that were non-inferior to those achieved by the separate-vaccines group.
- Furthermore, the post-Dose 3 data in Study P3T06 are in concordance with other non-pivotal published studies, in which either Pentacel (15) or an HCPDT//PRP-T combination vaccine (18) elicited very similar anti-PRP responses as seen in the groups given separately administered vaccines.

Finally, post-Dose 3 and post-Dose 4 seroprotection rates elicited by Pentacel in the non-controlled pivotal studies 494-03 and 5A9908 (post-Dose 4 only) were comparable to those elicited by Pentacel in Studies 494-01, P3T06, and M5A07, showing an overall consistent performance of anti-PRP responses elicited by this product.

2.3.6 Diphtheria and Tetanus

2.3.6.1 Comparison to Standard of Care Vaccines

Geometric Mean Titers

As shown in Table 40, the GMT ratios derived from the diphtheria and tetanus antibody responses in Study P3T06 fulfilled the statistical criteria supporting the non-inferiority of Pentacel to the US-licensed standard-of-care vaccines after 3 doses. Similarly, after the 4th Dose, the GMT ratios derived from the diphtheria response demonstrated the statistical non-inferiority of Pentacel vaccine. The upper bound 95% CI of the post-Dose 4 anti-tetanus GMT ratio was 1.71, thus not fulfilling the non-inferiority statistical criteria of <1.5 (see Table 40).

Table 40: Study P3T06: Post-Dose 3 and Post-Dose 4 GMTs and GMT Ratios of Antibody Levels to Diphtheria and Tetanus Antigens

Serology Sample/ Antigen	P3T06			
	Control [1] n GMT 95% CI	Pentacel n GMT 95% CI	GMT Ratio Control/Pentacel 90% CI	Non-inferiority Yes/No [4]
Post-Dose 3 [2]				
Diphtheria (IU/mL)	1099 0.94 (0.89, 0.99)	345 0.95 (0.86, 1.04)	0.99 (0.91, 1.08)	Yes
Tetanus (IU/mL)	1037 1.24 (1.18, 1.29)	331 1.10 (1.01, 1.19)	1.12 (1.04, 1.21)	Yes
Post-Dose 4 [3]				
Diphtheria (IU/mL)	328 5.69 (5.11, 6.34)	341 5.15 (4.66, 5.70)	1.10 (0.98, 1.25)	Yes
Tetanus (IU/mL)	334 4.98 (4.61, 5.37)	352 3.19 (2.96, 3.44)	1.56 (1.43, 1.71)	No

[1] Control means Daptacel, IPOL, and ActHIB vaccines for the Infant Series, and Daptacel and ActHIB vaccines for the 4th Dose.

[2] For post-Dose 3, pooled Control (Daptacel groups) data are presented and used in the non-inferiority comparisons.

[3] For post-Dose 4, only Group 1 (Daptacel and ActHIB at 15 months of age) data is included.

[4] Non-inferiority is achieved when the upper limit of the 90% CI of the GMT ratio is <1.5.

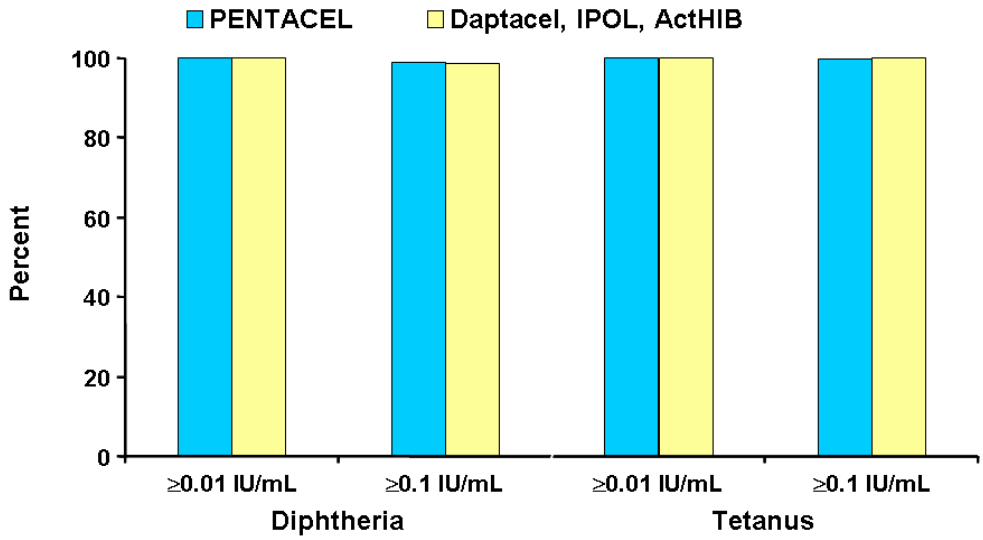
'n' is the number of subjects with available data from the PP Immunogenicity Population.

Seroprotection Rates

Figure 50 and Figure 51 present, respectively, the post-Dose 3 and post-Dose 4 seroprotection rates for diphtheria and tetanus elicited by Pentacel vaccine as compared to those elicited by the administration of Daptacel in Study P3T06.

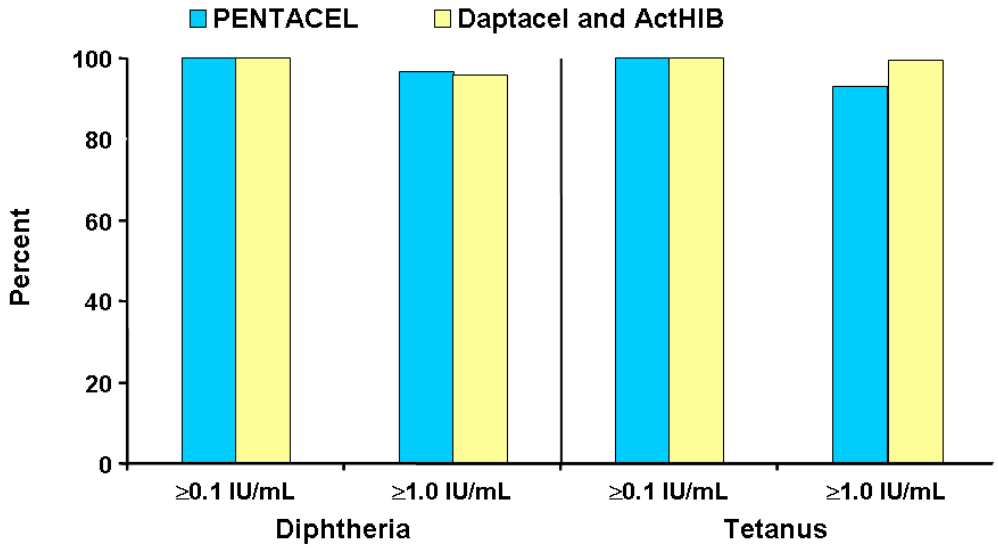
In this study, the seroprotection rates to diphtheria and tetanus after the 3rd dose of Pentacel vaccine fulfilled the statistical criteria of non-inferiority to the separately administered Control vaccines at the ≥0.01 IU/mL (primary criteria) and ≥0.1 IU/mL threshold levels (see Figure 52). Similarly, the seroprotection rates to diphtheria and tetanus after the 4th Dose of Pentacel vaccine fulfilled the statistical criteria of non-inferiority to the separately administered Control vaccines at the ≥0.1 IU/mL (primary criteria) and ≥1.0 IU/mL threshold levels (see Figure 52). Likewise, when the post-Dose 3 and post-Dose 4 differences in seroprotection rates were compared in an observational manner using 95% CIs (as requested by FDA), the upper limits of the 95% CI for the difference in seroprotection rates for diphtheria and tetanus also fulfilled the statistical criteria supporting the non-inferiority of Pentacel to the licensed control Daptacel (data not shown). Furthermore, in Study P3T06 the seroprotection rates were close to or at 100% for both groups.

Figure 50: Study P3T06: Pentacel vs. US Standard of Care Vaccines - Post-Dose 3 Diphtheria and Tetanus Seroprotection Rates



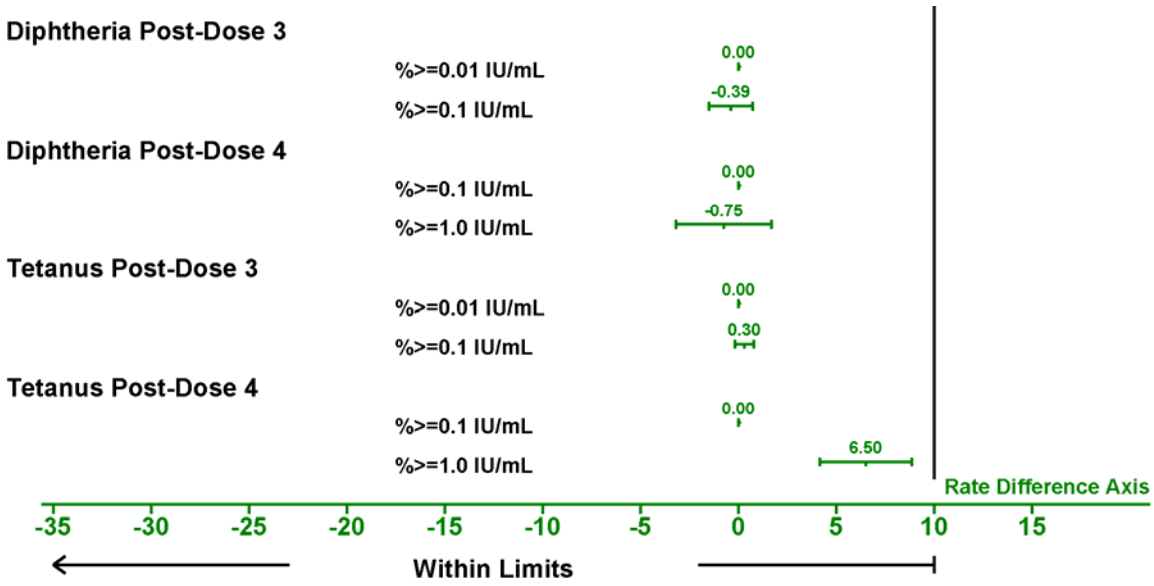
PENTACEL	100.0	98.8	100.0	99.7
Control	100.0	98.5	100.0	100.0

Figure 51: Study P3T06: Pentacel vs. US Standard of Care Vaccines - Post-Dose 4 Diphtheria and Tetanus Seroprotection Rates



PENTACEL	100.0	96.5	100.0	92.9
Control	100.0	95.7	100.0	99.4

Figure 52: Study P3T06: Non-inferiority testing - Post-Dose 3 and Post-Dose 4 Diphtheria and Tetanus

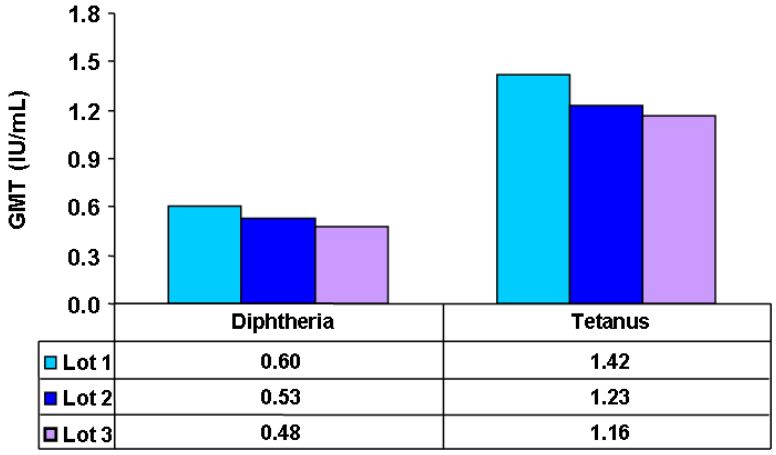


2.3.6.2 Lot Consistency

Geometric Mean Titers

Figure 53 presents the GMTs for diphtheria and tetanus after the 3rd dose of Pentacel vaccine, by lot, in Study 494-01. Diphtheria and tetanus antibody GMTs were similar between lot groups and the comparisons between the lots fulfilled the statistical criteria for equivalence for both antigens (see Figure 55).

Figure 53: Study 494-01: Pentacel Lot Consistency – Post-Dose 3 Diphtheria and Tetanus GMTs

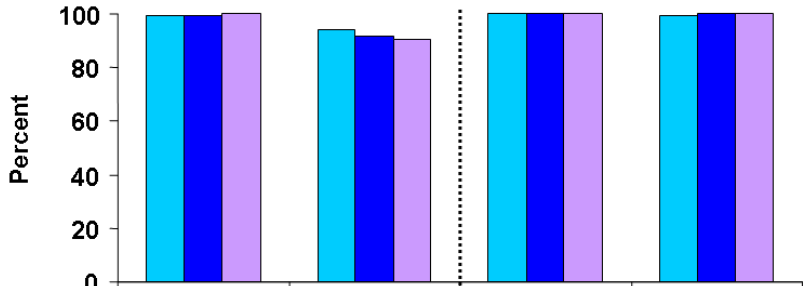


	Diphtheria	Tetanus
Lot 1	0.60	1.42
Lot 2	0.53	1.23
Lot 3	0.48	1.16

Seroprotection Rates

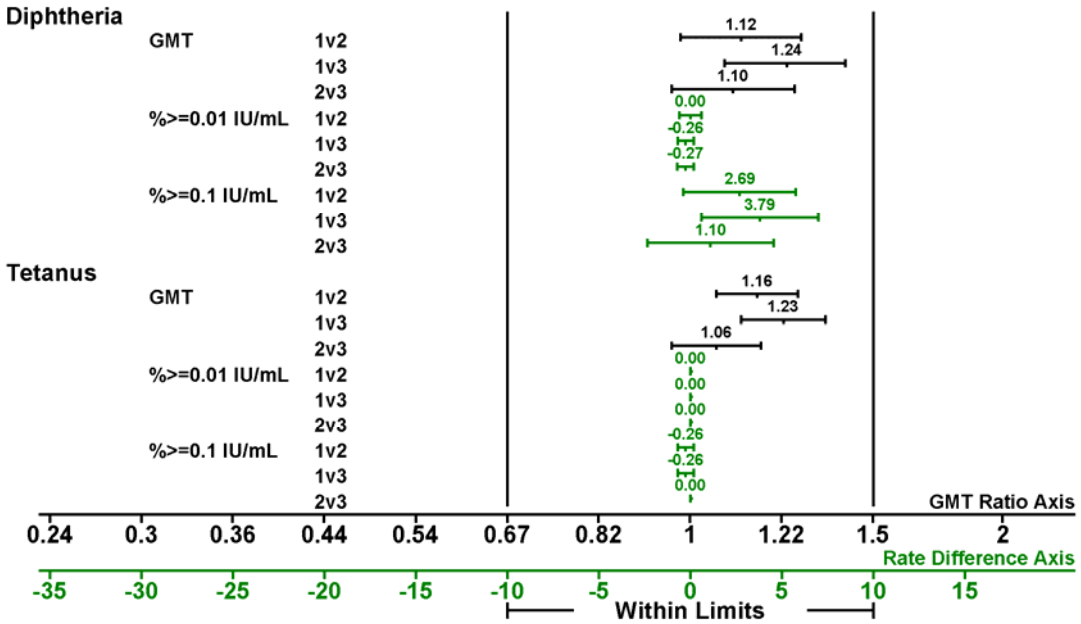
Figure 54 shows the seroprotection rates for the diphtheria and tetanus antigens. For diphtheria the seroprotection rates at the ≥0.01 and ≥0.1 IU/mL levels were from 99.7 to 100% and from 90.4 to 94.2%, respectively. For tetanus the seroprotection rates were 100% at the ≥0.01 IU/mL level and were from 99.7 to 100% at the ≥0.1 IU/mL level. The seroprotection rates for both antigens, at both antibody concentration threshold levels, fulfilled the statistical criteria for equivalence among the 3 lots of Pentacel vaccine (see Figure 55).

Figure 54: Study 494-01: Pentacel Lot Consistency – Post-Dose 3 Diphtheria and Tetanus Seroprotection Rates



	>=0.01 IU/mL (Diphtheria)	>= 0.1 IU/mL (Diphtheria)	>= 0.01 IU/mL (Tetanus)	>= 0.1 IU/mL (Tetanus)
Lot 1	99.7	94.2	100.0	99.7
Lot 2	99.7	91.5	100.0	100.0
Lot 3	100.0	90.4	100.0	100.0

Figure 55: Study 494-01: Pentacel Lot Consistency - Post-Dose 3 Diphtheria and Tetanus



2.3.6.3 Comparison to HCPDT, Poliovax, and ActHIB

Geometric Mean Titers

As shown in Table 41, the GMTs derived from the diphtheria antibody responses of Study 494-01 were comparable after 3 doses, as assessed by the overlap of their 95% CIs. Similarly, after the 4th Dose, the GMTs derived from the diphtheria responses elicited by the Pentacel and Control vaccines were comparable. Antibody GMTs against tetanus were higher (non-overlapping 95% CIs) in the Control group. Study 494-01 Infant Series did not include prospectively defined non-inferiority comparisons for the responses to the diphtheria and tetanus antigens.

Table 41: Study 494-01: Post-Dose 3 and Post-Dose 4 GMTs of Antibody Levels to Diphtheria and Tetanus Antigens

Antigen/ Serology Sample	Control [1] n GMT 95% CI	Pentacel n GMT 95% CI
Post-Dose 3		
Diphtheria (IU/mL)	399 0.48 (0.43, 0.53)	1125 0.53 (0.50, 0.57)
Tetanus (IU/mL)	397 1.81 (1.68, 1.95)	1125 1.27 (1.21, 1.33)
Post-Dose 4		
Diphtheria (IU/mL)	287 5.50 (4.91, 6.17)	862 5.67 (5.32, 6.04)
Tetanus (IU/mL)	287 6.98 (6.39, 7.62)	861 3.71 (3.51, 3.92)

[1] Control means HCPDT, Poliovax, and ActHIB components.

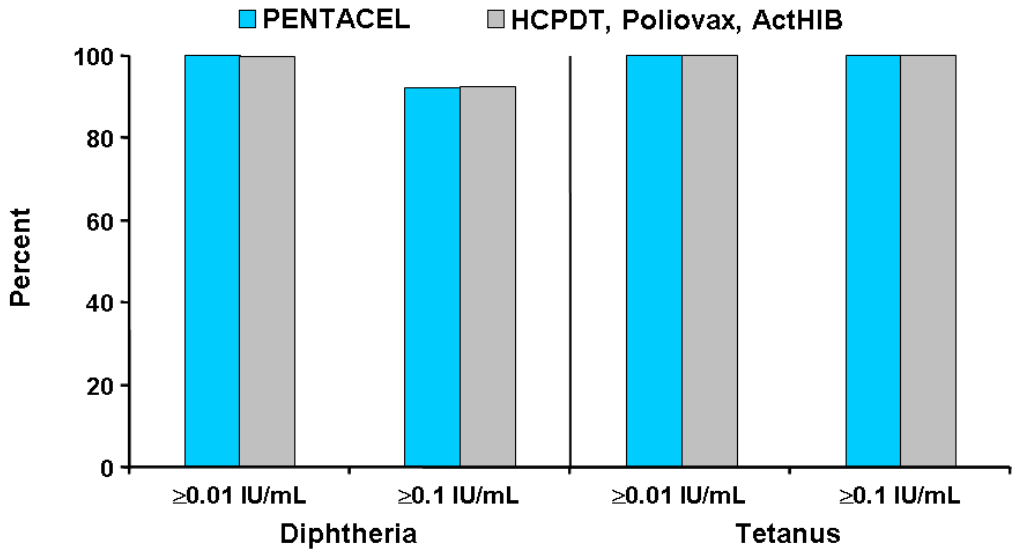
Notes: 'n' is the number of subjects with available data from the PP Immunogenicity Population.

Seroprotection Rates

Figure 56 and Figure 57 present, respectively, the post-Dose 3 and post-Dose 4 seroprotection rates for diphtheria and tetanus elicited by Pentacel vaccine as compared to those elicited by the separate administration of HCPDT and Poliovax components in Study 494-01.

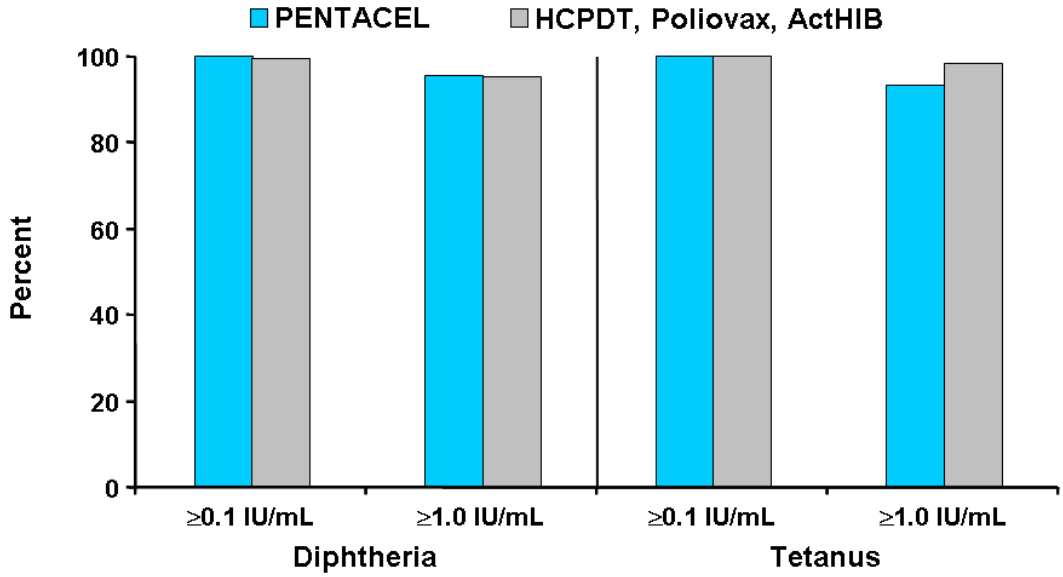
In Study 494-01, the seroprotection rates to diphtheria and tetanus after the 3rd dose of Pentacel vaccine fulfilled the statistical criteria of non-inferiority to the separately administered Control vaccines at the ≥0.01 IU/mL (primary criteria) and ≥0.1 IU/mL threshold levels (see Figure 58). Similarly, the seroprotection rates to diphtheria and tetanus after the 4th Dose of Pentacel vaccine fulfilled the statistical criteria of non-inferiority to the separately administered Control vaccines at the ≥0.1 IU/mL (primary criteria) and ≥1.0 IU/mL threshold levels (see Figure 57). Likewise, the post-Dose 3 and post-Dose 4 differences in seroprotection rates for the same antibody concentration thresholds also fulfilled non-inferiority criteria based on the upper bound of the 95% CIs (as requested by FDA). Furthermore, in Study 494-01, the seroprotection rates for Pentacel and Control vaccines to the indicated threshold levels were close to or at 100%.

Figure 56: Study 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 3 Diphtheria and Tetanus Seroprotection Rates



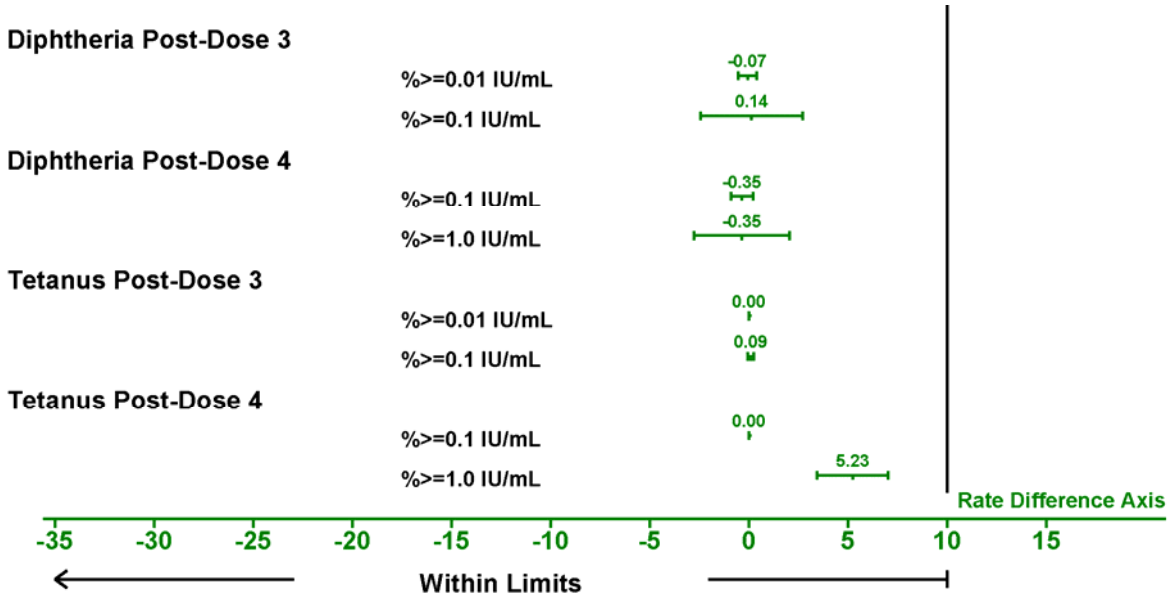
PENTACEL	99.8	92.1	100.0	99.9
Control	99.7	92.2	100.0	100.0

Figure 57: Study 494-01: Pentacel vs. HCPDT, Poliovax, ActHIB - Post-Dose 4 Diphtheria and Tetanus Seroprotection Rates



PENTACEL	100.0	95.5	100.0	93.4
Control	99.7	95.1	100.0	98.6

Figure 58: Study 494-01: Non-inferiority testing - Post-Dose 3 and Post-Dose 4 Diphtheria and Tetanus



2.3.7 Polio

2.3.7.1 Comparison to Standard of Care Vaccines

Geometric Mean Titers

Study P3T06 Infant Series provided prospectively defined non-inferiority comparisons for the responses to the poliovirus types 1, 2, and 3 antigens elicited by 3 doses of Pentacel or IPOL based on their GMTs. As shown in Table 42, the GMT ratios derived from the poliovirus antibody responses (IPOL / Pentacel) fulfilled the statistical criteria supporting the non-inferiority of Pentacel to IPOL vaccine after 3 doses.

Table 42: Study P3T06: Post-Dose 3 GMTs and GMT Ratios of Antibody Levels to Poliovirus Antigens

Antigen	Control [1] n GMT (95% CI)	Pentacel n GMT (95%CI)	GMT Ratio [2] Control/Pentacel 90% CI	Non-inferiority Yes/No [3]
Polio 1 ≥1:8 (1/dil)	1097 463.49 (436.93, 491.67)	350 398.13 (343.10, 461.99)	1.16 (1.04, 1.30)	Yes
Polio 2 ≥1:8 (1/dil)	1073 913.35 (858.19, 972.06)	348 1032.2 (905.86, 1176.15)	0.88 (0.79, 0.99)	Yes
Polio 3 ≥1:8 (1/dil)	1050 902.12 (847.82, 959.89)	338 969.82 (852.28, 1103.57)	0.93 (0.83, 1.04)	Yes

[1] Control means Daptacel, IPOL, and ActHIB vaccines.

[2] For post-Dose 3, pooled Control (Daptacel groups) data are presented and used in the non-inferiority comparisons.

[3] Non-inferiority is achieved when the upper limit of the 90% CI of the GMT ratio is <1.5.

Note: 'n' is the number of subjects with available data from the PP Immunogenicity Population.

Seroprotection Rates

Table 43 summarizes the post-Dose 3 seroprotection rates for poliovirus types 1, 2, and 3 elicited by Pentacel vaccine as compared to those elicited by the separate administration of Daptacel and IPOL vaccines in Study P3T06. Three doses of Pentacel vaccine elicited seroprotection rates to poliovirus types 1, 2, and 3 antigens in 100% or nearly 100% of the subjects in both groups, and thus the anti-poliovirus responses elicited by Pentacel vaccine after the 3rd dose of Pentacel vaccine fulfilled the statistical criteria of non-inferiority to the Control. Rates of seroprotection elicited by 4 doses of Pentacel were 100% for all 3 types of poliovirus.

Table 43: Study P3T06: Post-Dose 3 and Post-Dose 4 Seroprotection Rates of Antibody Levels to Poliovirus Antigens

Serology Sample/ Antigen	Control [1] n/N % 95% CI	Pentacel n/N % 95% CI	Control-Pentacel 90% CI	Non-inferiority Yes/No [2]
Post-Dose 3				
Polio 1 ≥1:8 (1/dil)	1097/1097 100.0 (99.7, 100.)	348/350 99.4 (98.0, 99.9)	0.57 (-0.09, 123)	Yes
Polio 2 ≥1:8 (1/dil)	1073/1073 100.0 (99.7, 100.0)	348/348 100.0 (98.9, 100.0)	0.00 (NA)	Yes
Polio 3 ≥1:8 (1/dil)	1050/1050 100.0 (99.6, 100.0)	338/338 100.0 (98.9, 100.0)	0.00 (NA)	Yes
Post-Dose 4				
Polio 1 ≥1:8 (1/dil)	NA	298/298 100.0 (98.8, 100.0)	NA	NA
Polio 2 ≥1:8 (1/dil)	NA	334/334 100.0 (98.9, 100.0)	NA	NA
Polio 3 ≥1:8 (1/dil)	NA	302/302 100.0 (98.8, 100.0)	NA	NA

[1] Control means Daptacel, IPOL, and ActHIB vaccines for Infant Series; pooled data from all 3 Control groups is used in the non-inferiority analyses.

[2] Non-inferiority is achieved when the upper limit of the 90% CI of the GMT ratio is <1.5.

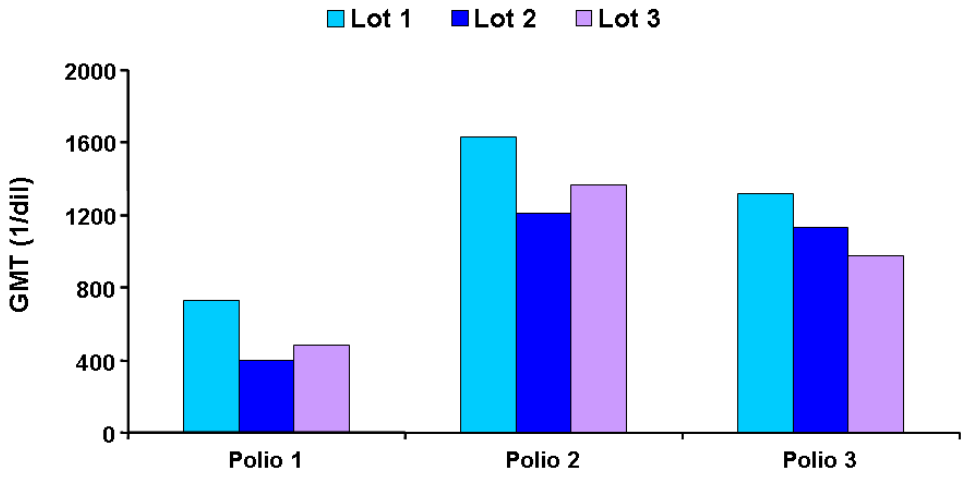
Note: 'n' is the number of subjects satisfying the criterion.
'N" is the number of subjects with available data from the PP Immunogenicity Population.
NA = not applicable.

2.3.7.2 Lot Consistency

Geometric Mean Titers

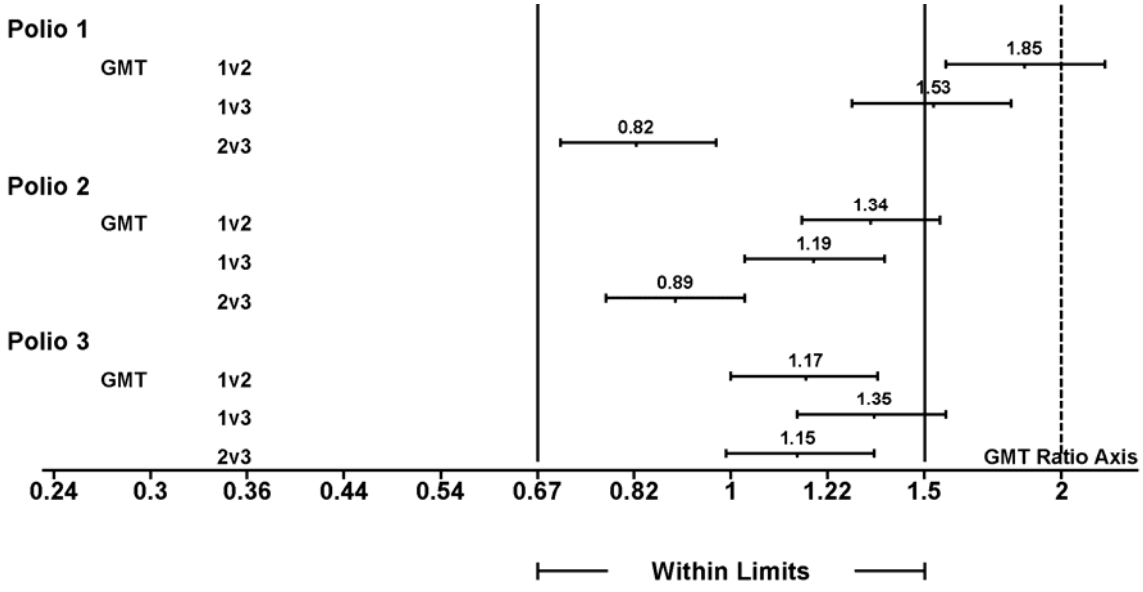
As shown in Figure 59, anti-Polio GMTs differed somewhat among the lots and thus did not meet the statistical criteria for equivalence, but were many-fold higher than seroprotective levels; thus, this variation is of no clinical importance.

Figure 59: Study 494-01: Pentacel Lot Consistency - Post-Dose 3 Polio GMTs



Lot 1	730.8	1628.0	1313.9
Lot 2	394.0	1212.0	1126.5
Lot 3	478.4	1363.8	976.7

Figure 60: Study 494-01: Pentacel Lot Consistency Testing - Post-Dose 3 Polio GMTs



Seroprotection Rates

In Study 494-01; 99% to 100% of participants achieved seroprotective antibody levels for poliovirus types 1, 2, and 3 (Table 44), fulfilling the statistical criteria for equivalence among the 3 lots of Pentacel vaccine.

Table 44: Study 494-01: Post-Dose 3 Seroprotection Rate Difference of Antibody Levels to Poliovirus Antigens, Pentacel Lots

Antigen	Pentacel			Lot Consistency			
	Lot 1 n/N % (95% CI)	Lot 2 n/N % (95% CI)	Lot 3 n/N % (95% CI)	Lot 1–Lot 2 (90% CI)	Lot 1–Lot 3 (90% CI)	Lot 2–Lot 3 (90% CI)	Equivalence Yes/No [1]
Polio 1 **≥1:8 (1/dil)**	377/377 100.0 (99.0, 100.0)	366/369 99.2 (97.6, 99.8)	358/358 100.0 (99.0, 100.0)	0.81 (0.05, 1.58)	0.00 N/A	-0.81 (-1.60, -0.03)	Yes
Polio 2 **≥1:8 (1/dil)**	376/376 100.0 (99.0, 100.0)	368/368 100.0 (99.0, 100.0)	358/358 100.0 (99.0, 100.0)	0.00 N/A	0.00 N/A	0.00 N/A	Yes
Polio 3 **≥1:8 (1/dil)**	374/374 100.0 (99.0, 100.0)	367/367 100.0 (99.0, 100.0)	359/359 100.0 (99.0, 100.0)	0.00 N/A	0.00 N/A	0.00 N/A	Yes

[1] Equivalence is achieved when the upper limit 90% CI is <5% and the lower limit is >-5%.

Note: 'n' is the number of subjects satisfying the condition in the PP Immunogenicity Population.
'N' is the number of subjects with available data in the PP Immunogenicity Population.

2.3.7.3 Comparison to HCPDT, Poliovax, ActHIB

Geometric Mean Titers

The Study 494-01 Infant Series did not include prospectively defined GMT non-inferiority comparisons for the responses to the poliovirus types 1, 2, and 3 antigens. As shown in Table 45, 3 and 4 doses of Pentacel vaccine elicited robust immune responses to the poliovirus types 1, 2, and 3 antigens. As assessed by the 95% CIs, 3 doses of the control vaccine (Poliovax) elicited a higher antibody titer to Polio 1. After the 4th Dose, the antibody GMTs against poliovirus types 2 and 3 were higher in the Pentacel vaccine group. However, given the robustness of these responses, the observed GMT differences are considered of no clinical significance.

Table 45: Study 494-01: Post-Dose 3 and Post-Dose 4 GMTs of Antibody Levels to Poliovirus Antigens

Antigen/ Serology Sample	Control [1] n GMT 95% CI	Pentacel n GMT 95% CI
Post-Dose 3		
Polio 1 ≥1:8 (1/dil)	388 766.00 (689.69, 850.74)	1104 518.14 (477.13, 562.67)
Polio 2 ≥1:8 (1/dil)	388 1520.60 (1377.37, 1678.71)	1102 1392.77 (1296.65, 1496.02)
Polio 3 ≥1:8 (1/dil)	387 1105.98 (986.23, 1240.27)	1100 1132.98 (1049.76, 1222.80)
Post-Dose 4		
Polio 1 ≥1:8 (1/dil)	285 2329.76 (2049.16, 2648.79)	857 2303.65 (2115.27, 2508.80)
Polio 2 ≥1:8 (1/dil)	284 2840.33 (2516.24, 3206.17)	854 4178.27 (3864.65, 4517.34)
Polio 3 ≥1:8 (1/dil)	287 3299.79 (2852.46, 3817.27)	851 4415.38 (4045.96, 4818.54)

[1] Control means HCPDT, Poliovax, and ActHIB components.

Notes: 'n' is the number of subjects with available data from the PP Immunogenicity Population.

Seroprotection Rates

Table 46 summarize the post-Dose 3 and post-Dose 4 seroprotection rates for polio types 1, 2, and 3 elicited by Pentacel vaccine as compared to those elicited by the separate administration of HCPDT and Poliovax components in Study 494-01.

Three doses of Pentacel vaccine elicited seroprotection rates to poliovirus types 1, 2, and 3 antigens in close to- or in 100% of the subjects in both groups (see Table 46), and thus the anti-poliovirus responses elicited by Pentacel vaccine after both the 3rd and 4th Doses fulfilled the statistical criteria of non-inferiority to the Control vaccine Poliovax. After the 4th Dose both groups elicited seroprotection in 100% of the subjects tested (see Table 46).

Table 46: Study 494-01: Post-Dose 3 and Post-Dose 4 Seroprotection Rates of Antibody Levels to Poliovirus Antigens

Serology Sample/ Antigen	Control [1] n/N % 95% CI	Pentacel n/N % 95% CI	Control-Pentacel 90% CI	Non-inferiority Yes/No [2]
Post-Dose 3				
Polio 1 ≥1:8 (1/dil)	388/388 100.0 (99.1, 100.0)	1101/1104 99.7 (99.2, 99.9)	0.27 (0.01, 0.53)	Yes
Polio 2 ≥1:8 (1/dil)	388/388 100.0 (99.1, 100.0)	1102/1102 100.0 (99.7, 100.0)	0.0 (NA)	Yes
Polio 3 ≥1:8 (1/dil)	387/387 100.0 (99.1, 100.0)	1100/1100 100.0 (99.7, 100.0)	0.0 (NA)	Yes
Post-Dose 4				
Polio 1 ≥1:8 (1/dil)	285/285 100.0 (98.7, 100.0)	857/857 100.0 (99.6, 100.0)	0.00 (NA)	Yes
Polio 2 ≥1:8 (1/dil)	284/284 100.0 (98.7, 100.0)	854/854 100.0 (99.6, 100.0)	0.00 (NA)	Yes
Polio 3 ≥1:8 (1/dil)	287/287 100.0 (98.7, 100.0)	851/851 100.0 (99.6, 100.0)	0.00 (NA)	Yes

[1] Control means HCPDT, Poliovax, and ActHIB components.

[2] Non-inferiority is achieved when the upper limit of the 90% CI of the difference in seroprotection rates (Control – Pentacel) is <5%.

Notes: 'n' is the number of subjects satisfying the criterion.
'N" is the number of subjects with available data from the PP Immunogenicity Population.

2.3.8 4th Dose Immune Responses Among Children 15-18 Months of Age

Geometric Mean Titers

Study 5A9908 was designed to demonstrate that the immune responses to the antigens in Pentacel vaccine were equivalent when a 4th Dose was administered to children 15 to 16 months of age compared to children 17 to 18 months of age. The post-4th Dose GMTs (secondary objective) to all the antigens in Pentacel vaccine between the 2 combined age groups fulfilled the prospectively defined statistical criteria of equivalence (see Table 47).

Table 47: Study 5A9908: Pre- and Post-Dose 4 GMTs and GMT Ratios

Antigens	Time	15+16 Months		17+18 Months		Comparison	Equivalence Yes/No
		n	GMT1 [1]	n	GMT2 [1]	GMT1/GMT2 (90% CI)	
PRP (µg/mL)	**Pre**	372	0.36	361	0.40	0.80 (0.68, 0.94)	Yes
	Post	374	29.17	361	36.45		
PT (EU/mL)	**Pre**	367	15.56	360	11.05	0.87 (0.79, 0.97)	Yes
	Post	374	236.83	359	271.13		
FHA (EU/mL)	**Pre**	371	17.34	360	14.19	0.84 (0.78, 0.91)	Yes
	Post	374	177.25	361	211.08		
PRN (EU/mL)	**Pre**	370	10.65	360	9.67	0.92 (0.82, 1.04)	Yes
	Post	374	176.81	361	191.84		
FIM (EU/mL)	**Pre**	367	40.42	360	35.20	0.91 (0.80, 1.03)	Yes
	Post	374	780.83	361	862.67		
Diphtheria (IU/mL)	**Pre**	366	0.13	360	0.09	0.88 (0.78, 0.99)	Yes
	Post	373	4.42	361	5.04		
Tetanus (IU/mL)	**Pre**	366	0.47	356	0.43	0.85 (0.78, 0.93)	Yes
	Post	374	4.22	356	4.95		
Polio 1 ≥1:8 (1/dil)	**Pre**	372	124.85	360	82.06	1.00 (0.86, 1.16)	Yes
	Post	374	4065.82	361	4068.56		
Polio 2 ≥1:8 (1/dil)	**Pre**	367	297.20	360	228.95	1.02 (0.89, 1.16)	Yes
	Post	373	7458.23	361	7335.73		
Polio 3 ≥1:8 (1/dil)	**Pre**	364	207.25	360	111.77	1.26 (1.08, 1.46)	Yes
	Post	373	8314.69	360	6622.00		

[1] GMTs are based on the number of subjects with available data from the PP Immunogenicity Population.

Note: Equivalence is demonstrated if the 2-sided 90% CI of the ratio of the GMTs of the 2 combined age groups (15 to 16 Months/17 to 18 Months) was >2/3 and <1.5.

Seroprotection/Four-fold Rise Rates

Table 48 presents a summary of the post-Dose 4 seroprotection/4-fold rise rates for all antigens in Pentacel in Study 5A9908. After a 4th Dose, the seroprotection/4-fold rise rates (primary objective) to all the antigens contained in Pentacel vaccine fulfilled the statistical criteria of equivalence between the 15 to 16 Month and the 17 to 18 Month age groups (see Table 48).

Table 48: Study 5A9908: Post-Dose 4 Seroprotection and 4-Fold Rise Rates

Antigens	Criteria	15 + 16 Months		17 + 18 Months		Comparison	Equivalence Yes/No [4]
		N	n (%=p1) [1]	N	n (%=p2) [1]	p1-p2 (90% CI)	
PRP	**≥1.0 µg/mL**	374	368 (98.4)	361	358 (99.2)	-0.77 (-2.10, 0.55)	Yes
PT [2] (EU/mL)	**≥4-fold rise**	367	343 (93.5)	358	350 (97.8)	-4.30 (-6.79, -1.82)	Yes
FHA [2] (EU/mL)	**≥4-fold rise**	371	322 (86.8)	360	333 (92.5)	-5.71 (-9.39, -2.02)	Yes
PRN [2] (EU/mL)	**≥4-fold rise**	370	349 (94.3)	360	334 (92.8)	1.55 (-1.45, 4.54)	Yes
FIM [2] (EU/mL)	**≥4-fold rise**	367	343 (93.5)	360	344 (95.6)	-2.10 (-4.87, 0.68)	Yes
Diphtheria	**≥0.1 IU/mL**	373	373 (100.0)	361	361 (100.0)	0.00 (NA [3])	Yes
	≥1.0 IU/mL	373	353 (94.6)	361	346 (95.8)	-1.21 (-3.79, 1.37)	Yes
Tetanus	**≥0.1 IU/mL**	374	374 (100.0)	356	356 (100.0)	0.00 (NA [3])	Yes
	≥1.0 IU/mL	374	359 (96.0)	356	347 (97.5)	-1.48 (-3.64, 0.68)	Yes
Polio 1	**≥1:8 (1/dil)**	374	373 (99.7)	361	361 (100.0)	-0.27 (-0.71, 0.17)	Yes
Polio 2	**≥1:8 (1/dil)**	373	373 (100.0)	361	361 (100.0)	0.00 (NA [3])	Yes
Polio 3	**≥1:8 (1/dil)**	373	373 (100.0)	360	360 (100.0)	0.00 (NA [3])	Yes

[1] Percentages are based on the number of subjects with available data from the PP Immunogenicity Population.

[2] The fold-rise is calculated by post-4th Dose / pre-4th Dose antibody level.

[3] Not applicable.

[4] Equivalence is demonstrated if the 2-sided 90% CI for the difference in seroprotection/ seroconversion rates between the 15 to 16 Month and the 17 to 18 Month age groups was >-10% and <10% (>-5% and <5% for Poliovirus).

2.3.9 Effect of Other Vaccines on the Immune Responses Elicited by Pentacel

2.3.9.1 Co-administration with a Pneumococcal Conjugate

2.3.9.1.1 Administration of Pentacel Given at Different Times From or Concurrently With a Pneumococcal Conjugate Vaccine During the Infant Series

Geometric Mean Titers

Study M5A07 was designed to assess the effect of Prevnar co-administration on the immune responses to Pentacel. Table 49 presents the post-Dose 3 antibody GMTs to the Hib and Pertussis antigens elicited by Pentacel co-administered with Prevnar at 2, 4, and 6 months of age (Group 1) as compared to Pentacel administered at 2, 4 and 6 months of age with Prevnar administered at 3, 5 and 7 months of age (Group 2). The antibody GMTs to Hib and each of the pertussis antigens elicited by Pentacel vaccine concurrently administered with Prevnar vaccine were statistically non-inferior to those elicited by the administration of Pentacel vaccine a month apart from Prevnar vaccine. The presentation of the antibody GMTs to diphtheria, tetanus, and poliovirus types 1, 2, and 3 was planned as a descriptive analysis. Anti-tetanus and anti-poliovirus responses were very similar between groups, while the anti-diphtheria GMT was higher in the staggered schedule group.

Table 49: Study M5A07: Post-Dose 3 GMTs by Study Group

Antigen	Pentacel+Prevnar n GMT (95% CI)	Pentacel n GMT (95% CI)	Pentacel/ Pentacel+Prevnar (90% CI)	Non-Inferiority Yes/No [1]
PRP (µg/mL)	433 3.32 (2.85, 3.87)	427 3.60 (3.09, 4.20)	1.09 (0.91, 1.30)	Yes
PT (EU/mL)	446 103.58 (97.87, 109.63)	439 102.78 (96.86, 109.06)	0.99 (0.93, 1.06)	Yes
FHA (EU/mL)	447 82.41 (77.40, 87.75)	439 77.80 (72.62, 83.35)	0.94 (0.87, 1.02)	Yes
PRN (EU/mL)	447 45.70 (41.59, 50.23)	439 44.28 (40.11, 48.89)	0.97 (0.86, 1.09)	Yes
FIM (EU/mL)	447 272.47 (251.39, 295.32)	439 280.97 (258.02, 305.97)	1.03 (0.93, 1.14)	Yes
Diphtheria (IU/mL)	432 0.59 (0.53, 0.64)	422 1.32 (1.22, 1.42)	NA	NA
Tetanus (IU/mL)	424 1.27 (1.18, 1.35)	416 1.30 (1.21, 1.39)	NA	NA
Polio 1 ≥1:8 (1/dil)	406 543.52 (480.61, 614.67)	396 593.09 (515.54, 682.31)	NA	NA

Antigen	Pentacel+Prevnar n GMT (95% CI)	Pentacel n GMT (95% CI)	Pentacel/ Pentacel+Prevnar (90% CI)	Non-Inferiority Yes/No [1]
Polio 2 ≥1:8 (1/dil)	422 846.36 (752.37, 952.08)	415 949.06 (847.95, 1062.22)	NA	NA
Polio 3 ≥1:8 (1/dil)	410 1025.73 (899.05, 1170.26)	396 1104.05 (969.80, 1256.88)	NA	NA

[1] Non-inferiority is achieved when the upper limit of the 90% CI of the GMT ratio (Group 2/Group 1) is <1.5.

NA = Not applicable.

Seroprotection/Four-fold Rise Rates

Table 50 presents the post-Dose 3 seroconversion/seroprotection rates to Hib, Diphtheria, Tetanus, Pertussis and Polio elicited by Pentacel in Study M5A07. Rates of seroprotection to Hib, diphtheria, tetanus, and poliovirus types 1, 2, and 3 and rates of seroconversion (≥4-fold rise) to the pertussis antigens were similar between the study groups.

Pentacel vaccine concurrently administered with Prevnar vaccine elicited anti-PRP seroprotection rates at the ≥0.15 µg/mL and ≥1.0 µg/mL levels that were non-inferior to those elicited by Pentacel vaccine given 1 month apart from Prevnar vaccine (see Table 50). In addition, the rates of 4-fold seroconversion to the pertussis antigens elicited by Pentacel vaccine concurrently administered with Prevnar vaccine were non-inferior to those observed in the group with the staggered schedule. Statistical non-inferiority was also achieved for diphtheria, tetanus, and poliovirus types 1, 2, and 3.

Table 50: Study M5A07: Post-Dose 3 Seroconversion/Seroprotection Rates: Non-inferiority of Pentacel when Given at Different Times From or Concurrently with a Pneumococcal Conjugate Vaccine

Antigen	Criteria	Pentacel+Prevnar n/N % (95%CI)	Pentacel n/N % (95%CI)	Pentacel– Pentacel+Prevnar (95%CI)	Non-inferiority Yes/No [1]
PRP	**≥0.15 µg/mL**	415/433 95.8 (93.5, 97.5)	407/427 95.3 (92.9, 97.1)	-0.53 (-3.27 , 2.22)	Yes
	≥1.0 µg/mL	334/433 77.1 (72.9, 81.0)	340/427 79.6 (75.5, 83.3)	2.49 (-3.01, 7.99)	Yes
PT (EU/mL)	**≥4-fold rise**	399/445 89.7 (86.5, 92.3)	395/437 90.4 (87.2, 93.0)	0.73 (-3.23, 4.68)	Yes
FHA (EU/mL)	**≥4-fold rise**	360/441 81.6 (77.7, 85.1)	357/436 81.9 (77.9, 85.4)	0.25 (-4.86, 5.36)	Yes
PRN (EU/mL)	**≥4-fold rise**	327/444 73.6 (69.3, 77.7)	314/438 71.7 (67.2, 75.9)	-1.96 (-7.84, 3.92)	Yes

Antigen	Criteria	Pentacel+Prevnar n/N % (95%CI)	Pentacel n/N % (95%CI)	Pentacel– Pentacel+Prevnar (95%CI)	Non-inferiority Yes/No [1]
FIM (EU/mL)	**≥4-fold rise**	387/442 87.6 (84.1, 90.5)	384/438 87.7 (84.2, 90.6)	0.11 (-4.24, 4.47)	Yes
Diphtheria	**≥0.01 IU/mL**	432/432 100.0 (99.1, 100.0)	422/422 100.0 (99.1, 100.0)	0.00 (NA)	Yes
Tetanus	**≥0.01 IU/mL**	424/424 100.0 (99.1, 100.0)	416/416 100.0 (99.1, 100.0)	0.00 (NA)	Yes
Polio 1	**≥1:8 (1/dil)**	406/406 100.0 (99.1, 100.0)	395/396 99.7 (98.6, 100.0)	-0.25 (-0.75, 0.24)	Yes
Polio 2	**≥1:8 (1/dil)**	422/422 100.0 (99.1, 100.0)	415/415 100.0 (99.1, 100.0)	0.00 (NA)	Yes
Polio 3	**≥1:8 (1/dil)**	410/410 100.0 (99.1, 100.0)	396/396 100.0 (99.1, 100.0)	0.00 (NA)	Yes

[1] Non-inferiority if achieved when the upper limit of the 2-sided 95% CI of Pentacel-Pentacel+Prevnar is <10%.

Notes: 'n' is the number of subjects who met the criteria of the test indicated.
'N' is the total number of subjects with available serology data from the PP Immunogenicity Population.

Study M5A07 demonstrated that the concurrent administration of Prevnar with Pentacel during the Infant Series did not decrease the immune response to the acellular Pertussis or Hib antigens as compared to the same responses in the group that received a staggered schedule of immunizations. The post-Dose 3 anti-diphtheria GMT was higher (non-overlapping 95% CIs) in subjects that received the staggered immunization schedule, probably due to the effect of administering 2 diphtheria antigens (e.g., diphtheria toxoid contained in Pentacel or CRM_{197} contained in Prevnar) on a monthly schedule (2, 3, 4, 5, and 6 months) compared with co-administration of the 2 diphtheria antigens at 2, 4, and 6 months (diphtheria toxoid and CRM_{197}, concurrently).

2.3.9.1.2 Administration of the 4th Dose of Pentacel With or Without a Pneumococcal Conjugate Vaccine

Seroprotection/Four-fold Rise Rates

Study 494-03 compared the seroconversion and seroprotection rates of the antigens in Pentacel vaccine when the 4th Dose of Pentacel vaccine was either administered alone (Group 1) or co-administered with Prevnar vaccine (Group 3) (see Table 51). The co-administration of Pentacel with Prevnar elicited immune responses to all of the antigens in Pentacel that were non-inferior to the immune responses elicited by Pentacel alone. Subjects that were concurrently immunized with Pentacel and Prevnar vaccines had seroprotection rates to Hib (≥1.0 µg/mL), diphtheria and tetanus (≥0.1 IU/mL and ≥1.0 IU/mL), and 4-fold rise rates to PT, FHA, and PRN pertussis antigens that fulfilled the statistical criteria demonstrating the non-inferiority to the immune responses elicited by the administration of Pentacel alone. For FIM, the rate of seroconversion was statistically lower when Pentacel was administered with Prevnar (80.4% [148/184]) than

when Pentacel was administered alone (87.2% [157/180]). However, given the high post-Dose 4 antibody levels achieved against this antigen in both groups (GMT: 434.35 EU/mL for Group 1 and 324.96 EU/mL for Group 3, respectively), it is unlikely that this difference has any clinical significance (see Table 51).

Table 51: Study 494-03: Post-Dose 4 Seroprotection/Four-fold Rise Rate: Non-inferiority Analysis – Effect of Pneumococcal Conjugate Vaccine on the Immune Response to Pentacel

Antigen	Criteria	Pentacel	Pentacel+Prevnar	Pentacel–Pentacel+Prevnar (90% CI)	Non-inferiority Yes/No [2]
		n/N % (95%CI)	n/N % (95%CI)		
PRP	**≥0.15 µg/mL**	218/218 100.0 (98.3, 100.0)	211/213 99.1 (96.6, 99.9)	0.94 (-0.15, 2.03)	Yes
	≥1.0 µg/mL	216/218 99.1 (96.7, 99.9)	208/213 97.7 (94.6, 99.2)	1.43 (-0.58, 3.44)	Yes
PT (EU/mL)	**≥4 fold-rise [1]**	165/180 91.7 (86.6, 95.3)	168/184 91.3 (86.3, 94.9)	0.36 (-4.45, 5.17)	Yes
FHA (EU/mL)	**≥4 fold-rise [1]**	157/180 87.2 (81.4, 91.7)	159/184 86.4 (80.6, 91.0)	0.81 (-5.02, 6.64)	Yes
PRN (EU/mL)	**≥4 fold-rise [1]**	152/180 84.4 (78.3, 89.4)	150/184 81.5 (75.1, 86.9)	2.92 (-3.55, 9.40)	Yes
FIM (EU/mL)	**≥4 fold-rise [1]**	157/180 87.2 (81.4, 91.7)	148/184 80.4 (74.0, 85.9)	6.79 (0.47, 13.10)	No
Diphtheria	**≥0.1 IU/mL**	217/217 100.0 (98.3, 100.0)	212/212 100.0 (98.3, 100.0)	0.00 (NA)	Yes
	≥1.0 IU/mL	214/217 98.6 (96.0, 99.7)	203/212 95.8 (92.1, 98.0)	2.86 (0.24, 5.49)	Yes
Tetanus	**≥0.1 IU/mL**	215/215 100.0 (98.3, 100.0)	210/210 100.0 (98.3, 100.0)	0.00 (NA)	Yes
	≥1.0 IU/mL	202/215 94.0 (89.9, 96.7)	191/210 91.0 (86.2, 94.5)	3.00 (-1.21, 7.21)	Yes
Polio 1	**≥1:8 (1/dil)**	218/218 100.0 (98.3, 100.0)	211/211 100.0 (98.3, 100.0)	0.00 (NA)	Yes
Polio 2	**≥1:8 (1/dil)**	218/218 100.0 (98.3, 100.0)	210/210 100.0 (98.3, 100.0)	0.00 (NA)	Yes

Antigen	Criteria	Pentacel	Pentacel+Prevnar	Pentacel–Pentacel+Prevnar (90% CI)	Non-inferiority Yes/No [2]
		n/N % (95%CI)	n/N % (95%CI)		
Polio 3	**≥1:8 (1/dil)**	218/218 100.0 (98.3, 100.0)	209/210 99.5 (97.4, 100.0)	0.48 (-0.31, 1.26)	Yes

[1] The fold-rise is calculated by post-Dose 4/pre-Dose 4 titer (pre-Dose 1 results were not collected).

[2] Non-inferiority is achieved when the upper limit of the 2-sided 90% CI of Group 1–Group 3 <10% (or 5% for Polio 1, Polio 2 and Polio 3).

Notes: Group is defined as per randomization. Group 1: Received 4th Dose of Pentacel at 15 months. Group 3: Received 4th Dose of Pentacel concomitantly with the 4th Dose of Prevnar at 15 months.
'n' is the number of subjects who met the criteria of the test indicated.
'N' is the total number of subjects with available serology data from the PP Immunogenicity Population.
NA = Not Applicable.

2.3.9.2 Co-Administration with MMR and Varicella Vaccines

The interaction of Pentacel vaccine with other licensed vaccines was assessed in Study 494-03 (4th Dose).

Seroprotection/Four-fold Rise Rates

The co-administration of Pentacel with MMR and Varicella vaccines elicited immune responses to all of the antigens in Pentacel that were non-inferior to the immune responses elicited by Pentacel alone in Study 494-03 (see Table 52). Subjects that were concurrently immunized with Pentacel, MMR, and Varicella vaccines (Group 2) had seroprotection rates to PRP (≥1.0 µg/mL), diphtheria, and tetanus (≥0.1 IU/mL and ≥1.0 IU/mL), polio (≥8 1/dil) and 4-fold rise to all Pertussis antigens that fulfilled the statistical criteria demonstrating the non-inferiority to the immune responses elicited by the administration of Pentacel alone (Group 1; see Table 52) indicating that co-administration of MMR and Varicella vaccines did not affect the immune responses induced by Pentacel vaccine.

Table 52: Study 494-03: Post-Dose 4 Seroprotection/Four-fold Rise Rate Non-inferiority Analysis – Effect of MMR and Varicella Vaccines on the Immune Response to Pentacel

Antigens	Criteria	Pentacel (Group 1)	Pentacel+MMR+ Varicella (Group 2)	Group 1–Group 2 (90% CI)	Non-inferiority Yes/No [2]
		n/N % (95%CI)	n/N % (95%CI)		
PRP	**≥0.15 µg/mL**	218/218 100.0 (98.3, 100.0)	219/221 99.1 (96.8, 99.9)	0.90 (-0.14, 1.95)	Yes
	≥1.0 µg/mL	216/218 99.1 (96.7, 99.9)	214/221 96.8 (93.6, 98.7)	2.25 (0.04, 4.46)	Yes
PT (EU/mL)	**≥4 fold-rise [1]**	165/180 91.7 (86.6, 95.3)	175/188 93.1 (88.5, 96.3)	-1.42 (-5.97, 3.14)	Yes

Antigens	Criteria	Pentacel (Group 1)	Pentacel+MMR+ Varicella (Group 2)	Group 1– Group 2 (90% CI)	Non-inferiority Yes/No [2]
		n/N % (95%CI)	n/N % (95%CI)		
FHA (EU/mL)	**≥4 fold-rise [1]**	157/180 87.2 (81.4, 91.7)	160/188 85.1 (79.2, 89.9)	2.12 (-3.80, 8.03)	Yes
PRN (EU/mL)	**≥4 fold-rise [1]**	152/180 84.4 (78.3, 89.4)	166/188 88.3 82.8, 92.5)	-3.85 (-9.74, 2.03)	Yes
FIM (EU/mL)	**≥4 fold-rise [1]**	157/180 87.2 (81.4, 91.7)	166/188 88.3 82.8, 92.5)	-1.08 (-6.70, 4.55)	Yes
Diphtheria	**≥0.1 IU/mL**	217/217 100.0 (98.3, 100.0)	221/221 100.0 (98.3, 100.0)	0.00 NA	Yes
	≥1.0 IU/mL	214/217 98.6 (96.0, 99.7)	217/221 98.2 (95.4, 99.5)	0.43 (-1.54, 2.40)	Yes
Tetanus	**≥0.1 IU/mL**	215/215 100.0 (98.3, 100.0)	222/222 100.0 (98.4, 100.0)	0.00 NA	Yes
	≥1.0 IU/mL	202/215 94.0 (89.9, 96.7)	198/222 89.2 (84.3, 92.9)	4.76 (0.42, 9.11)	Yes
Polio 1	**≥1:8 (1/dil)**	218/218 100.0 (98.3, 100.0)	222/222 100.0 (98.4, 100.0)	0.00 NA	Yes
Polio 2	**≥1:8 (1/dil)**	218/218 100.0 (98.3, 100.0)	222/222 100.0 (98.4, 100.0)	0.00 NA	Yes
Polio 3	**≥1:8 (1/dil)**	218/218 100.0 (98.3, 100.0)	220/220 100.0 (98.3, 100.0)	0.00 NA	Yes

[1] The fold-rise is calculated by post-Dose 4/pre-Dose 4 titer (pre-Dose 1 results were not collected).

[2] Non-inferiority: Upper limit of the two-sided 90% CI of Group 1–Group 2 <10% (or 5% for Polio 1, Polio 2 and Polio 3).

Notes: Group is defined as per randomization. Group 1: Received 4th Dose of Pentacel at 15 months. Group 2: Received 4th Dose of Pentacel concomitantly with the 1st Dose of MMR and Varicella vaccines at 15 months.
'n' is the number of subjects who met the criteria of the test indicated.
'N' is the total number of subjects with available serology data from the PP Immunogenicity Population.
NA = Not Applicable.

2.3.10 Effect of Pentacel on the Immune Responses Elicited by Other Vaccines

2.3.10.1 Effect on the Immune Response to a Hepatitis B Vaccine

In the development of Pentacel vaccine it was also important to assess whether its co-administration with other recommended vaccines would interfere with their immune response as compared to the co-administration of the concomitant vaccines with either, the licensed-equivalent standard of care vaccines (Study P3T06) or separately administered formulation-equivalent components (Study 494-01). Pentacel and Control vaccines in these studies were administered at 2, 4 and 6 months of age. Hepatitis B vaccine was administered at 0, 2 and 6 months of age. As assessed by the overlap of the 95%CIs, the GMTs (see Table 53) and seroprotection rates (≥10 mIU/mL) (see Table 54) elicited by a hepatitis B vaccine co-administered with Pentacel during the Infant Series were comparable to the responses elicited by the hepatitis B vaccine co-administered with the Control vaccines in Studies 494-01 and P3T06.

Table 53: Studies P3T06 and 494-01: Post-Dose 3 GMTs for Hepatitis B

Parameter	P3T06		494-01	
	Pentacel n GMT 95% CI	Control [1] n GMT 95% CI	Pentacel n GMT 95% CI	Control [1] n GMT 95% CI
GMT (mIU/mL)	325 120.98 97.05, 150.81	998 126.97 113.19, 142.44	1076 365.08 330.96, 402.72	386 303.25 260.29, 353.31

1 Control for P3T06 means Daptacel, IPOL, and ActHIB vaccines and Control for 494-01 means HCPDT, Poliovax, and ActHIB components.

Table 54: Studies P3T06 and 494-01: Post-Dose 3 Seroprotection Rates for Hepatitis B

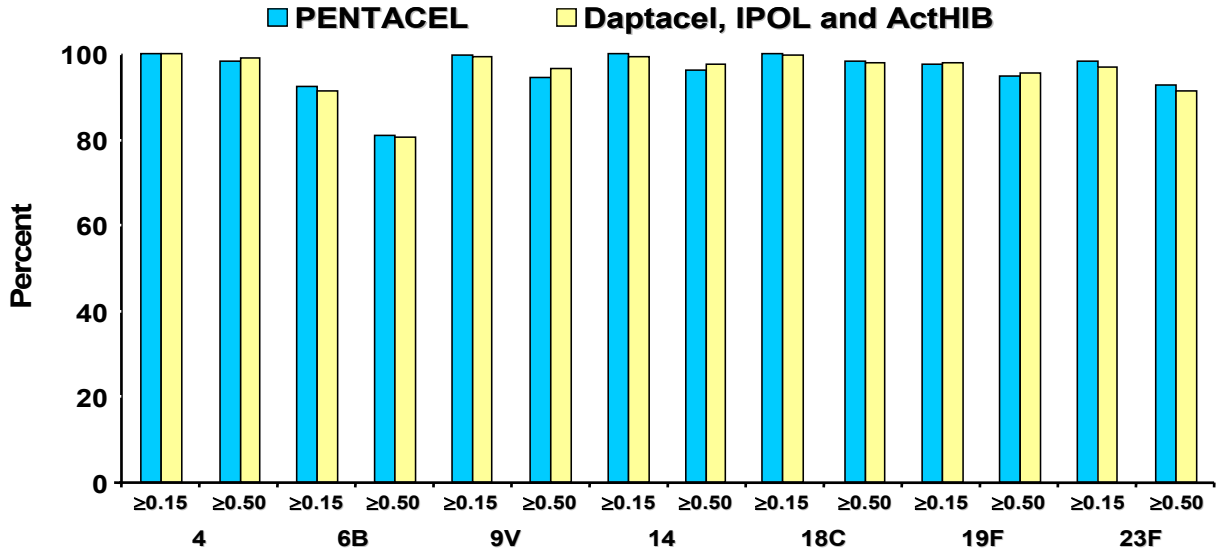
Parameter	P3T06		494-01	
	Pentacel n/N % 95% CI	Control [1] n/N % 95% CI	Pentacel n/N % 95% CI	Control [1] n/N % 95% CI
% ≥10 mIU/mL	292/325 89.8 86.0, 92.9	922/998 92.4 90.6, 94.0	1054/1076 98.0 96.9, 98.7	378/386 97.9 96.0, 99.1

1 Control for P3T06 means Daptacel, IPOL, and ActHIB vaccines and Control for 494-01 means HCPDT, Poliovax, and ActHIB components.

2.3.10.2 Effect on the Immune Responses to a Pneumococcal Conjugate Vaccine

In the development of Pentacel vaccine it was also important to assess whether its co-administration with Prevnar at 2, 4, and 6 months of age would interfere with the immune responses to the pneumococcal antigens as compared to the co-administration of Prevnar vaccine with either, the separately administered US standard of care vaccines (Study P3T06). As assessed by the overlap of the 95% CIs, the GMTs (data not shown) and seroresponse rates (≥0.15 µg/mL or ≥0.5 µg/mL) (see Figure 61) elicited by Prevnar co-administered with Pentacel during the Infant Series were comparable to the responses elicited by Prevnar vaccine co-administered with the standard of care vaccines in Study P3T06.

Figure 61: Study P3T06: Pentacel vs. US Standard of Care Vaccines - Post-Dose 3 Pneumococcal Seroprotection Rates



PENTACEL	100.0	98.1	92.5	81.0	99.7	94.4	100.0	96.3	100.0	98.1	97.5	94.7	98.1	92.8
Control	100.0	98.9	91.4	80.7	99.3	96.7	99.3	97.4	99.5	97.8	97.9	95.6	96.9	91.3

The effect of the co-administration of the 4th Dose of Pentacel vaccine with the 4th Dose of Prevnar on the seroresponse rates to the pneumococcal antigens was assessed in Study 494-03 4th Dose. This study evaluated the non-inferiority of Prevnar vaccine administered at the same visit as the 4th Dose of Pentacel vaccine at 15 months of age (Group 3) to Prevnar vaccine administered at 15 months and the 4th Dose of Pentacel vaccine a month later (Group 4). Seroresponse rates for all of the Pneumococcal serotypes at both the ≥0.15 and ≥0.5 thresholds in the co-administered group were non-inferior to those in the staggered administration group (see Table 55), indicating that co-administration of Pentacel vaccine does not affect the immune response induced by Prevnar vaccine.

Table 55: Study 494-03: Non-inferiority Analysis – Effect of a 4th Dose of Pentacel on the Immune Response to a Pneumococcal Vaccine

Antigen	Criteria	Prevnar+Pentacel (Group 3)	Prevnar+MMR+ Varicella (Group 4)	Group 4– Group 3 (90% CI)	Non-inferiority Yes/No [1]
		n/N % (95%CI)	n/N % (95%CI)		
Serotype 4	**≥0.15 µg/mL**	155/155 100.0 (97.6, 100.0)	158/158 100.0 (97.7, 100.0)	0.0 NA	Yes
	≥0.5 µg/mL	153/155 98.7 (95.4, 99.8)	157/158 99.4 (96.5, 100.0)	0.66 (-1.16, 2.47)	Yes
Serotype 6B	**≥0.15 µg/mL**	151/155 97.4 (93.5, 99.3)	157/158 99.4 (96.5, 100.0)	1.95 (-0.39, 4.29)	Yes
	≥0.5 µg/mL	148/155 95.5 (90.9, 98.2)	154/158 97.5 (93.6, 99.3)	1.98 (-1.44, 5.41)	Yes
Serotype 9V	**≥0.15 µg/mL**	155/155 100.0 (97.6, 100.0)	158/158 100.0 (97.7, 100.0)	0.0 NA	Yes
	≥0.5 µg/mL	153/155 98.7 (95.4, 99.8)	157/158 99.4 (96.5, 100.0)	0.66 (-1.16, 2.47)	Yes
Serotype 14	**≥0.15 µg/mL**	155/155 100.0 (97.6, 100.0)	158/158 100.0 (97.7, 100.0)	0.0 NA	Yes
	≥0.5 µg/mL	154/155 99.4 (96.5, 100.0)	158/158 100.0 (97.7, 100.0)	0.65 (-0.41, 1.70)	Yes
Serotype 18C	**≥0.15 µg/mL**	155/155 100.0 (97.6, 100.0)	157/158 99.4 (96.5, 100.0)	-0.63 (-1.67, 0.40)	Yes
	≥0.5 µg/mL	153/155 98.7 (95.4, 99.8)	156/158 98.7 (95.5, 99.8)	0.02 (-2.06, 2.11)	Yes
Serotype 19F	**≥0.15 µg/mL**	155/155 100.0 (97.6, 100.0)	157/158 99.4 (96.5, 100.0)	-0.63 (-1.67, 0.40)	Yes
	≥0.5 µg/mL	151/155 97.4 (93.5, 99.3)	152/158 96.2 (91.9, 98.6)	-1.22 (-4.48, 2.05)	Yes
Serotype 23F	**≥0.15 µg/mL**	153/155 98.7 (95.4, 99.8)	156/158 98.7 (95.5, 99.8)	0.02 (-2.06, 2.11)	Yes
	≥0.5 µg/mL	148/155 95.5 (90.9, 98.2)	151/158 95.6 (91.1, 98.2)	0.09 (-3.76, 3.93)	Yes

[1] Non-inferiority is achieved when the upper limit of the 2-sided 90% CI of Group 4–Group 3<10%.

Note: Group is defined as per randomization. Group 3: Received 1st dose of MMR and varicella at 12 months and 4th Dose of Pentacel and Prevnar concomitantly at 15 months. Group 4: Received 1st dose of MMR and varicella and 4th Dose of Prevnar at 15 months, and 4th Dose of Pentacel at 16 months.
'n' is the number of subjects who met the criteria of the test indicated. 'N' is the total number of subjects with available serology data from the PP Immunogenicity Population. NA = Not Applicable.

2.3.10.3 Effect on the Immune Response to MMR and Varicella Vaccines

The effect of the co-administration of the 4th Dose of Pentacel vaccine with the measles, mumps and rubella (MMR) and Varicella vaccines on the seroresponse rates to the MMR and Varicella antigens was also assessed in Study 494-03 4th Dose. This study evaluated the non-inferiority of MMR and Varicella vaccines administered at the same visit as the 4th Dose of Pentacel vaccine at 15 months of age (Group 2)to MMR and Varicella vaccines administered at 15 months and the 4th Dose of Pentacel vaccine a month later (Group 4). The measles, mumps, rubella and varicella seroresponse rates (see Table 56) in the co-administered group were non-inferior to those in the staggered administration group (see Table 56), indicating that co-administration of Pentacel vaccine does not affect the immune response induced by the MMR and Varicella vaccines.

Table 56: Study 494-03: Non-inferiority Analysis – Effect of 4th Dose of Pentacel on the Immune Response to MMR and Varicella Vaccines

Antigen	Criteria	MMR+Varicella +Pentacel (Group 2)	MMR+Varicella +Prevnar (Group 4)	Group 4– Group 2 (90% CI)	Non-inferiority Yes/No [1]
		n/N % (95%CI)	n/N % (95%CI)		
Measles	ELISA ≥300 or Neutralization ≥120 mIU/mL	152/154 98.7 (95.4, 99.8)	141/144 97.9 (94.0, 99.6)	-0.78 (-3.25, 1.68)	Yes
Mumps	ELISA ≥500 U/mL or Neutralization ≥60 (1/dil)	151/154 98.1 (94.4, 99.6)	140/144 97.2 (93.0, 99.2)	-0.83 (-3.73, 2.07)	Yes
Rubella	≥10 IU/mL	149/154 96.8 (92.6, 98.9)	140/144 97.2 (93.0, 99.2)	0.47 (-2.79, 3.72)	Yes
Varicella	ELISA ≥300 mIU/mL or FAMA ≥4 (1/dil)	143/154 92.9 (87.6, 96.4)	135/144 93.8 (88.5, 97.1)	0.89 (-3.87, 5.65)	Yes

[1] Non-inferiority is achieved when the upper limit of the two-sided 90% CI of Group 4 – Group 2 <5% (except <10% for varicella).

Notes: Group is defined as per randomization. Group 2: Received 4th Dose of Prevnar at 12 months and 4th Dose of Pentacel concomitantly with the 1st Dose of MMR and varicella vaccines at 15 months. Group 4: Received 1st Dose of MMR and varicella vaccines and 4th Dose of Prevnar at 15 months, and 4th Dose of Pentacel at 16 months.
'n' is the number of subjects who met the criteria of the test indicated.
'N' is the total number of subjects with available serology data from the PP Immunogenicity Population.

2.3.11 Immunogenicity Conclusions

The immunogenicity data generated from the pivotal and supportive studies presented in this document support the licensure of Pentacel vaccine in the United States.

Lot consistency was demonstrated in Study 494-01 Infant Series by:

- The rates of seroprotection for the PRP and polio antigens were statistically equivalent among the 3 consistency lots. The PRP GMT was statistically higher in Lot 3 than in Lot 2 and the Polio GMTs were higher in Lot 1 than in the other lots. However, none of these differences are considered to be clinically significant, as the majority of subjects achieved seroprotective antibody levels (Polio: ≥1:8 1/dil; PRP: ≥0.15 μg/mL) for these antigens.
- The rates of seroprotection or 4-fold rise and the GMTs for the diphtheria toxoid, tetanus toxoid, and all pertussis antigens, were statistically equivalent among the 3 lots.

The non-inferiority of Pentacel vaccine to the separate administration of the US-licensed standard-of care vaccines Daptacel, IPOL, ActHIB (Studies P3T06 Infant Series and 4th Dose); to the separate administration of its formulation-equivalent components HCPDT, Poliovax, and ActHib (Studies 494-01 Infant Series and 4th Dose); and to the antibody levels generated by Daptacel vaccine in the Sweden I efficacy Trial (the Pertussis Serology Bridge) was supported by the following observations:

- Out of the 48 co-primary statistical comparisons designed to assess the anti-pertussis immune responses elicited by Pentacel vaccine in Studies P3T06, 494-01, and the serology bridges to the Sweden I Efficacy Study, 44 demonstrated the non-inferiority of Pentacel vaccine to either the formulation-equivalent components, the licensed-equivalent vaccines, or to the Sweden I Efficacy Trial that established the efficacy of the 5-component pertussis vaccine. The statistically lower-than-Controls post-Dose 4 anti-PRN GMTs observed in Studies 494-01 and P3T06 would not be expected to have an affect on the post-Dose 4 protective efficacy given that the anti-PRN GMT responses elicited by Pentacel vaccine were non-inferior to those observed in the Sweden I Efficacy Trial. Three doses of Pentacel vaccine consistently elicited robust immune responses to diphtheria, tetanus, and poliovirus types 1, 2, and 3 that were significantly boosted by a 4th Dose of the same vaccine. Of all the comparisons made to demonstrate that Pentacel vaccine elicited immune responses to the diphtheria, tetanus, and poliovirus types 1, 2, and 3 antigens that were non-inferior to those elicited by the Control vaccines, only 1 failed to meet the strict statistical criteria. The single failure was for the anti-tetanus GMT after the 4th Dose of Pentacel vaccine as compared to the same responses elicited by Daptacel vaccine. Given that Pentacel vaccine elicited very high anti-tetanus seroprotection rates at the ≥0.1 IU/mL and ≥1.0 IU/mL, and that these rates were statistically non-inferior to those elicited by Daptacel vaccine or HCPDT, the marginal statistical difference in the post-Dose 4 GMTs is not considered to be clinically significant.
- Pentacel vaccine elicited consistent anti-PRP responses across all the licensure trials, including in the 2 controlled studies. In Study 494-01, the anti-PRP responses elicited by Pentacel vaccine at the ≥0.15 μg/mL after Dose 3 and ≥1.0 μg/mL after Dose 4 were non-inferior to those elicited by ActHIB co-administered with the HCPDT and Poliovax components. Although the post-Dose 3 seroprotection rate comparison at the ≥1.0 μg/mL level and the comparisons based on GMTs did not fulfill the non-inferiority statistical criteria due to the higher performance of ActHIB vaccine in the Control group, this is of little relevance as the HCPDT component is not licensed or used as a stand-alone vaccine and Poliovax is licensed but not co-administered with HCPDT and ActHIB. In contrast, the anti-PRP

responses elicited by Pentacel vaccine in Study P3T06 were very similar to those elicited by the US-licensed Control vaccines (ActHIB vaccine co-administered with Daptacel and IPOL vaccines), fulfilling the non-inferiority criteria based on seroprotection rate and GMTs at post-Dose 3, pre-Dose 4, and post-Dose 4 time-points.

The compatibility of co-administration of Pentacel vaccine with other licensed and recommended vaccines was demonstrated in Studies M5A07 Infant Series, P3T06 Infant Series, 494-01 Infant Series, and 494-03 4th Dose:

- Three doses of Pentacel vaccine co-administered with Prevnar vaccine during the Infant Series elicited immune responses to the PRP and pertussis antigens of Pentacel vaccine that were non-inferior to those elicited by Pentacel vaccine administered alone (1 month apart from Prevnar vaccine) in Study M5A07 Infant Series.
- The 4th Dose of Pentacel vaccine co-administered with the 4th Dose of Prevnar vaccine elicited immune responses to the antigens of Pentacel vaccine that were non-inferior (except for FIM) to those elicited by Pentacel vaccine administered alone (after co-administration with Prevnar during the Infant Series) in Study 494-03.
- The 4th Dose of Pentacel vaccine co-administered with MMR and Varicella vaccines elicited immune responses to the antigens of Pentacel vaccine that were non-inferior to those elicited by Pentacel vaccine administered alone in Study 494-03.
- The immune responses to a hepatitis B vaccine (Recombivax HB vaccine) co-administered with Pentacel vaccine during the Infant Series were comparable to the responses elicited by the hepatitis B vaccine co-administered with the Control vaccines in Studies 494-01 and P3T06.
- The immune responses to Prevnar vaccine co-administered with Pentacel vaccine during the Infant Series were comparable to the responses elicited by Prevnar co-administered with the US-licensed Control vaccines in Study P3T06.
- The 4th Dose of Prevnar vaccine co-administered with 4th Dose of Pentacel vaccine elicited immune responses that were non-inferior to those elicited by Prevnar without Pentacel vaccine in Study 494-03.
- MMR and Varicella vaccines co-administered with the 4th Dose of Pentacel vaccine elicited immune responses to their respective antigens that were non-inferior to those elicited by MMR and Varicella vaccines without Pentacel vaccine in Study 494-03.

The consistency of immunogenicity across the indicated 4th Dose age range was demonstrated in Study 5A9908:

- A 4th Dose of Pentacel vaccine administered at either 15 to 16 months of age or 17 to 18 months of age elicited immune responses to the antigens in Pentacel vaccine that were statistically equivalent.

The immunogenicity data presented in this document is supported by epidemiologic data from Canada showing that Pentacel vaccine has improved the control of Pertussis and Hib disease in that country since its introduction in 1997. Notably, Pentacel vaccine has been the exclusive vaccine used in that country for the control of diphtheria, tetanus, pertussis, polio, and Hib diseases in children immunized through 18 months of age.

3 Post-Marketing Experience with Pentacel

3.1 Post-Marketing Safety Experience with Pentacel

3.1.1 Spontaneous Reports of Adverse Events

Pentacel was registered in Canada on 12 May 1997, and is currently licensed in 8 other countries. Between 1 May 1997 and 30 April 2006, a total of 13,546,580 doses of Pentacel were distributed worldwide, 12,543,855 (92%) of them in Canada. During this period, 288 AE reports after Pentacel administration were received through post-marketing spontaneous reports, reports from health authorities and literature data. No unexpected safety risks or signals were identified.

The safety profile shows that a predominance of the AEs fall under the MedDRA System Organ Classes (SOCs) of General disorders and administration site conditions, Psychiatric disorders, Nervous system disorders, Skin and subcutaneous tissue disorders, and Gastrointestinal disorders. The ten most frequently reported adverse events, both serious and non-serious, were:

Table 57: Post-Marketing Experience: The Ten Most Frequently Reported Adverse Events Following Pentacel Vaccination

MedDRA AE Preferred Term[1]	Number of AEs [2]
Injection site reaction	65
Pyrexia	64
Crying	51
Injection site inflammation	35
Irritability	31
Urticaria	25
Vomiting	24
Rash	20
Convulsion[3]	19
Injection site mass	16

1 MedDRA coding dictionary version 9.0
2 AE: adverse event. Includes both medically-confirmed and consumer cases
3 Includes MedDRA PT terms of Convulsion, Febrile convulsion, Status epilepticus and Convulsion local

The number of adverse events reflects MedDRA Preferred Terms of adverse events coded in the sanofi pasteur pharmacovigilance database.

The sections below present data for events that were of special interest due to the age group and morbidity specifics of the vaccinated population.

Convulsions

During the period under review, there were 19 convulsive adverse events. Of those, 13 were medically-confirmed and 6 were from consumer reports. Among the 13 medically-confirmed events, there were 8 events of convulsions (not otherwise specified), 2 of febrile convulsions, 2 of status epilepticus, and 1 of convulsions local. Three events were post-Dose 1 of Pentacel, 3 were post-Dose 2, 1 was post-Dose 3 and 5 were post-Dose 4; for one event such data were not

provided. Eleven of the medically-confirmed convulsive events occurred in Canada and 2 - in Brazil. The latency period ranged from 1 hour to 24 days (median: 5 days).

Eight of the events (1 Febrile seizure, 1 Status epilepticus, 1 Convulsion local [reported as Focal seizures] in the presence of fever, and 5 non-febrile Seizures) occurred within 7 days of immunization, of which one event of febrile convulsions had an onset 12 hours after immunization. The median age of the patients who developed convulsions was 10 months (range: 2 – 24 months). In one case, Pentacel had been co-administered with Prevnar, in another with MMR, and in a third with Recombivax HB.

The reporting rate of any type of medically-confirmed convulsion within 7 days of Pentacel vaccination was 0.10 per 100,000 doses; the reporting rate of febrile seizure within 7 days of immunization was 0.01 per 100,000 doses.

In published literature, the incidence of seizures occurring within 48 hours of administration of DTwP vaccine has been estimated to be 1 case per 1750 doses administered, or 57 per 100,000 doses (19). US data (retrospective population-based assessment), covering the period 1997-2000, quote a rate of medically-attended febrile seizures within 7 days of DTaP vaccination of 0.08 per 100,000 doses (20).

The number of convulsive events following Pentacel vaccination reported in post-marketing surveillance is lower than the expected number of such instances, based on literature data.

Hypotonic-Hyporesponsive Episodes

The generally accepted definition of a HHE followed the US Public Health System criteria published by Braun et al. (6). This definition is used when presenting the reported post-marketing Pentacel reports of HHE.

There were a total of 12 cases (reports) that met the criteria for HHE, of which 10 were medically confirmed and 2 were from consumers.

Among the 10 medically-confirmed HHE cases, 8 were coded as HHE and 2 as Hypotonia. Eight reports were from Canada and two from Brazil. Median age of onset was 2.9 months (range: 2.0–5.0 months). Seven episodes occurred post-Dose 1 of Pentacel and 2 were post-Dose 2; in one instance vaccine dose information was not provided. The male to female ratio was 6:3 (one patient of unknown gender). The median interval between vaccination and HHE was 2.6 hours, ranging from immediate to 6 hours. One female patient, who experienced an HHE after the first Pentacel vaccination, reportedly also experienced an adverse event after the 2nd dose of Pentacel at the age of 4 months. In addition to the 10 medically confirmed cases of HHE, there were 2 consumer reports of HHE. Both were from Canada; one was coded as HHE and one as Hypotonia. The reporting rate of HHE was 0.07 per 100,000 doses.

Health Canada Immunization Monitoring Program, Active (IMPACT) (prospective active surveillance) data for the period 1996-1998 showed a 75% decrease of hospitalizations due to HHE following the introduction of Pentacel (21). For the same time period, stimulated passive surveillance data from Alberta, Canada showed an HHE rate of 23.6 per 100,000 doses following acellular pertussis vaccine versus 116.6 per 100,000 doses following whole-cell pertussis vaccine; no HHE episodes where reported after doses 3 and 4 of Pentacel (22). Another publication from the Canadian IMPACT program found a 67% reduction in HHEs (occurring within 48 hours of immunization) associated with pertussis-containing vaccines upon adoption of acellular pertussis vaccine in place of a whole-cell vaccine (23). The average number of reports of HHEs per month decreased from 1.29 for 1995-1996 to 0.42 for 1998-2001.

Encephalopathy

A total of 3 encephalopathy cases were reported after Pentacel use, with a reporting rate of 0.02 per 100,000 doses distributed worldwide.

In the one case, the reported events had a latency of 30 days, unlike usual post-vaccination cases of encephalopathy which occur within 7 days after vaccination. The patient presented with complex symptomatology, not attributed to any specific trigger or medical condition.

Two of the three cases could be attributed to other identifiable causes, i.e., influenza A viral infection. Both cases were reported by members of the Canadian IMPACT program in a poster, presented at the 2002 Canadian National Immunization Conference, and were later listed in a published article (24). The researchers from IMPACT concluded that neither of these cases was attributable to vaccination.

An IMPACT publication reported that not a single case of acute encephalopathy, in patients hospitalized between 1993 and 2001, was attributed to pertussis vaccination (25). The members of IMPACT concluded that the risk of development of encephalopathy as a result of acellular pertussis-containing vaccines is extremely small; less than 1 in 2.2 million doses.

Cases with Fatal Outcome

Between 1 May 1997 and 30 April 2006, fourteen cases with fatal outcome were received by sanofi pasteur from spontaneous sources or were retrieved from the literature. Five of these cases were of Sudden Infant Death Syndrome (SIDS), 4 of death due to unknown cause, and 5 of death due to known cause other than SIDS. All cases were medically-confirmed.

Sudden Infant Death Syndrome

Spontaneous reports and literature sources have yielded 5 reports of SIDS, all from Canada, occurring in 2-month-old infants following vaccination with Pentacel. Per autopsy results, no other cause for the fatal outcomes was found. Time since vaccination ranged from 1 day to 13 days.

- Case 1: The infant had a slight cold without fever at time of vaccination and received acetaminophen that evening. The next morning the infant was found dead. The approximate time of death was determined to be 5 A.M.
- Case 2: The infant was healthy at the time of vaccination. Experienced drowsiness post-vaccination. At approximately 1 A.M. on day 2 post-vaccination, the infant was found not breathing.
- Case 3: The patient was placed to sleep on his side, with blankets in the crib, and was found on his stomach. There was questionable evidence of vomiting on the sheets. The mother was a smoker and used antidepressants during pregnancy. The pregnancy was uncomplicated. The infant was noted to have an odd shaped skull at birth.
- Case 4: The infant had vomiting. Was in a crib with an adult-size pillow, 4 blankets and stuffed animals, and was found face down on the pillow. There was a recent emergency room visit for congestion. Lower respiratory tract cultures grew *K. pneumoniae*, enterococcus and *Candida albicans* (possible contaminants). *Bordetella pertussis* and *parapertussis* cultures were negative. The mother was a smoker.
- Case 5: The infant was sick with an unspecified cold for about 2 months. She was visiting with her father and had been sleeping in a single bed. The infant had been put to sleep on her

side and was found more on her stomach with the blankets in the bed. The infant vomited, gasped for air, then became unresponsive.

The reporting rate of confirmed SIDS in Canada was 0.04 per 100,000 doses distributed.

Health Canada reports that every year, 1 out of 2000 live-birth babies dies of SIDS (26). Between 1985-1989 and 1994-1998, the post-neonatal mortality rate due to SIDS decreased markedly from 0.97 to 0.54 per 1,000 neonatal survivors (27).

The number of SIDS cases following Pentacel vaccination reported during the post-marketing surveillance is lower than the expected number of SIDS based on Canadian published data.

Death Due to Unknown Cause

Between 1 May 1997 and 30 April 2006, there were 4 reports of fatal outcome following Pentacel vaccination, where the cause of death was unexplained or unconfirmed. One patient was a Sickle-cell disease carrier and was receiving antibiotic therapy while with high fever; another patient died while sleeping, positioned on stomach; viral infection was suspected, based on autopsy findings in the third patient; and in the fourth – no autopsy was performed and no accompanying or risk factors were reported.

Death Due to Known Cause

There were 5 reports of fatal outcome in which cases the cause of death was identified.

- Case 1: One case (previously reported as SIDS) occurred in a 2-month-old male infant, born at 32 weeks of gestation with a birth weight of 1.6 kg. Spent 3 weeks in neonatal Intensive Care Unit due to prematurity-related problems. The mother was on antihypertensive treatment while breastfeeding and the infant was still breastfed at the time of death. Nine hours after the vaccination the patient became blue and was taking only occasional breaths. He was admitted to the hospital and died the same day. It was determined that the event was a sudden infant death resulting from invasive Group B streptococcal infection, which was ongoing since birth (conclusion of the Canadian Advisory Committee on Causality Assessment).
- Case 2: Two-month-old female infant was admitted to the hospital 1 day post-Dose 1 of Pentacel. The death happened on day 3 post-vaccination, and was considered a result of unspecified congenital anomaly. The following autopsy findings were noted: cardiac myopathy; cardiomegaly, increased endocardial fibroelastosis; small pericardial effusion; small posterior ventricular pericardial petechiae and haemorrhage of right atrial appendage; pulmonary congestion, congested liver and abdominal ascites.
- Cases 3 and 4: Two cases were retrieved from literature sources.
  - One case was reported in an IMPACT publication (28). A 5-month-old infant, gender unknown, who had received Dose 1 of Pentacel at the age of 2 months (reportedly Dose 2 of Pentacel had not been administered), developed *H. influenzae* type b pneumonia and meningitis, confirmed by positive blood and cerebral spinal fluid cultures. Spent 6 days on a ventilator in the Intensive Care Unit before dying of the reported infection.
  - Another case (29) discussed 3-month-old infant of unknown gender, who had received one dose of Pentacel at 2 months of age. The patient died subsequent to severe *H. influenzae* type b infection, with initial shock and meningitis.
- Case 5: Twenty-month-old female, developed afebrile convulsions/seizure unspecified amount of time after Pentacel administration (dose number not reported) and died. The patient was not hospitalized.

Discussion

During the period of almost 9 years since the introduction of Pentacel, approximately 13.5 million doses have been distributed worldwide, the vast majority in Canada. Review of the post-marketing data has not identified any unexpected safety risk. No safety signal was seen when comparing the number of expected versus the number of reported adverse events of interest (due to specifics of the age group and morbidity specifics of the vaccinated population) following Pentacel vaccination.

There are limitations inherent to the passive surveillance data when using post-marketing data from spontaneous sources. One of the limitations is underreporting. Thus, the direct comparison of the reporting rates calculated from passive surveillance data with population-based incidence rates may not be entirely valid. However, the reporting specificity depends on the severity of the event, and is high for severe life-threatening events and cases with fatal outcome. In this summary, the calculation of expected number of cases of SIDS, convulsions, and HHEs was made based on Canadian published population-based data. Passive surveillance systems are subject to multiple limitations, including underreporting, reporting of temporal associations or unconfirmed diagnoses, and lack of denominator data and unbiased comparison groups. (30) Even accounting for underreporting, the observed number of cases of SIDS and convulsions was much smaller than expected. If there was a signal, then the number of observed cases would have exceeded the number of expected, and this was not found in our review. Altogether, the post-marketing data confirm the excellent safety profile of Pentacel.

3.2 Canadian Post-Marketing Epidemiology

In licensing combination vaccines in the US, CBER recommends that immunogenicity be compared to that of the separate but concurrent administration of the combination's individual components. In addition, CBER recommends that if such components are already included in a licensed formulation, then the combination vaccine should be compared to the licensed formulation (10). In 1997, CBER provided the following guidance to industry:

> "If licensure is sought for a combination vaccine in which the observed immune responses did not meet the pre-specified criteria for non-inferiority, data should be submitted to support the contention that the lower immune response will not affect protective efficacy" (10),(31).

While it is encouraging that Pentacel met nearly all of the immunologic non-inferiority comparisons to the US licensed standard of care vaccines and its unlicensed components, it is also gratifying to know that 9 years of clinical experience in Canada support the effectiveness of Pentacel against pertussis and invasive Hib disease in infants and young children.

Pentacel vaccine was introduced in Canada province-by-province between July 1997 and April 1998 and since then Pentacel has been the exclusive vaccine used to prevent diphtheria, tetanus, pertussis, polio, and Hib diseases through early childhood. In Canada, Pentacel is administered routinely at 2, 4, 6, and 18 months of age and as of April 2006, over 12.5 million doses have been distributed nationwide. Following the 4-dose series with Pentacel, Quadracel (Pentacel without the Hib component) is used exclusively as the booster vaccine at 4-6 years of age to provide continued protection against pertussis and polio for school-aged children.

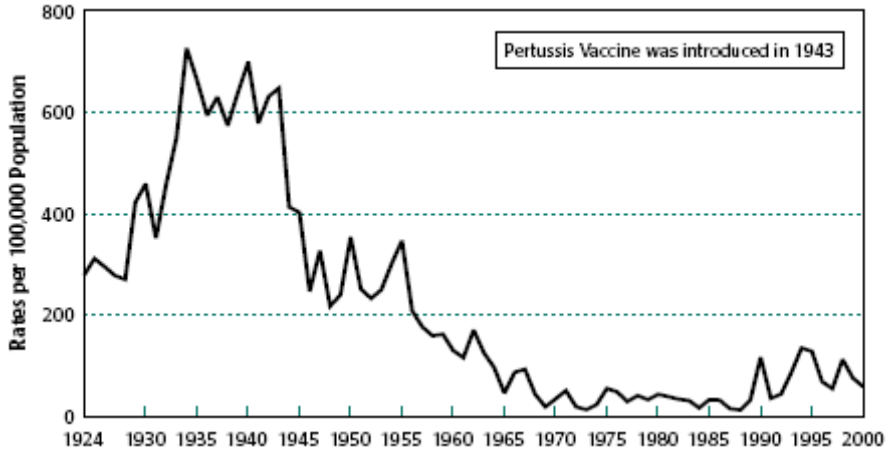
Epidemiologic data presented in the following sections provide evidence of excellent control with Pentacel vaccine of pertussis and invasive Hib disease in Canadian children.

3.2.1 Epidemiology of Pertussis in Canada

Pertussis has been a nationally reportable disease in Canada since 1924. Whole-cell pertussis vaccines were introduced in Canada in 1943 and the overall incidence of pertussis declined 90% over a 40-year period. Cases identified by health-care providers are reported to regional and provincial health authorities that, in turn, report them to the Public Health Agency of Canada. Cases of pertussis are confirmed for persons from whom *B. pertussis* is isolated by culture or identified by polymerase chain reaction from appropriate clinical specimens, or for persons who are epidemiologically linked to a laboratory-confirmed case and have one or more of the following symptoms without another cause: paroxysmal cough of any duration, or cough associated with vomiting, apnea, or inspiratory whoop.

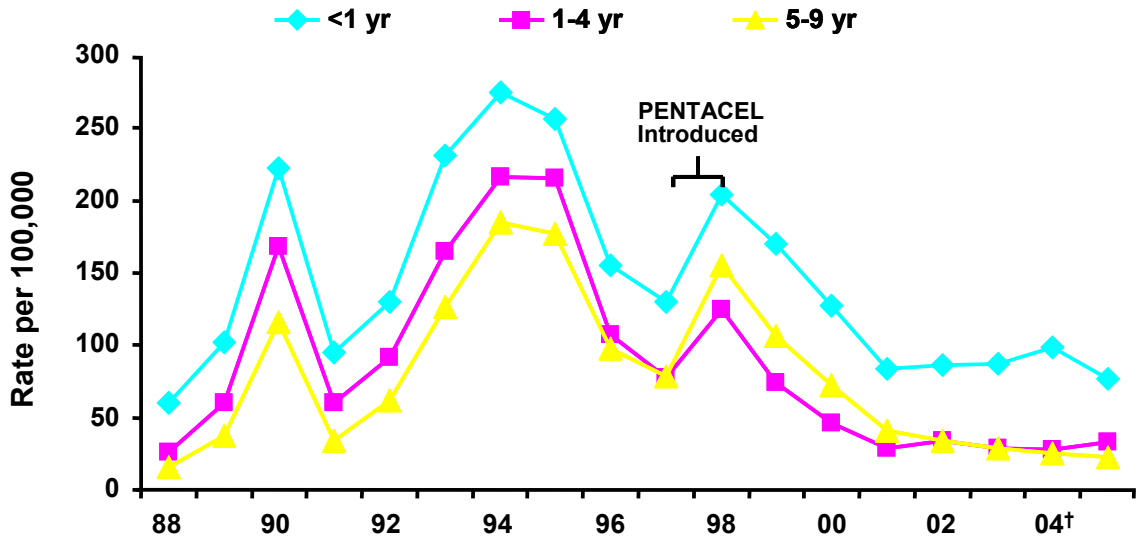
Similar to the epidemiology of pertussis in the US, the incidence of pertussis declined dramatically after introduction of whole cell vaccines in the late 1940s. However, in the 1990s, incidence rates of pertussis increased among all age groups in Canada. Figure 62 shows national pertussis incidence data for Canada over a 77-year period. The peak incidence of pertussis was 181.6 cases/100,000 persons in 1934 and it declined to a nadir of only 4.3 cases/100,000 in 1988. In the 1990s, the annual rate increased to 9.7-35.0 cases/100,000 persons (average of 6,358 cases reported/year in the 1990s) (Public Health Agency of Canada).

Figure 62: Pertussis Incidence Rates, Canada, 1924-2000 (32)



Shown in Figure 63 are the age-specific incidence rates of pertussis in Canada during 1988-2005 for children up to 9 years of age. The highest rates occur among infants <1 year of age, the majority of whom are <6 months of age, those too young to have completed the Infant Series. As in all countries, the epidemiologic cycle peaks every 3-5 years in Canada. Reported incidence rates of pertussis peaked in 1990, 1994 to 1995, and 1998. Since 1998, incidence rates of pertussis have decreased substantially among children immunized with Pentacel vaccine: a 78% decline among children aged 1-4 years and an 89% decline among those aged 5-9 years. The last peak occurred just as Pentacel was being introduced, and no peak has occurred since then. A naturally occurring peak was expected sometime between 2001 and 2003, but none has materialized, even as recently as 2005.

Figure 63: Age-Specific Rates of Pertussis, Canada, 1988-2005†

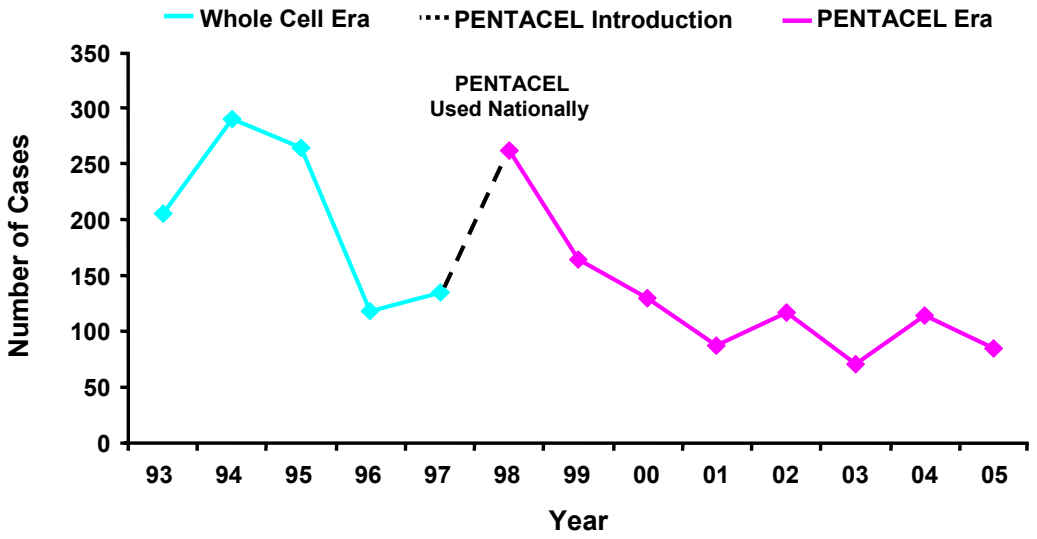


† Provisional data for 2003-2005. Source: (33) and Notifiable Diseases Reporting System, Public Health Agency of Canada

Pertussis surveillance has been actively monitored by a group of investigators in a network of Canadian pediatric hospitals known as the Immunization Monitoring Program, Active (IMPACT). IMPACT is comprised of 12 Canadian pediatric centers, accounting for 90% of the nation's tertiary care pediatric hospital beds; patients ≤16 years of age are referred from all provinces and territories (25). A nurse is stationed at each medical center and performs active surveillance for hospitalized cases of pertussis by monitoring daily admissions records, working with the microbiology laboratory and reviewing charts with specific discharge diagnosis codes.

Bettinger and colleagues recently reviewed pertussis surveillance data collected from IMPACT centers for the period of 1991-2005 [(34) and Scott Halperin, personal communication]. The investigators referred to the earlier part of this period (1991-1996) as the whole-cell vaccine era and the later part (1999-2005) as the acellular pertussis (Pentacel) vaccine era. Data collected during the year in which Pentacel vaccine was introduced province-by-province (1997-1998) were not included in the analyses. Over 2,000 children were admitted to IMPACT hospitals with pertussis during the period of the study. Overall, the data show declining rates of pertussis during the Pentacel era compared to the whole-cell era (Figure 64). Among children 1-4 years of age, incidence rates of pertussis declined 85% (0.7 cases/100,000 during the Pentacel era compared to 4.6 cases/100,000 during the whole-cell era). Although follow-up time was limited for older children, incidence rates declined 50% for the 5-9 year age group (0.1 cases/100,000 during the Pentacel era compared to 0.2 cases/100,000 during the whole-cell era). The decline for the youngest infants (<1 year of age) was 37%, but many of these infants had not completed the Infant Series. Compared to the whole-cell era, a significantly smaller proportion of Pentacel era cases occurred among infants and children old enough to have received 2-3 vaccine doses (4 months to 9 years of age); 38.0% versus 18.2%, respectively).

Figure 64: Pertussis Cases in the IMPACT Surveillance Network, 1993–2005[1]



Source: Bettinger et al. 6th Canadian Immunization Conference, Montreal, Quebec, Dec 5-8, 2004 and Scott Halpern, MD.

Source: (34); and Scott Halperin, personal communication.

[1] 1991-1992 data are not shown because only 5 of 12 IMPACT centers were active during this period.

The investigators concluded that these data indicate improvement of the control of severe pertussis disease (including hospitalizations) with Pentacel compared to whole-cell vaccine. This study provides strong evidence that pertussis disease is well controlled among infants and young children given Pentacel vaccine.

In a recently published study from the Northwest Territories, pertussis surveillance was reported during 1993-2004 (35). During 1993-1996, when whole-cell pertussis vaccine was used, a total of 86 cases were reported in children ≤9 years of age. The corresponding number of cases reported after Pentacel was introduced in 1997 was 46 cases during 1997-2000. The most significant reductions in the number of cases were among infants <1 year old (47% decline) and children 1-4 years of age (79% decline). During the most recent period (2001-2004), only 6 cases were reported among children ≤9 years of age. Relative to 1993-1996, the number of cases reported during 2001-2004 declined 94% among 1-4 year olds and 89% among 5-9 year olds. The progressive decline of pertussis cases in all three age groups was associated with widespread use of Pentacel and Quadracel vaccines. Similar data have been reported from Newfoundland and Labrador (36) and from British Columbia [(37) and Scott Halperin, personal communication].

3.2.2 Summary of Pertussis Surveillance Data in Canada

National, IMPACT and provincial and territorial surveillance data provide strong evidence that:

- Pertussis is well controlled in populations given a primary immunization series with Pentacel vaccine at 2, 4, 6, and 18 months of age.
- Pentacel and Quadracel vaccines provide sustained protection against pertussis through 9 years of age.

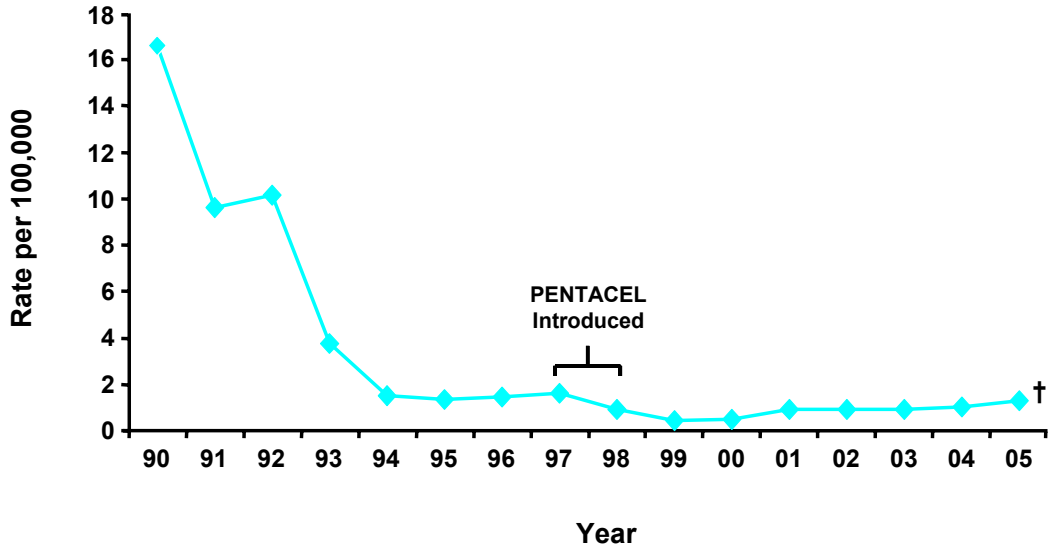
The data from Canada clearly demonstrate that Pentacel has established excellent control of pertussis, reducing the burden of disease.

3.2.3 Epidemiology of Invasive Hib Disease in Canada

In Canada, hospitals and clinics report cases of invasive Hib disease to regional and provincial health authorities who, in turn, report them to the Public Health Agency of Canada. Reportable cases include children aged <5 years with a positive culture for *H. influenzae* from a normally sterile body site or demonstration of Hib antigen in cerebral spinal fluid. Available strains of *H. influenzae* are serotyped at provincial health authority laboratories.

Prior to the use of Hib conjugate vaccines, the incidence of invasive Hib disease in Canada was similar to rates reported in the US. Hib conjugate vaccines were licensed for use in infants in 1992. Between 1992 and 1997, the incidence of invasive Hib disease among children aged <5 years declined significantly (Figure 65). In 1997-1998, all provinces transitioned from a combination DTwP-IPV-PRP-T vaccine to Pentacel vaccine. After the introduction of Pentacel vaccine, incidence rates of invasive Hib disease in Canadian children have remained very low (38). In 1990, the annual rate among children <5 years of age was 16.6 cases/100,000 and by 1997, the rate decreased to 1.6/100,000. Since 1998, the average incidence has been <1.0/100,000 per year.

Figure 65: Incidence of Invasive Hib* Disease in Children Aged <5 Years, Canada, 1990-2005



† Includes non b *H. influenzae*

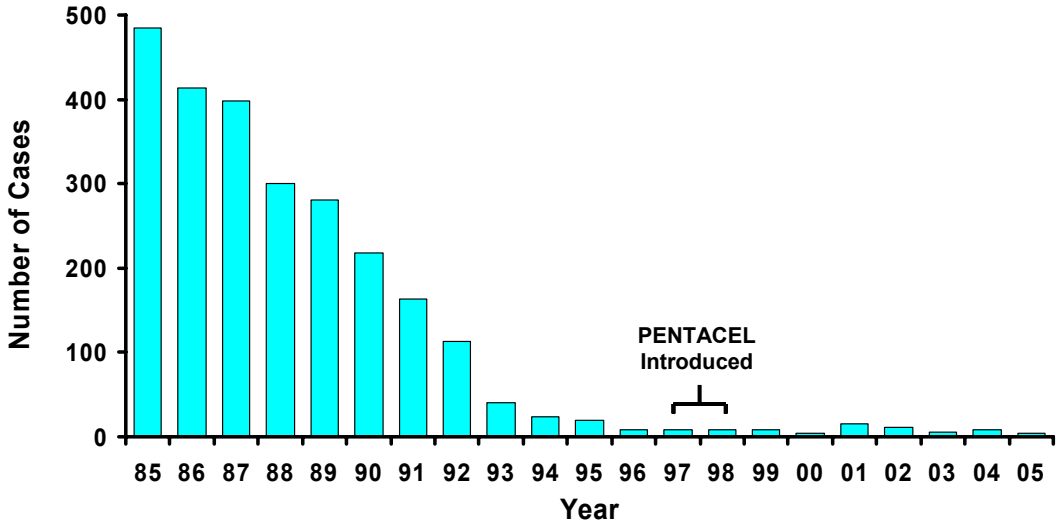
* Not all *H. influenzae* were confirmed as type b

Provisional data for 2003-2005. Source: Public Health Agency of Canada, 2006.

Since 1992, investigators in the IMPACT hospital network have monitored for cases of invasive Hib disease among children in Canada. In a retrospective review by IMPACT investigators, 485 invasive Hib cases were found to have occurred in 1985, before the first Hib vaccine was licensed. In contrast, since 1997, an average of fewer than 10 cases have been reported each year, representing a decrease of >99% (Figure 66) (39),(40),(41),(29),(42),(43). Scheifele et al recently reviewed Hib surveillance data for 2001-2005. During this 5-year period, only 34 Hib cases were reported among children admitted to IMPACT hospitals [(39) and D. Scheifele, personal communication). Decreasing case counts have been reported in recent years: 14 in 2001, 8 in 2002, 2 in 2003, 6 in 2004, and 4 in 2005. Among the 34 cases, all but 6 were incompletely immunized or had chronic underlining medical conditions. Of particular interest are the Canadian Aboriginal populations (e.g. First Nation and Inuit), because, like Native American children and

Eskimos in the US, they are at markedly increased risk of developing invasive Hib disease. Eleven of the 34 children were Aboriginal; of these, 2 were unvaccinated, 7 were partially vaccinated, and only 2 had received 3 doses of Pentacel (1 of whom had a history of recurrent pneumonias). Thus, only 2 breakthrough cases occurred among this very high risk population over a 5 year period.

Figure 66: Invasive Hib Disease Among Children Admitted to Hospitals in the IMPACT Surveillance Network, 1985-2005



†Immunization Monitoring Program, Active

Source: (39),(40),(41),(29),(42),(43)

In addition to the national and IMPACT reporting systems, the Public Health Agency of Canada and the Arctic Investigations Program of the Centers for Disease Control and Prevention (CDC) perform coordinated surveillance for Hib disease in the polar regions of Canada and the entire state of Alaska (International Circumpolar Surveillance program). In Canada, the regions under surveillance include the Yukon, Northwest Territories, Nunavut, and Northern Labrador and Quebec. The total population in these areas is approximately 137,000, of which about 75,000 (55%) are Aboriginal. Alaska has a higher total population (664,000), but Native Americans (120,000) represent a lower proportion (18%).

In Canada, during the 5-year period, 2000-2004, only 4 cases of invasive Hib disease occurred among children <5 years of age (44),(45). Among the 4 cases, 3 were Aboriginal. The immunization histories are unknown, but three were too young to be fully immunized (1.6, 3.7, and 3.9 months).

In Alaska, during a comparable 5-year period, 2002-2006, PRP-OMP (meningococcal protein conjugate) was used to prevent Hib disease; 7 cases of invasive Hib disease were reported, of which 6 were Native American [(46); and Thomas Hennessy, personal communication]. Among the 7 cases, 1 was unvaccinated, 3 were partially immunized, and 3 were fully immunized.

The rate of invasive Hib disease was no greater among the Canadian Aboriginal population (0.8 cases/100,000 per year) vaccinated with Pentacel than among Alaska Natives (1.0 cases/100,000 per year) vaccinated with PRP-OMP vaccine. These data confirm that only a few cases of Hib

disease occur among very high risk Native populations in Canada, and most are unvaccinated or partially vaccinated.

3.2.4 Summary of Hib Surveillance Data in Canada

National, IMPACT, and regional surveillance data confirm that invasive Hib disease is rare among Canadian children. The excellent control of Hib disease in recent years can be attributed entirely to the use of Pentacel vaccine because this has been the only Hib-containing vaccine given to infants and toddlers in Canada for nearly a decade. Only 1-2 breakthrough cases per year occur among approximately 1.7 million Canadian children <5 years of age. Cases are rare among Aboriginal Native populations; only 2-3 total breakthrough cases in the last 5 years. Most cases of invasive Hib disease occur among Canadian children who are unvaccinated or partially vaccinated, or among children with underlying medical conditions.

3.3 US Perspective

3.3.1 Estimated Vaccine Coverage in Canada and US

To understand how the excellent control of pertussis and invasive Hib disease in Canada might relate to the expected performance of this vaccine in the US, it is important to compare the immunization coverage rates in the two countries. In recent years, surveys of vaccine uptake have been performed both in the US and Canada. The results of these surveys indicate that immunization rates are similar in the two countries despite disparate vaccines and immunization programs.

In 2002, Canadian health authorities conducted a nationwide telephone survey to determine vaccine immunization rates among children aged 24 to 35 months of age (47). Telephone surveys were completed for 629 children. Similarly, each year in the US, a telephone survey is conducted nationwide by the CDC (National Immunization Survey) to determine immunization rates (48). National Immunization Survey uses random-digit-dialing to collect vaccination data from households in each of the 50 states. Shown in Table 58 are the rates for completing 3 and 4 doses of each relevant vaccine in the US and Canada. Although data are available for US children as recent as 2005, the most recent matching data for Canada are from 2002, so the results of surveys conducted in both countries for 2002 are shown in Table 58.

Table 58: Estimated Vaccine Coverage, Canada and the United States, 2002

	Estimated Vaccine Coverage at 2 Years of Age[1, 2] (%)			
	3 Doses		4 Doses	
Immunization	**Canada**	**US**	**Canada**	**US**
DTaP	93.3[3]	94.9	76.8[3]	81.6
IPV		90.2		NR
Hib		93.1		NR

[1] Canada telephone survey of 629 children 24 to 35 months of age conducted in 2002

[2] US telephone survey of 31,693 children 19 to 35 months of age conducted in 2002; health-care provider vaccination records obtained for 21,317 of the children

[3] Immunization rates for all components of Pentacel (DTaP, IPV and Hib) assumed to be the same as the rate for DTaP

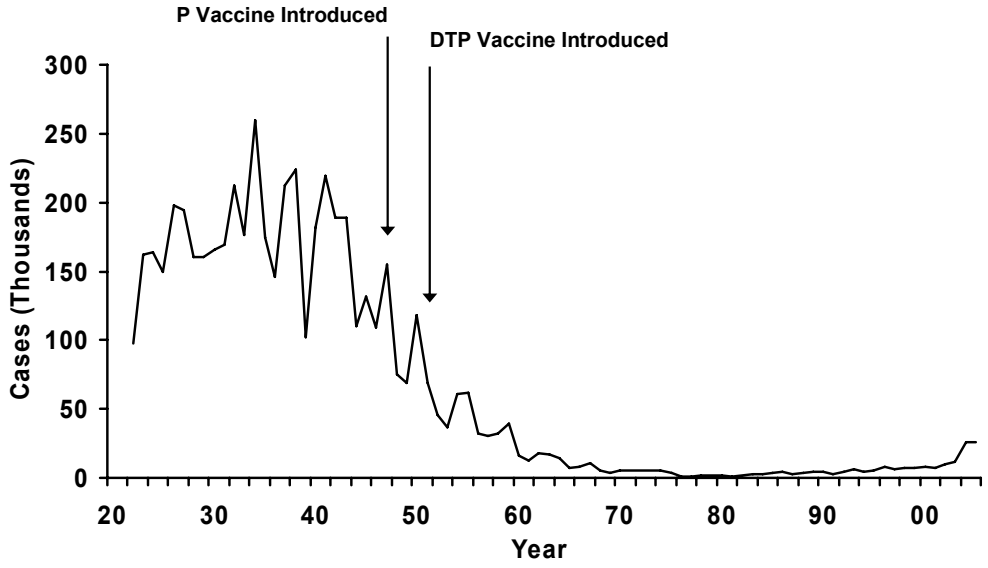
NR = Not reported

As shown in Table 58, approximately 93% of Canadian children complete 3 doses of Pentacel by 2 years of age. The same proportion of 2-year-old children complete 3 doses of DTaP, IPV, and Hib vaccines in the US. Approximately 77% of Canadian children complete 4 doses of Pentacel by 2 years of age; slightly more children complete 4 doses of DTaP in the US. Therefore the benefits observed with Pentacel in Canada are accomplished with immunization rates that are similar to the immunization rates in the US.

3.3.2 Epidemiology of Pertussis and Invasive Hib Disease in the US

Figure 67 displays the epidemiology of pertussis in the US during 1922-2005. The pattern in the US is generally similar to the epidemiology of pertussis in Canada (Figure 62). As in Canada, the highest incidence of pertussis in the US occurs among infants <6 months of age. However, a substantial burden of disease occurs among infants 6-11 months of age and even preschool and young school aged children. In 2005, the incidence rate per 100,000 population per year was 160.8 in infants aged <6 months, 33.3 in infants 6-11months, 15.6 in children 1-4 years, and 12.4 in children 5-9 years of age (49). Among the cases for whom the vaccination history was known, 55% of the infants 6-11 months of age and 21% of children 1-4 years of age received <3 doses of DTaP vaccine. Therefore, a substantial burden of pertussis occurs in infants and young children, many of whom lack adequate vaccination.

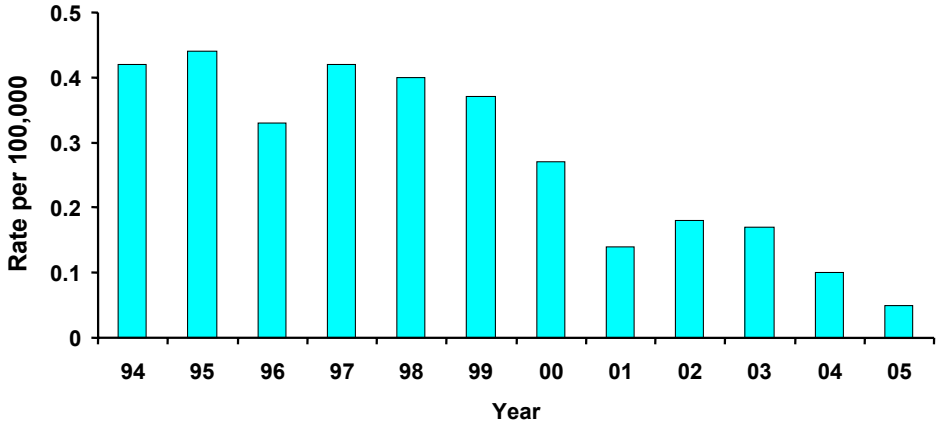
Figure 67: Epidemiology of Pertussis: United States, 1922 – 2005



Source: (50),(51),(52),(53)

Surveillance conducted by the CDC has demonstrated marked reductions of invasive Hib disease since Hib conjugate vaccines were introduced in the US for toddlers in 1988 and for infants in 1990 (54). Shown in Figure 68 are incidence rates and numbers of Hib cases among children <5 years of age during 1994-2005 from data collected by the CDC National Notifiable Diseases Surveillance System. During the past decade, CDC has documented steadily improving control of Hib disease in the US. A similar pattern can be seen from data collected from the Active Bacterial Core Surveillance program (55). As in Canada, the majority of Hib cases in the US occur among infants and young children who are unvaccinated or partially vaccinated.

Figure 68: Invasive Hib Disease in US Children <5 Years, National Data, 1994 – 2005



Note: Rates per 100,000 persons; Only cases confirmed as type b are shown.

Source: (56),(57),(58),(59),(60),(61),(62),(63),(64)

In 1993, ActHIB vaccine was licensed for use in infants in the US. During the past decade, the proportion of ActHIB doses distributed among all Hib vaccines in the US has steadily climbed to approximately 60% (data on file, sanofi pasteur). Therefore, the improved control of invasive Hib disease was accomplished during a time when the primary Hib vaccine used in the US has been ActHIB, which is identical to the Hib component used in Pentacel.

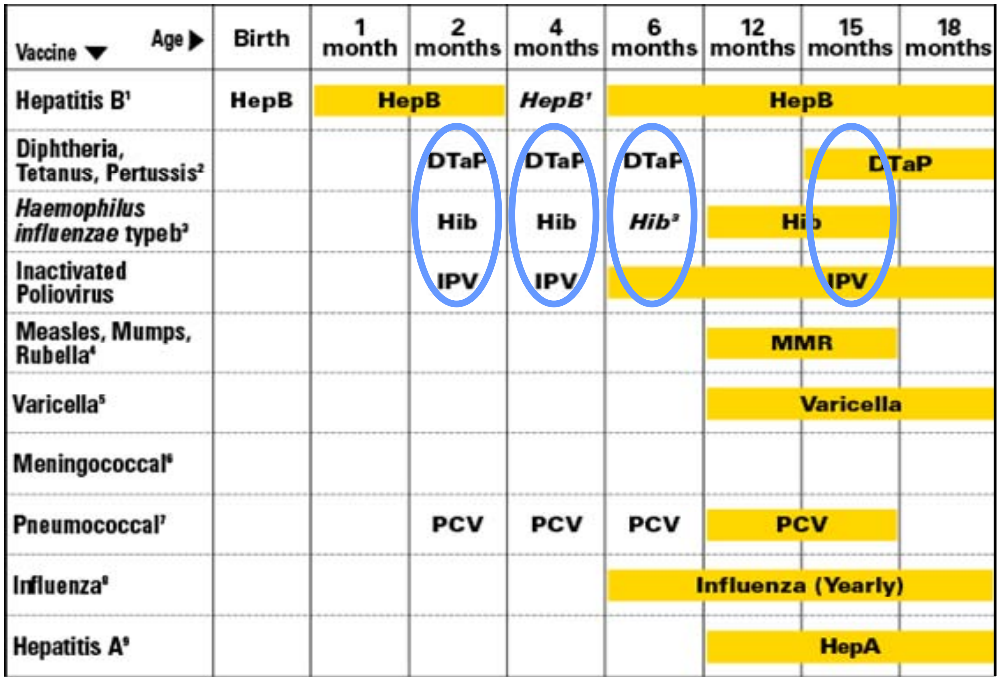
3.3.3 Summary of Vaccine Coverage Rates and Epidemiology of Pertussis and Hib in US

The epidemiology of pertussis among children is generally similar in the US and Canada. In Canada, the use of Pentacel has provided sustained protection against this disease among pre-school and school aged children. The epidemiology of invasive Hib disease is similar in the US and Canada, with excellent control in both countries. Approximately 60% of Hib vaccine used in the US is PRP-T (ActHIB), and 100% of Hib vaccine used in Canada is PRP-T (Pentacel). In addition, based on national immunization surveys, vaccine coverage rates during the first 2 years of life are similar in the US and Canada. In light of all of these data, there is every reason to expect Pentacel to perform as well in the US as it has in Canada.

4 Additional Anticipated Benefits of Pentacel

Shown below is the 2006 childhood immunization schedule through 18 months of age (65). The schedule is becoming progressively more complicated. Combination vaccines have the potential to simplify the immunization schedule, if the right antigens are included in the product. For example, it makes sense to combine DTaP, IPV, and Hib components because these vaccines tend to be given concomitantly during the Infant Series and 2nd year of life. Not only does Pentacel combine DTaP, IPV, and Hib components, but it conveniently excludes hepatitis B vaccine. This facilitates administration of hepatitis B vaccine at birth followed by appropriately spaced 2nd and 3rd doses, at 1-2 months and 6-18 months to optimize the immunologic response.

Figure 69: 2007 Recommended Childhood Immunization Schedule: Birth – 18 Months



Source: (65)

Up to 23 separate injections are administered through the first 18 months of life to comply with the current US immunization schedule. Combination vaccines have the potential to reduce the number of injections. For example, TriHIBit vaccine (DTaP-Hib) saves 1 injection; Comvax (Hib-hepatitis B) saves 3 injections; and Pediarix (DTaP-IPV-HepB) saves 5 injections over the course of the immunization schedule. However, Pentacel would save 7 injections, greater than any other single combination vaccine.

Given the number of vaccines in the current schedule, it is not surprising that children are not always immunized on time. In fact, a recent study found that only 18% of children received all vaccinations at the recommended ages or acceptably early (i.e., within minimum age allowances) (66). In addition, during the 1990s, at least 44% of children diagnosed with pertussis were undervaccinated for age. With this background, the CDC conducted a study of vaccination timeliness using data from the 2003 National Immunization Survey involving 14,810 children 24-35 months of age. (67). The investigators evaluated the cumulative number of days undervaccinated for 6 vaccines; 4 doses DTaP, 3 IPV, 3-4 Hib, 3 hepatitis B, 1 MMR, and 1 varicella. Children were considered late if the vaccine was given more than 1 month after the recommended age and severely undervaccinated if the vaccine was more than 6 months delayed.

Remarkably, the CDC reported that only 17% of children received all of their vaccines on time. Children were undervaccinated for a mean of 172 days taking into account all 6 vaccines through 24 months of age and 37% were undervaccinated for more than 6 months for at least 1 vaccine. Regarding specific vaccines, just 9% were severely undervaccinated for IPV, but 16% and 21% of children were severely undervaccinated for DTaP and Hib vaccines, respectively. The disparate results across vaccines indicate that children are coming to their health care provider for some, but not all vaccine injections. The expectation is that if children receive Pentacel each time that they currently receive IPV, then the timeliness for DTaP and Hib vaccines would be improved to that observed for IPV.

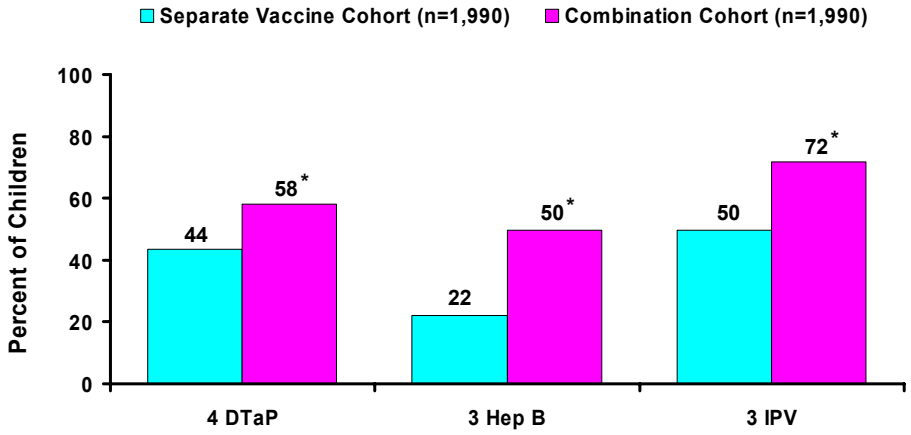
In another example of missed opportunities for vaccination, shown in Table 59, are data from the CDC's 2005 National Immunization Survey (68). Displayed in the table are immunization rates at 7 and 13 months of age for all 5 states that purchase ActHIB vaccine for all resident children. In these states, the vaccination coverage for DTaP and Hib vaccines should be the same because both require 3 doses by 6 months of age. Also, since these are universal purchase states, access to vaccine should not be an issue. However, the gap between DTaP and Hib vaccine coverage rates is as much as 8%. This gap would be eliminated for children receiving Pentacel, since it includes both DTaP and Hib vaccines as well as IPV.

Table 59: DT/DTaP and Hib Vaccination Rates, 2005 - States with Universal Use of PRP-T

	7 Months		13 Months	
	3 DT/DTaP (%)	3 PRP-T (%)	3 DT/DTaP (%)	3 PRP-T (%)
Massachusetts	87	83	99	98
New Hampshire	73	72	95	94
South Dakota	65	57	90	82
Vermont	72	71	96	93
Washington	70	66	88	86

Recent studies have demonstrated that combination vaccines improve vaccine coverage rates and timeliness of immunizations. Dr. Gary Marshall and colleagues conducted an observational study of immunizations among children born in 2003 using Georgia Medicaid administrative claims data (69). Two cohorts of children were evaluated; one cohort received at least one dose of DTaP-IPV-HepB (Pediarix) vaccine and the separate vaccine control cohort did not receive this combination product. Control children were matched 1:1 to combination children by gender, birth date, and race. Coverage rates for 4 DTaP, 3 hepatitis B, and 3 IPV (i.e., antigens contained in the combination vaccine) were significantly higher ($P<0.001$) for children in the combination cohort than those in the separate vaccine cohort (Figure 70). In addition, coverage rates for 3-4 Hib, 1 MMR, and 1 varicella were significantly higher ($P<0.001$) for children who received the combination vaccine.

Figure 70: Georgia Medicaid 2003: Coverage Rates by 2 Years of Age

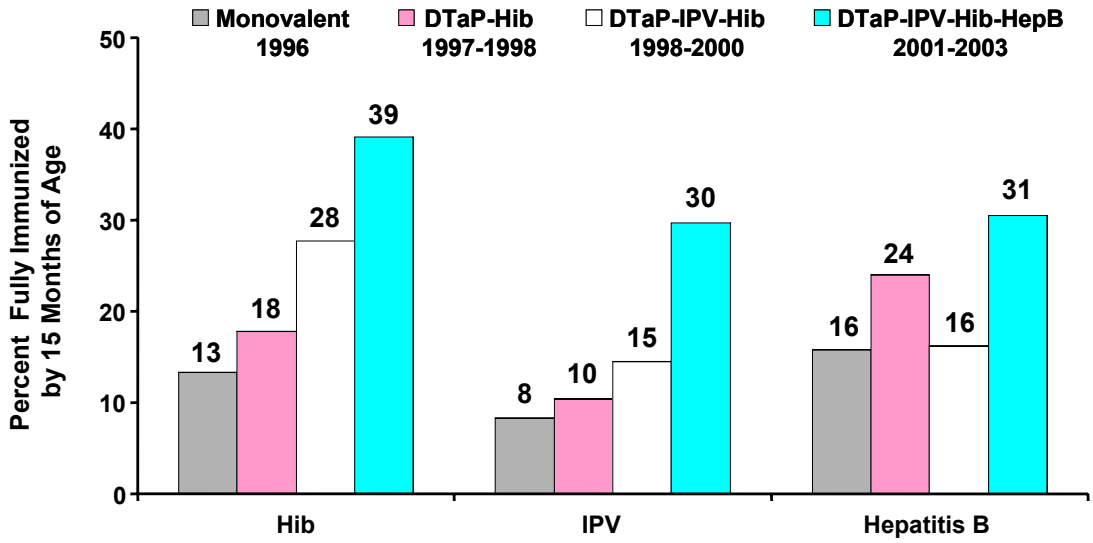


* $P<0.001$

In an accompanying presentation, Marshall and colleagues reported the vaccine timeliness of the same Georgia Medicaid population (70). The cumulative number of days undervaccinated was significantly less ($P<0.001$) for children in the combination cohort for 4 DTaP, 3 hepatitis B, 3 IPV than for children in the separate vaccine cohort. In addition, significantly more children in the combination cohort received their vaccines on time ($P<0.001$) compared to those in the separate vaccine cohort for 3 IPV, 3 hepatitis B, and 1 varicella. Similar benefits of DTaP-IPV-HepB combination vaccine were observed in a study of children enrolled in a managed health care plan in Utah (71). The results from all three presentations support the long-held belief that combination vaccines improve vaccine coverage rates and timeliness of immunizations. If licensed in the US, Pentacel is expected to provide similar benefits.

In addition to the US, other countries have struggled with issues of complicated childhood immunization schedules. Germany, a nation with a similar vaccination schedule as the US and a good surveillance system, has responded by introducing progressively higher-valence combination vaccines over the past decade. In a recently published study, nationwide telephone surveys were conducted to assess vaccine coverage rates and timeliness at 15 months of age among children born during 1996-2003 (72). Vaccination histories were confirmed for all of the 2,701 study children using vaccination booklets that were completed by the health-care provider.

Figure 71: Improved Timeliness with Combination Vaccines in Germany, 1996 – 2003



The proportion of children vaccinated by 15 months of age progressively increased with use of higher valent vaccines (Figure 71) (72). For example, the proportion of children fully vaccinated with Hib vaccine increased from 13% when using monovalent vaccines to 18%, 28%, and 39% when using 4-, 5-, and 6-valent vaccines, respectively. Similar but less dramatic improvements of vaccine coverage were observed with use of higher valent vaccines for hepatitis B and IPV components. In addition, the median age of vaccination progressively moved to younger ages for Hib, hepatitis B, and IPV components ($P<0.001$) with use of higher valent vaccines. It is expected that use of Pentacel vaccine would result in similar improvements of vaccine coverage and timeliness for children in the US.

5 Conclusions and Recommendations

The potential risks for any combination vaccine, include an unacceptable safety or efficacy profile compared to the vaccines it replaces or interference with other licensed vaccines currently recommended for the same age group.

The safety data for Pentacel vaccine provided by the 4 pivotal studies demonstrated that Pentacel vaccine is at least as safe as the US-licensed standard-of-care vaccines (Daptacel, IPOL, and ActHIB) that it is likely to replace. With regard to local adverse events, for each of the first 3 vaccine doses at 2, 4, and 6 months of age, Pentacel vaccine administration was associated with significantly fewer solicited local adverse reactions than Control injections of either Daptacel vaccine or HCPDT during the first 3 days post-immunization, the time during which vaccine reactions are generally the most frequent. With regard to systemic adverse events, fever is the reaction that generally causes the most concern, since in addition to causing discomfort for the child and alarm among parents, it often elicits suspicion in physicians of possible infection (especially when it occurs at an early age), leading to medical evaluation and intervention. In contrast to other recently licensed combination vaccines (73), Pentacel vaccine was shown to be non-inferior to the Control study arms for fever in the Infant Series in general and after the first dose in particular. Similarly, a 4th Dose of Pentacel vaccine had a comparable reactogenicity profile to its US licensed standard of care vaccines and formulation-equivalent components. Therefore, the safety profile of Pentacel vaccine supports the following claims:

- Administration of Pentacel vaccine is as least as safe as the separate administration of the US licensed standard of care vaccines (Daptacel, IPOL, and ActHIB) that it is expected to replace.
- Pentacel vaccine may be safely given concomitantly with hepatitis B and pneumococcal conjugate vaccines to infants, and with MMR, varicella, and pneumococcal conjugate vaccines to toddlers.

For the immunogenicity analyses, in the 4 pivotal and 1 supportive trials, there was a total Per-Protocol database of 2670 Pentacel vaccine recipients for the Infant Series and 2808 Pentacel vaccine recipients for the 4th Dose that supports the following conclusions:

- The lot consistency of Pentacel was demonstrated in clinical trial 494-01.
- The immune performance of Pentacel vaccine was demonstrated to be comparable to that of separate but concurrently administered US-licensed standard-of-care vaccines. Pertussis efficacy can be inferred from the non-inferior GMTs compared to the Sweden I efficacy trial. In addition, a consistency of immune responses is seen across the clinical trials, and there were very similar immune responses elicited by Pentacel vaccine in Study M5A07 versus Daptacel, ActHIB, and IPOL vaccines in Study P3T07 (5).
- Pentacel vaccine does not adversely affect the immunogenicity of concomitantly administered vaccines, nor do concomitantly administered vaccines affect the immunogenicity of Pentacel vaccine.

Pentacel vaccine provides the maximum reduction of vaccine injections because it contains DTaP, IPV, and Hib components and it fits best with the US childhood immunization schedule. The reduction in doses per visit offered by Pentacel vaccine will facilitate compliance to the recommended schedule of immunizations and will also allow for inclusion of future vaccines in the vaccination schedule. Use of Pentacel facilitates separate administration of hepatitis B vaccine, allowing use of an optimal schedule for this antigen. Pentacel is expected to improve coverage rates and timeliness of vaccinations, as demonstrated with other combination vaccines in

the US and Germany. It has a proven track record of safety and effectiveness with over 9 years of exclusive use in Canada. Finally, similar epidemiology of pertussis and Hib in the US and Canada predicts similar success with Pentacel in the US. In conclusion, the clinical trial data presented in this document, combined with the epidemiological experience in Canada, where Pentacel vaccine is credited with keeping a tight control on Hib and pertussis diseases, show that Pentacel vaccine would be a valuable addition to the defenses available against vaccine-preventable diseases in US children.

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