

Pentacel®

Immunogenicity, Safety, Indications, and Use

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**ACIP meeting
June 25, 2008**

Outline

- **Overview of Pentacel[®]**
- **Safety and Immunogenicity**
- **Indications and Uses**
- **Notice to Readers**

Components of Pentacel[®] and other DTaP Vaccines

Vaccine Antigenic Component	DAPTACEL (DTaP)	Infanrix (DTaP)	Tripedia (DTaP)	TriHIBit (Tripedia + ActHIB)	Pediarix (Infanrix + IPV + HBV)	Kinrix (Infanrix + IPV)	Pentacel (DTaP + IPV + Hib)	Quadracel [†] (DTaP + IPV)
Manufacturer	sp	GSK	sp	sp	GSK	GSK	sp	sp
PT (µg)	10	25	23.4	23.4	25	25	20	20
FHA (µg)	5	25	23.4	23.4	25	25	20	20
PRN (µg)	3	8			8	8	3	3
FIM 2 + 3 (µg)	5						5	5
D (Lf)	15	25	6.7	6.7	25	25	15	15
T (Lf)	5	10	5	5	10	10	5	5
IPV T1 (Mahoney) (DAU)					40	40	40	40
Polio T2 (MEF-1) (DAU)					8	8	8	8
Polio T3 (Saukett) (DAU)					32	32	32	32
Hib (PRP-T) (ActHIB) (units/ug Tetanus toxoid conj)				10/24			10/24	
HbsAg recombinant protein (mcg)					10			

* Not approved for use in U.S.

Pentacel[®] in 2008 Childhood Schedule

Recommended Immunization Schedule for Persons Aged 0–6 Years—UNITED STATES • 2008

For those who fall behind or start late, see the catch-up schedule

Vaccine ▼	Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B ¹		HepB	HepB	HepB	<i>see footnote 1</i>	HepB	HepB	HepB				
Rotavirus ²				Rota	Rota	Rota						
Diphtheria, Tetanus, Pertussis ³				DTaP	DTaP	DTaP	<i>see footnote 3</i>	DTaP				DTaP
<i>Haemophilus influenzae</i> type b ⁴				Hib	Hib	Hib ⁴	Hib					
Pneumococcal ⁵				PCV	PCV	PCV	PCV				PPV	
Inactivated Poliovirus				IPV	IPV		IPV					IPV
Influenza ⁶							Influenza (Yearly)					
Measles, Mumps, Rubella ⁷							MMR					MMR
Varicella ⁸							Varicella					Varicella
Hepatitis A ⁹							HepA (2 doses)				HepA Series	
Meningococcal ¹⁰											MCV4	

 Range of recommended ages

 Certain high-risk groups

Outline

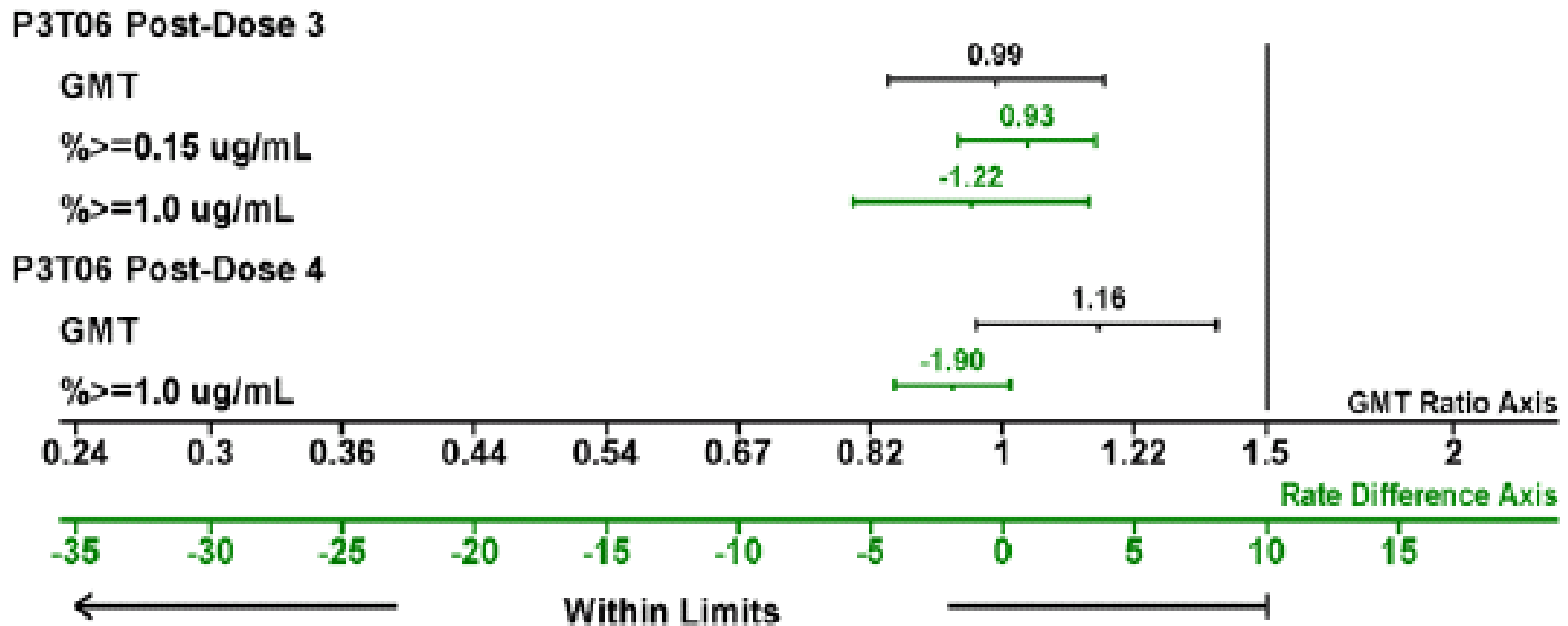
- Overview of Pentacel[®]
- **Safety and Immunogenicity**
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Pentacel[®] Safety and Reactogenicity

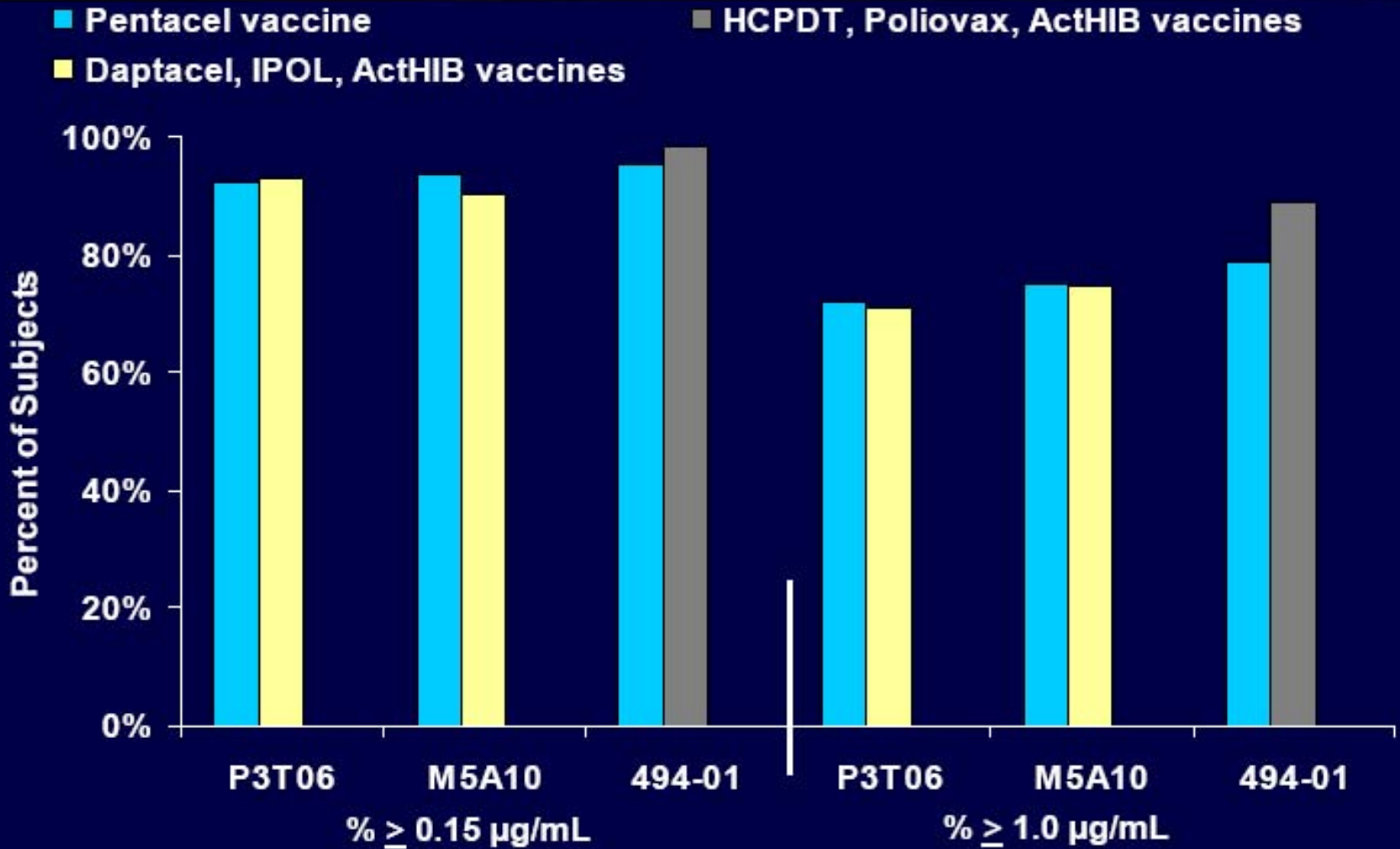
- **Comparable solicited local and systemic adverse events**
 - **Tenderness, swelling, redness**
 - **Increased circumferential swelling**
- **Comparable serious adverse events**
- **Comparable low rates of fever $>38.5^{\circ}\text{C}$**

Study P3T06: Hib Seroprotection Rates Post doses 3 and 4

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



Hib Seroprotection Rates, Post-Dose 3



Courtesy sanofi pasteur

06-25-08



Study 494-01: Hib Seroprotection Rates Post doses 3 and 4

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

494-01 Post-Dose 3

GMT

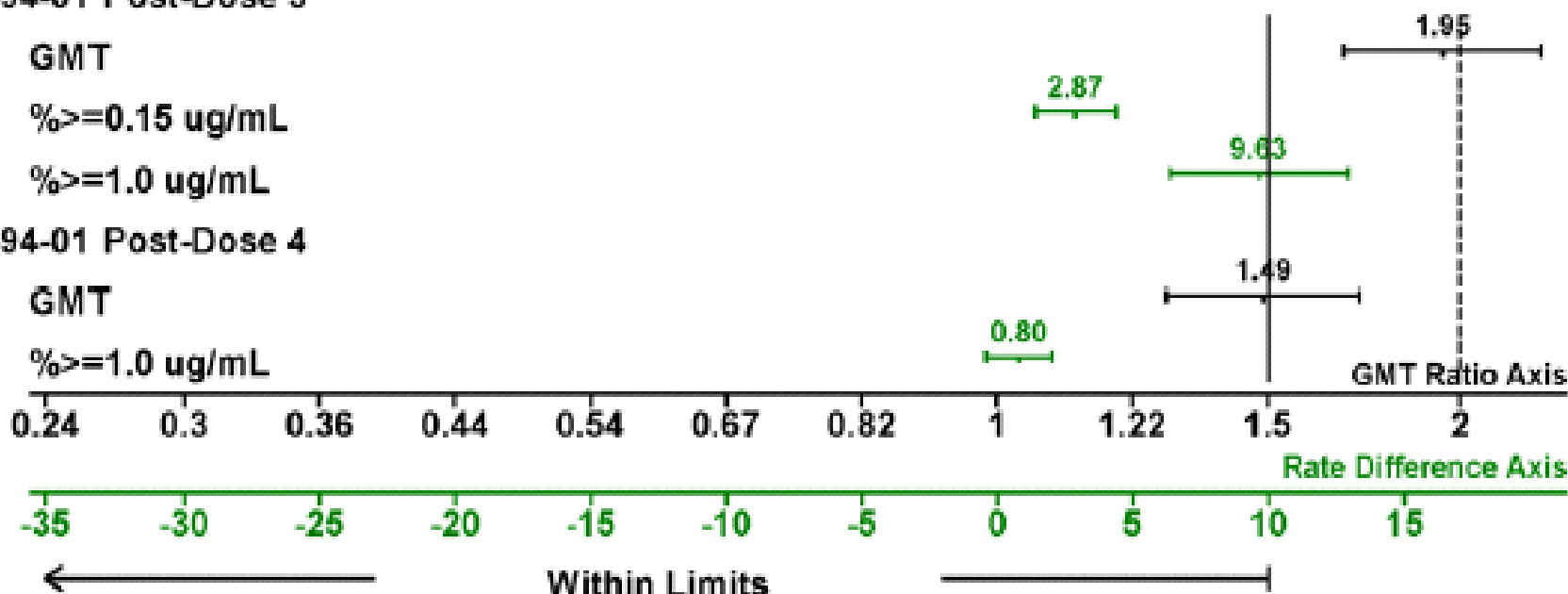
% \geq 0.15 ug/mL

% \geq 1.0 ug/mL

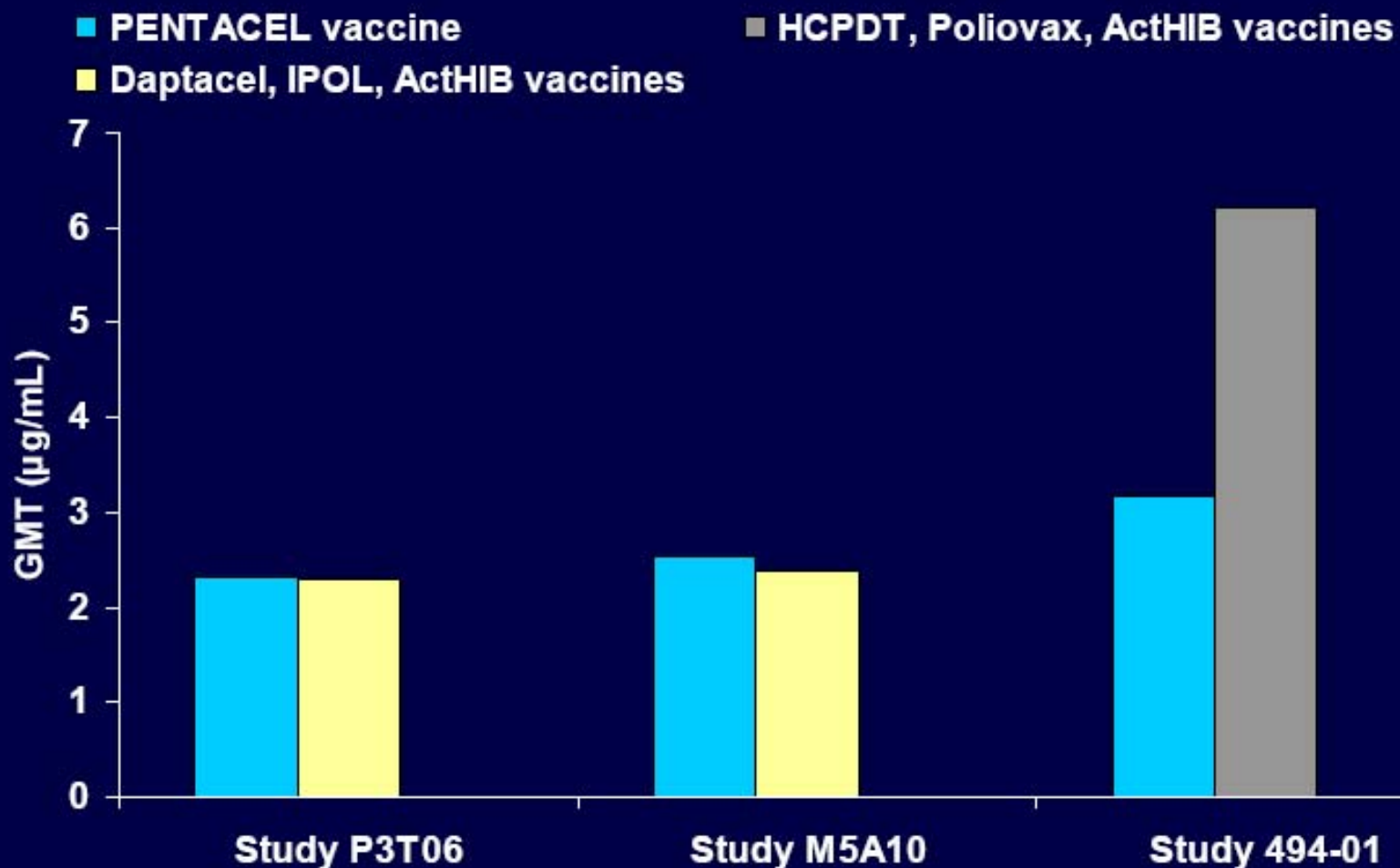
494-01 Post-Dose 4

GMT

% \geq 1.0 ug/mL



Hib GMTs, Post-Dose 3



Courtesy sanofi pasteur

06-25-08



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Pentacel[®] Indications and Use

- **Licensed for ages 6 weeks through 4 years**
- **Indicated for ages 2, 4, 6 and 15-18 months**
- **Minimum dose 1 – 2 interval 4 weeks**
- **Dose 3 not before age 14 weeks**
- **Dose 4 as early as 12 months if clinician feels missed opportunity to vaccinate and if six months since dose 3**
- **Co-administration at separate injection sites**

Polio Interchangeability

- Routine polio immunization is recommended at 2, 4, 6-18 months, and 4-6 years (school entry)
- Pentacel may be used for 1 or more doses in children who have received 1 or more doses of another IPV vaccine
- Pentacel at 2, 4, 6, 15-18 months would provide 4 valid doses of IPV when an accelerated schedule is needed

DTaP Interchangeability

- **“...whenever feasible, the same manufacturer’s DTaP product should be used for the primary series but that vaccination should not be deferred if the specific DTaP vaccine brand previously administered is unavailable or unknown.”**

MMWR 1999 Combined Vaccine Statement

Special Population Considerations

- American Indian/Alaskan Native (AI/AN) children increased risk for Hib disease during first 6 months of life
- PRP-OMP Hib vaccine leads to more rapid seroconversion to protective antibody concentrations in first 6 months of life
- Failure to use PRP-OMP vaccines associated with excess cases
- “it may be prudent for clinics that serve predominantly AI/AN children to use only PRP-OMP-containing Hib vaccines.”

Proposed Notice to Readers

- **FDA Licensure of Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (Pentacel[®]) in Infants and Children**

Thank you

Back Up Slides

Anti-PRP Seroprotection Post Dose 3 in Pentacel Prelicensure Studies (Adapted from Table 5 of Product Insert)

	Achieving anti-PRP ≥0.15 µg/mL		Achieving anti-PRP ≥1.0 µg/mL		Anti-PRP GMC (µg/mL)	
	Pentacel	Control	Pentacel	Control	Pentacel	Control
Study 494-01	95.4 %	98.3 %	79.1 % †	88.8 %	3.19 ‡	6.23
Study P3T06	92.3 %	93.3 %	72.1 %	70.8 %	2.31	2.29
Study M5A10	93.8 %	90.3 %	75.1 %	74.8 %	2.52	2.38

† Non-inferiority criterion **not met** for percent achieving anti-PRP ≥1.0 µg/mL following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel), 12.9%, exceeds the non-inferiority criterion <10%]

‡ Non-inferiority criterion **not met** for GMC following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI of GMC ratio (ActHIB/Pentacel), 2.26, exceeds the non-inferiority criterion <1.5]

Table 5: Anti-PRP Seroprotection Rates and GMCs One Month Following Three Doses of Pentacel Vaccine or Separate DTaP + IPV + ActHIB Vaccines Administered at 2, 4, and 6 Months of Age in Studies 494-01, P3T06, and M5A10

	Study 494-01	
	Pentacel Vaccine N = 1,127	HCPDT + POLIOVAX + ActHIB Vaccines N = 401
% achieving anti-PRP ≥ 0.15 $\mu\text{g/mL}$	95.4*	98.3
% achieving anti-PRP ≥ 1.0 $\mu\text{g/mL}$	79.1†	88.8
Anti-PRP GMC ($\mu\text{g/mL}$)	3.19‡	6.23
	Study P3T06	
	Pentacel Vaccine N = 365	DAPTACEL + IPOL + ActHIB Vaccines N = 1,128
% achieving anti-PRP ≥ 0.15 $\mu\text{g/mL}$	92.3*	93.3
% achieving anti-PRP ≥ 1.0 $\mu\text{g/mL}$	72.1*	70.8
Anti-PRP GMC ($\mu\text{g/mL}$)	2.31§	2.29
	Study M5A10	
	Pentacel Vaccine N = 826	DAPTACEL + IPOL + ActHIB Vaccines N = 421
% achieving anti-PRP ≥ 0.15 $\mu\text{g/mL}$	93.8**	90.3
% achieving anti-PRP ≥ 1.0 $\mu\text{g/mL}$	75.1**	74.8
Anti-PRP GMC ($\mu\text{g/mL}$)	2.52††	2.38

*Percent achieving specified level following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel) <10%]

† Non-inferiority criterion not met for percent achieving anti-PRP ≥ 1.0 $\mu\text{g/mL}$ following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel), 12.9%, exceeds the non-inferiority criterion <10%]

‡ Non-inferiority criterion not met for GMC following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI of GMC ratio (ActHIB/Pentacel), 2.26, exceeds the non-inferiority criterion <1.5]

§ Non-inferiority criterion not pre-specified.

** Percent achieving specified level following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 95% CI for difference in rates (ActHIB minus Pentacel) <10%]

†† GMC following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 90% CI of GMC ratio (ActHIB/Pentacel) <1.5]



Catch-up Immunization Schedule

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for Persons Aged 4 Months–18 Years Who Start Late or Who Are More Than 1 Month Behind

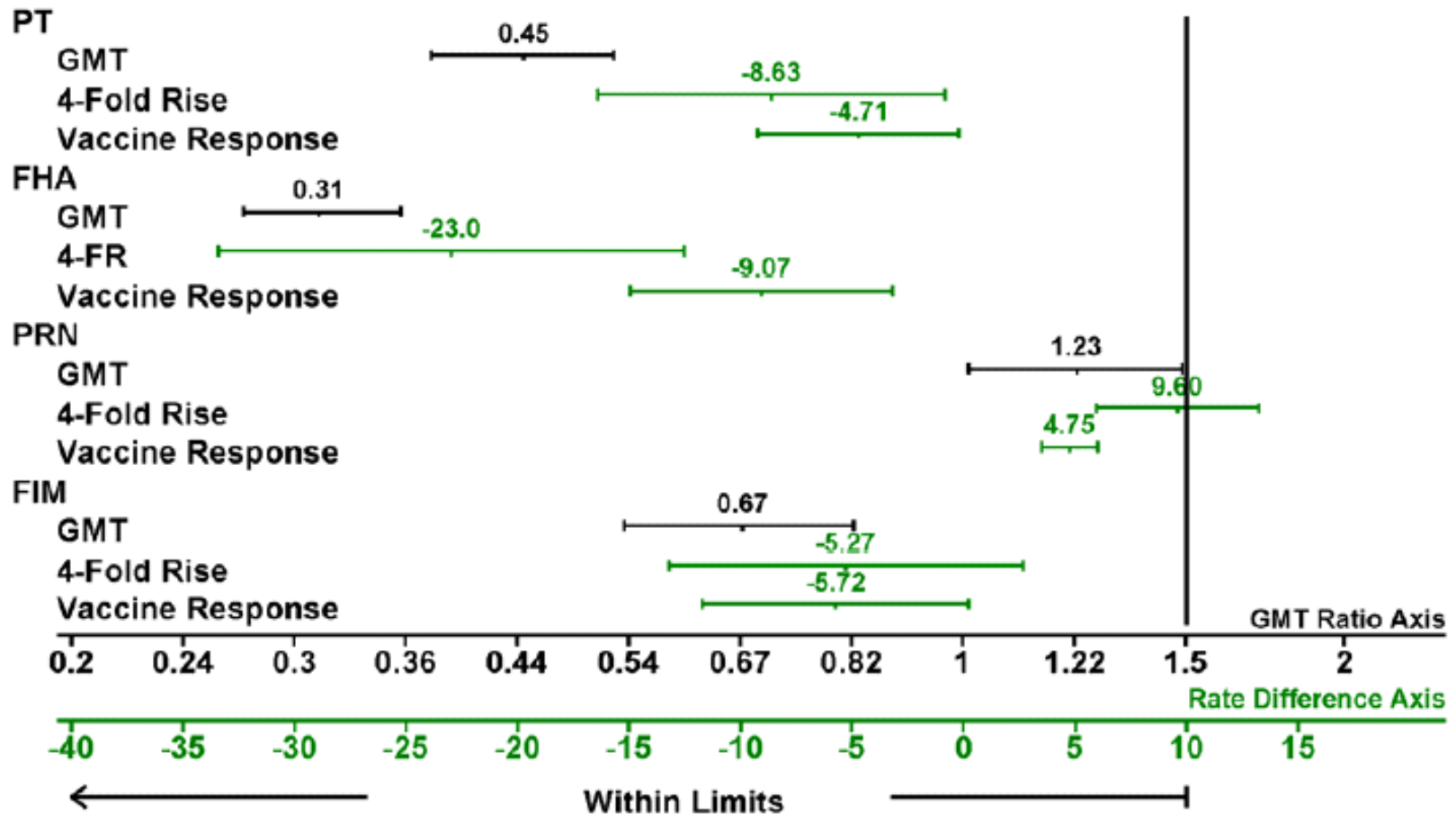
The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.

CATCH-UP SCHEDULE FOR PERSONS AGED 4 MONTHS–6 YEARS

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B ¹	Birth	4 weeks	8 weeks (and 16 weeks after first dose)		
Rotavirus ²	6 wks	4 weeks	4 weeks		
Diphtheria, Tetanus, Pertussis ³	6 wks	4 weeks	4 weeks	6 months	6 months ³
<i>Haemophilus influenzae</i> type b ⁴	6 wks	4 weeks if first dose administered at younger than 12 months of age 8 weeks (as final dose) if first dose administered at age 12-14 months No further doses needed if first dose administered at 15 months of age or older	4 weeks ⁴ if current age is younger than 12 months 8 weeks (as final dose)⁴ if current age is 12 months or older and second dose administered at younger than 15 months of age No further doses needed if previous dose administered at age 15 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months–5 years who received 3 doses before age 12 months	
Pneumococcal ⁵	6 wks	4 weeks if first dose administered at younger than 12 months of age 8 weeks (as final dose) if first dose administered at age 12 months or older or current age 24–59 months No further doses needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months 8 weeks (as final dose) if current age is 12 months or older No further doses needed for healthy children if previous dose administered at age 24 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months–5 years who received 3 doses before age 12 months	
Inactivated Poliovirus ⁶	6 wks	4 weeks	4 weeks	4 weeks ⁶	
Measles, Mumps, Rubella ⁷	12 mos	4 weeks			
Varicella ⁸	12 mos	3 months			
Hepatitis A ⁹	12 mos	6 months			

Pentacel and Pertactin, Study 494-01

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



Summary of Immunogenicity and Reactogenicity Studies

- **Adverse events similar to those observed following separately administered vaccines**
- **Non-inferiority demonstrated for DTP components**
- **Non-inferiority for Hib component shown in two of three major studies**
- **Immunologic responses following Dose 3 and 4 similar to those following separately administered component vaccines**

Pentacel Clinical Studies for US Licensure†

		N	PENTACEL
P3T06	Pentacel vs. Standard of Care (SC) (DAPTACEL, IPOL, ActHIB)	1939	485
494-01	Lot consistency, Pentacel vs. Formulation Equivalent (FE) (HCPDT, Poliovax, ActHIB)	3538	2506
M5A07	Interaction with Prevnar (Infant Series)	1166	1166
494-03	Interaction with Prevnar, MMR and Varivax vaccines (4 th Dose)	1207	1207
5A9908	Administration at 15-16 vs. 17-18 months of age	1782	1782

Total number of Pentacel recipients:

7146

Slide from sp
presented at VRBAC January 2007

06-25-08

†All subjects who received at least one dose



Study 494-01: Anti-PRP Levels Post-dose 3

	Pentacel N = 1127	ActHIB N = 401	Non-inferiority analyses
Anti-PRP			ActHIB – Pentacel (90% CI)¹
% \geq 0.15 ug/mL	95.4	98.3	2.87 (1.38, 4.36)
% \geq 1.0 ug/mL	79.1	88.8	9.63 (6.36, 12.90)
			ActHIB/Pentacel (90% CI)²
GMC	3.19	6.23	1.95 (1.68, 2.26)

Study 494-01 and Study P3T06

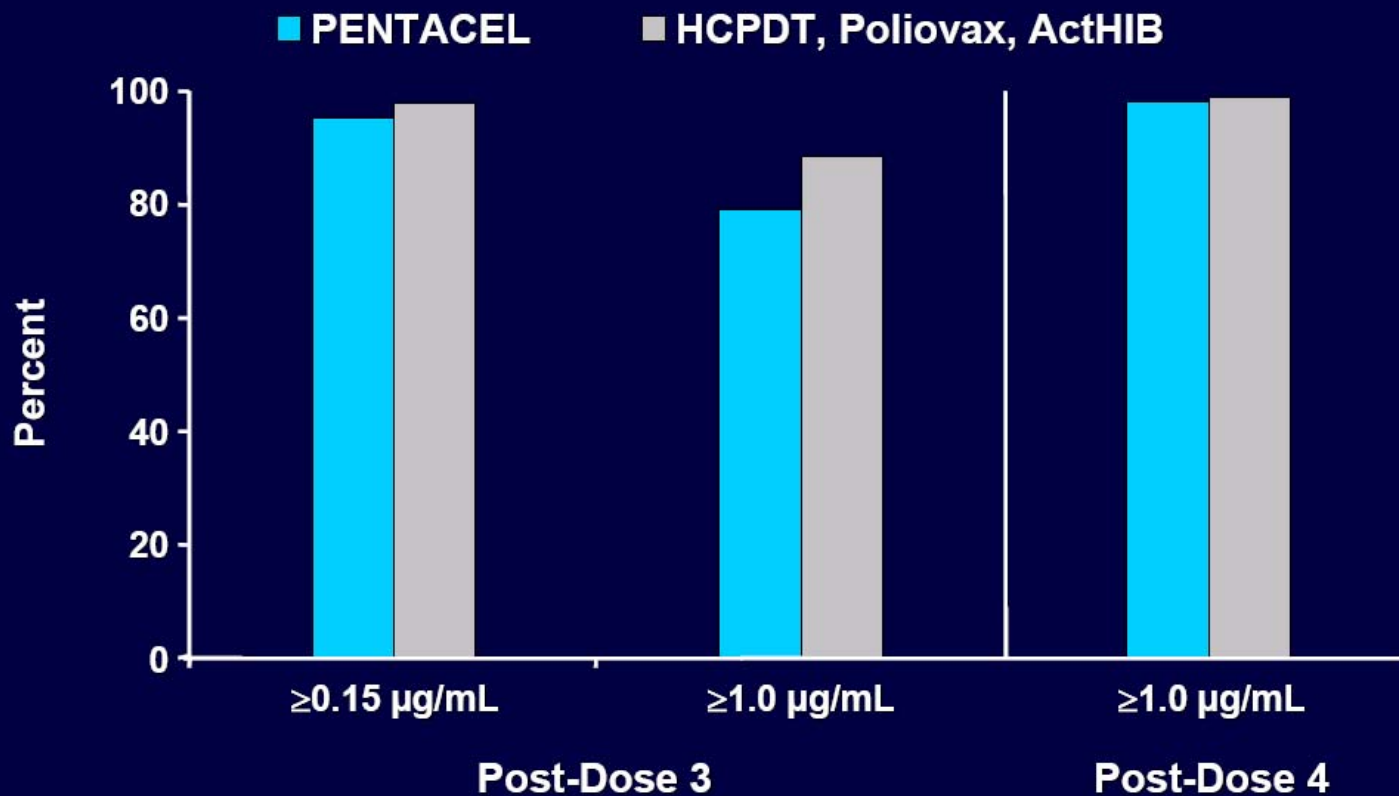
Exploratory analysis: PRP Ab levels pre-dose 4

Anti-PRP	Study 494-01		Study P3T06	
	Pentacel (n=829)	ActHIB (n=276)	Pentacel (N=335)	ActHIB* (n=323)
% ≥0.15ug/mL (95% CI)	68.6 (65.4, 71.8)	80.8 (75.6, 85.3)	65.4 (60.0, 70.5)	60.7 (55.1, 66.0)

*Study P3T06 Group 1 (DAPTACEL + ActHIB)

494-01: PENTACEL vs HCPDT, Poliovax, ActHIB

Post-Doses 3 and 4: Hib Seroprotection Rates



PENTACEL	95.4	79.1	98.2
Control	98.3	88.8	99.0

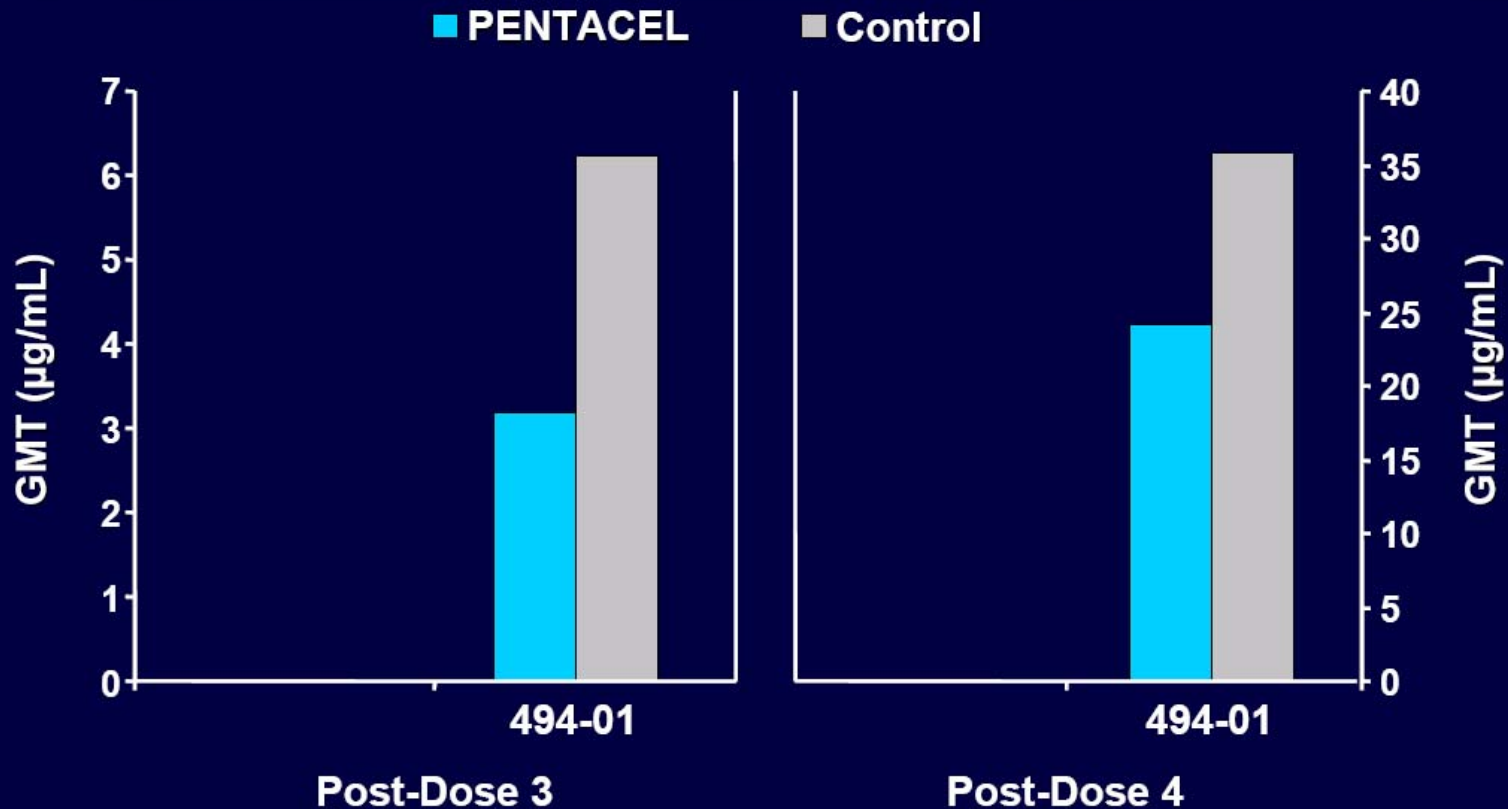
C-89

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P3T06 and 494-01: Comparison of Hib GMTs Post-Doses 3 and 4



PENTACEL		3.19
Control		6.23

		24.12
		35.90

C-90

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presented at VRBAC January 2007

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