8.3.6.4 Racial and ethnic distribution of invasive disease cases

The racial and ethnic distribution of the entire study population can be estimated based on the subset of actively monitored subjects from whom this information was collected (Section 8.2). Race and ethnicity was identified for all subjects with invasive disease and provided with the case narratives. In the table below, compiled from case narratives (not included in the PLA), the invasive disease burden by ethnic group is presented with the racial/ethnic distribution of the study population for comparison. It appears that cases of invasive disease are somewhat under-represented among subjects of Asian ancestry, and over-represented among African-Americans.

Table 11: Efficacy Study 118-8
Ethnic Distribution (%) of Invasive Disease Cases

Monitored Subset	Asian %	AfrAm %	Hispanic %	Cauc %	Multiethnic /Other %
7VPnC (N=3708)	13.4	7.7	19.6	39.3	19.4
MnCC (N=3693)	13.0	8.4	17.9	40.5	19.3
Invasive Disease					
Primary Analysis per protocol (N=17)	6	18	12	47	18
Follow-up analysis per protocol (N=40)	8	28	12	42	10
All Cases/serotypes (N=61)	5	25	16	48	7

% of invasive disease cases compiled from case narratives.

9.0 Review comments regarding efficacy against invasive disease

The efficacy study provides data indicating that Prevnar is effective in preventing invasive pneumococcal disease among infants and small children when administered at 2, 4, 6 and 12-15 months of age. At the primary analysis, the point estimate of protective efficacy against vaccine serotypes was 100% for both per protocol and intent-to-treat analyses, with a lower bound of the 95% confidence interval for efficacy above 75% for both analyses. Thus, the vaccine was shown to be highly efficacious as it was studied in the efficacy trial.

Examination of the narratives for the cases of invasive disease observed in the control group provides an idea of the burden of disease which may have been prevented in the study population had 7VPnC been administered to the control group and demonstrated similar efficacy. At the primary analysis, 2 cases of meningitis, one with residual hearing loss, and 4 hospitalizations may have been prevented. In the extended follow-up period, 2 deaths due to pneumococcal disease of vaccine serotype, and 5 cases of meningitis may have been prevented. It also seems likely that the burden of severe disease would be greater in the general pediatric population, and certainly in high risk populations, for whom health care may not be as readily available.

In the sections that follow, some issues encountered in the review are discussed, and some qualifications of the efficacy results are made.

9.1 Case ascertainment

In FDA/CBER's review of efficacy for invasive disease, assurance was sought that no cases of invasive disease had been missed, as a few missed cases in the pneumococcal vaccine group would have had a large effect on both the vaccine efficacy estimate and the confidence intervals. To this end, the sponsor was asked to provide all bacterial culture results for the study population at the time of the primary analysis. Culture results through the study period ending August 20, 1998 were received with the PLA submission (culture data for subjects through the extended follow-up period were not available at the time of the PLA submission or during the review period).

The summary of all non-pneumococcal culture positive results revealed no imbalance across treatment groups. All positive cultures were identified by genus, and most were speciated. Thus, it appears unlikely that positive pneumococcal cultures may have been missed due to indeterminate identification.

Table 12: Efficacy Study 118-8
All Non Pneumococcal Blood Cultures for Study Subjects, Primary Analysis (August 1998)

Vaccine Group	Negative	Non-pneumo Positive
7VPnC	2722	104
MnCC	2613	103

Adapted from Table in PLA supplemental submission of July 28, 1999.

The number of blood cultures reported as negative was not evenly balanced across groups, with an excess of negative cultures evident in the 7VPnC group. No explanation is readily apparent. One might be concerned about an excess of febrile reactions following vaccinations, leading to additional blood culture requests. While this is a plausible hypothesis, as febrile reactions post vaccination were more common in the 7VPnC group (see below), it is not clear from the available information that this explains the imbalance observed. Certainly, the imbalance is not large and could be due to chance alone.

(Also of note with respect to the culture data is that, through April 20, 1999, six blood isolates of meningococcus were identified, 3 in each vaccine group. None of the isolates was serotype C).

9.2 Confidence intervals and determination of follow-up time

Given that the estimate of vaccine efficacy (VE) is a function of the ratio of follow-up times between the two vaccine groups, precise knowledge of follow-up time is preferred. Exact follow-up times for all subjects were not available at the time of the primary analysis in August. As of April 30, 1998, the cumulative follow-up times for the 7VPnC and MnCC groups were nearly identical at 10,047 and

10,098 child-years, respectively. Follow-up times in the two vaccine groups established in April, were used to project an estimated follow-up time for the August analysis.
Variation of actual from projected follow-up time would not affect the vaccine efficacy estimate, but could alter the confidence intervals. As discussed in **section 8.1**, the sponsor, and FDA (Dr. Pamela Getson), conducted supplementary analyses demonstrating that the plausible ratios of follow-up times between the two vaccine groups at the August analysis would not vary substantially with additional data. It was demonstrated that if the proportion of follow-up in the 7VPnC group were differentially reduced by as much as 33%, the lower bound of the 95% confidence interval for efficacy in the primary analysis would remain above 71%. Thus, any difference in projected follow-up to actual follow-up is likely to be inconsequential.

Calculation of the confidence intervals in the per protocol analysis was further complicated because included in the total follow-up time is follow-up time attributed to subjects who left the Kaiser health plan between their 3rd and 4th doses or after their 4th dose, but before the study's end. While early termination from the health plan could decrease the probability that extra cases would be ascertained, it would not be expected to introduce a systematic bias in the relative group proportions of "missed case" ascertainment. The sponsor determined that the relative group proportions of follow-up time accrued to subjects leaving the health plan were similar (7.1%, 7VPnC vs. 6.6 %, MnCC). Adjustments to the accumulated child-years which is reduced by the loss-to-follow-up fraction, may be appropriate for calculation of confidence intervals, even though the risk reduction point estimate will not vary.

Results of the intent-to-treat analysis provide additional support for the efficacy estimate of the per protocol analysis. Follow-up time in the intent-to-treat analysis accrues from the time of enrollment for each subject and continues through April 30, 1998. The intent-to-treat follow-up analysis is unaffected by dropouts and protocol violations. The lower bound of the 95% confidence interval for invasive disease due to vaccine serotype in the intent-to-treat analysis was above 80%, consistent with a high level of protective efficacy.

9.3 Extended follow-up for invasive disease

Efficacy data was collected beyond the date of the primary analysis in order to assure that disease rates in the extended follow-up period did not differ markedly from those observed at the primary analysis. Vaccine efficacy estimates and 95% confidence intervals were provided for the extended follow-up period through April 1999 (see Section **8.3.6.1)**. Several points regarding the extended follow-up data deserve mention:

- Variation of actual from projected follow-up time is likely to be greater when projecting follow-up time a year into the future (April 1998 to April 1999).

Therefore, the confidence intervals provided reflect uncertainty inherent in the projection of follow-up time.

- The stop date for extended follow-up was not pre-specified, and results of bacterial cultures were known as they became available subsequent to the primary analysis. Thus, extended follow-up could have been truncated earlier if the split of cases in extended follow-up were not favorable.
- Complete culture data, including non-pneumococcal culture data, for the extended follow-up period are not available. It is not possible to evaluate case ascertainment in the same manner that was possible for the primary analysis.
- Complete and quality controlled safety data for the extended follow-up period were not available for review. Therefore, it is not possible to balance the apparent benefit of protective efficacy against the potential risks of vaccination over the extended follow-up period.

While the efficacy data for the extended follow-up period is informative, the quality of the data is not comparable to data available for the primary analysis. Inclusion of extended follow-up efficacy data in the package insert prior to receipt of a complete data set may not be appropriate, but could be considered after additional safety and culture data are submitted as a PLA supplement.

9.4 Efficacy after 3 or 4 doses

In the primary (per protocol) analysis, 10 cases of invasive disease occurred in the control group vs. 0 cases in the 7VPnC group after 3 doses, but before the 4th dose (lower 95% CI, 55%). A claim of efficacy might be made that a schedule of 3 doses of vaccine administered at 2, 4, and 6 months of age is protective. However, the claim would only be justified for short-term efficacy. All that can be inferred from the efficacy trial is that the vaccine was protective for the period between 6 months plus 2 weeks of age to 12 months of age, as most children then received the 4th dose.

Antibody levels are likely to wane over time. The efficacy study does not inform whether antibody levels achieved after 3 doses in infancy would be adequate to protect beyond 1 year of age. While it seems likely that a vaccine effect after 3 doses would be detectable beyond 1 year of age, it also seems likely that the efficacy estimate would fall short of 100%. To this point, in the extended follow-up, one case of invasive disease in the pneumococcal vaccine group occurred in a normal, fully vaccinated (4 doses) child at 24 months of age.

9.5 Implications for bridging and "catch-up" schedules

Until definitive information is available about protective levels of antibody or other surrogates of protection, a reasonable interpretation of the available data is that antibody levels achieved after 3 doses are adequate for short term protection, and levels achieved after 4 doses may be required for longer term protection. Thus, for purposes of bridging to the efficacy data, it may be important to make comparisons to both post-dose 3 and post-dose 4 antibody levels.

9.6 Conclusions and comments regarding vaccine efficacy against invasive disease

The 7-valent pneumococcal CRM_{197} conjugate vaccine, Prevnar, is highly efficacious in preventing invasive pneumococcal disease when administered to healthy children at 2, 4, 6 and 12-15 months of age. Adjustment of confidence intervals upon receipt of more complete follow-up time would likely be trivial.

Among the cases of invasive disease in the extended follow-up dataset were 2 deaths and 6 cases of meningitis attributable to pneumococcal disease, all of which occurred in the in control group. While the study was not powered to examine death or meningitis as efficacy outcomes, it is likely that by preventing invasive disease, the vaccine will be effective in preventing these serious outcomes in the general population.

10.0 Analysis of Safety

10.1 Safety database

Safety of the 7VPnC vaccine was assessed in a total of seven clinical studies. In five of these studies (118-3, 118-7, 118-8, 118-12, 118-16), safety was evaluated among infants. Safety of a 4th dose of vaccine administered at 12-15 months was evaluated in three studies (118-3, 118-7, 118-8). Study (118-9) examined safety of a single dose in toddlers. Study 118-2 provides the only safety data for adults in the application.

Table 13: Safety Database: Number of Children Who Received 7VPnC Vaccine and the Number of Doses Administered

Infant Studies	Age (mos)	Primary Series		4th Dose	
		Subjects	Doses	Subjects	Doses
118-3	2, 4, 6, 12-15	106	303	58	58
118-7	2, 4, 6, 12-15	202	570	138	138
118-8 Enrollment as of 4/30/98 Data cut-off for safety	2, 4, 6, 12-15	17,066	46,305	9,047	9,047
118-12	2, 4, 6	256	740	--	--
118-16	2, 4, 6	538	1538	--	--
	TOTAL	18,168	49,456	9,243	9,243
		(20,029)	(54,817)	(11,136)	(11,136)
Older Infants (>6 Month) and Children					
118-9	15-24 (1 dose)	60	60	--	--
118-12	7, 9, 15-18	54	105	24	24
Adult Studies					
118-2	18-65 yrs	15	15	--	--

Adapted from Table 2, page 15, of Integrated Clinical Summary, Volume 33 part IV of PLA

The bulk of the safety data regarding local and systemic reactions and other adverse events derives from the NCKP Efficacy study. Monitoring for safety outcomes in the efficacy study is described below.

Reactogenicity data from studies 118-12 (lot consistency) and 118-16 (manufacturing bridging) are particularly relevant to a description of the safety profile of 7VPnC because: 1) the control groups in these two studies did not receive MnCC or other active control vaccine, thus allowing a clearer assessment of local and systemic reactions; 2) DTaP + HbOC was administered concurrently, consistent with current standard of care. Important contributions of other studies to the safety evaluation are also discussed (For descriptions of supporting studies, please refer to Attachment B).

10.2 Safety data from the NCKP Efficacy Trial (118-8)

10.2.1 Description of safety data

Safety data from the NCKP efficacy study accumulated through April 30, 1998, were reported in the application. Follow-up of subjects continued until April 20, 1999, however complete and quality controlled data sets for the extended follow-up period were not included in the application. Additional safety data, consisting of line listings of ER visits, hospitalizations, and "out of plan adverse events" occurring from April 30, 1998, through December 31, 1998, was submitted as a planned update to the application on July 7, 1999.

In addition, late in the review period, investigator's at NCKP were able to provide mortality data, including breakdown by cases of Sudden Infant Death Syndrome (SIDS) through April, 1999.

10.2.1 Safety Variables

Specific local reactions and systemic events following vaccine injections were actively monitored in a subset of approximately 6000 infants who received DTP-HbOC concomitantly with the study vaccines early in the trial. Infants were randomly selected for active monitoring of vaccine reactions if the last digit of their medical record number was 2, 4, 6, or 8. The same cohort of infants was monitored after each dose.

Injection site reactions were monitored for 48 hours following immunizations by use of diary cards. Fever was recorded on the day of immunization, and at bedtime for 2 days after, and at any other time within 14 days that the infant felt warmer than usual. Other systemic events were monitored for 14 days and recorded by parents on a diary card. At approximately 48-72 hours and 10-14 days after each dose, these data were collected by telephone interviews with parents.

Amendment #4, implemented April 1997, provided for monitoring of acute safety data via diary cards and telephone interviews in a subset (N=1500) of the population of children who received DTaP and HbOC concurrently with the primary series of study vaccine. At the time of implementation, 20,272 infants and children had already received at least one dose DTP-HbOC with study vaccines.

Table 14: Efficacy Study 118-8
Number of Subjects with Concomitant Doses of DTaP and DTP-HbOC Among Children Who Received At Least 3 Doses of Study Vaccine Prior to Age 12 Months (Through April 30, 1998)

Number of Doses		Number of Children	%
DTP-HbOC	DTaP		
1	0	15	.05
2	0	407	1.48
3	0	20,780	75.39
0	1	6	.02
0	2	93	.34
0	3	4,634	16.81
1	1	41	.15
2	1	925	3.36
1	2	663	2.41
		27,564	

Reproduced from Table 8, page 87 Volume 13, of PLA

10.3 Local Reactions

10.3.1 Local Reactions in the Efficacy Study

Rates of local reactions at DTP-HbOC injection sites (right leg) and 7VPnC or MnCC injections (left leg) were compared pairwise within the same child using the sign test. Local reactions occurring within 48 hours of an injection were reported with greater frequency and severity for DTP-HbOC injection sites than 7VPnC injection sites for each dose of the primary series.

Local reaction rates for 7VPnC and MnCC injection sites were also compared between treatment groups. Rates of induration and tenderness were greater in the 7VPnC group, compared to the MnCC group for each dose of the primary series. Clinically significant induration (> 2.4 cm) and tenderness (interferes with leg movement) were also more frequent at 7VPnC inoculation sites than at MnCC injection sites after doses 2 and 3.

Frequency of local reactions due to 7VPnC did not increase appreciably with sequential doses of the primary series.

Table 15: Efficacy Study 118-8
Local Reactions within 48 hours of Inoculations Among Infants Receiving DTP-HbOC, OPV, Hepatitis B, and 7VPnC or MnCC Vaccines

	7VPnC N=2890 %	DTP-HbOC N=2890 %	p-value[1]	MnCC N=2877 %	DTP-HbOC N=2877 %	p-value[1]	p-value[2] 7VPnC vs. MnCC
Dose 1							
Erythema	12.4	21.9	0.0001	11.2	22.4	0.0001	0.124
> 2.4cm	1.2	4.6	0.0001	1.4	3.9	0.0001	0.416
Induration	10.9	22.4	0.0001	9.0	23.8	0.0001	**0.013**
> 2.4cm	2.6	7.2	0.0001	2.1	7.5	0.0001	0.307
Tenderness	28.0	36.4	0.0001	24.7	34.0	0.0001	**0.001**
Interferes with Leg Movement	7.9	10.7	0.0001	6.7	9.2	0.0001	0.062
Dose 2	N=2725	N=2725		N=2678	N=2678		
Erythema	14.3	25.1	0.0001	11.5	27.9	0.0001	**0.003**
> 2.4cm	1.0	2.9	0.0001	0.8	3.4	0.0001	0.364
Induration	12.3	23.0	0.0001	7.1	24.2	0.0001	**0.001**
> 2.4cm	2.4	5.6	0.0001	1.1	5.4	0.0001	**0.001**
Tenderness	25.2	30.5	0.0001	18.3	26.4	0.0001	**0.001**
Interferes with Leg Movement	7.4	8.4	0.015	4.4	5.8	0.0003	**0.001**
Dose 3	N=2538	N=2538		N=2532	N=2532		
Erythema	15.2	26.5	0.0001	12.7	26.8	0.0001	**0.011**
> 2.4cm	2.0	4.4	0.0001	1.3	4.1	0.0001	**0.028**
Induration	12.8	23.3	0.0001	9.7	23.2	0.0001	**0.001**
> 2.4cm	2.9	6.7	0.0001	1.5	6.1	0.0001	**0.002**
Tenderness	25.6	32.8	0.0001	18.2	28.5	0.0001	**0.001**
Interferes with Leg Movement	7.8	10.0	0.0001	4.7	7.2	0.0001	**0.001**

Adapted from Tables 48, 49, and 50 of Study Report, volume 13, Part IV of PLA.
[1] P-value, calculated using the sign test, assesses the difference between 7VPnC injection sites and DTP-HbOC/HepB injection sites in the 7VPnC recipients, and between MnCC injection sites and DTP-HbOC/HepB injection sites in the MnCC recipients.
[2] P-value, calculated using the Chi-Square test, assesses the difference between 7VPnC and MnCC injection sites in all subjects for which data were available.
N may vary for local reactions and dose number depending on available data.

After the 4th dose, local reactions at DTP-HbOC injection sites were significantly more common that reactions at 7VPnC injection sites. However, compared to the MnCC control subjects, rates of tenderness, and tenderness interfering with leg movement, were reported significantly more often among 7VPnC recipients, 36% and 18% vs. 28% and 13% (table not shown).

In the subset of subjects who received DTaP concurrently with study vaccines, HbOC and study vaccine were administered in the same leg (left), and DTaP +/- Hep B was administered in the opposite leg. The worse reaction of each leg was recorded. Comparisons of local reactions when 7VPnC or MnCC were administered concurrently with DTaP are shown below.

Rates of erythema, induration, and tenderness interfering with movement were significantly greater for 7VPnC than for DTaP after the first dose, but not subsequent

doses. Rates of local reactions at 7VPnC injection sites do not appear to increase with sequential doses of the primary series.

Rates of erythema and induration at 7VPnC injection sites were significantly greater than rates for MnCC injection sites after doses 1 and 2.

Table 16: Efficacy Study 118-8
Local Reactions Within 48 Hours of Injection
Among Infants Receiving DTaP, and 7VPnC or MnCC Vaccine, First 3 doses

	7VPnC N=693 %	DTaP N=693 %	p-Value[1]	MnCC N=691 %	DTaP N=691 %	p-Value[1]	p-Value[2] 7VPnC vs. MnCC
Dose 1							
Erythema	10.0	6.7	**0.0006**	6.5	5.6	0.3449	**0.026**
> 2.4cm	1.3	0.4	0.0313	0.6	0.9	0.5000	0.164
Induration	9.8	6.6	**0.0021**	4.2	4.3	>.999	**0.001**
> 2.4cm	1.6	0.9	0.1250	0.1	0.3	>.999	0.004
Tenderness	17.9	16.0	0.0533	17.9	18.9	0.2649	0.970
Interferes with Leg Movement	3.1	1.8	**0.0039**	2.5	2.5	>.999	0.505
Dose 2	N=526	N=526		N=489	N=489		
Erythema	11.6	10.5	0.5118	7.6	10.8	0.0113	**0.030**
> 2.4cm	0.6	0.6	>.999	0.8	1.4	0.5078	0.717[3]
Induration	12.0	10.5	0.3123	5.1	7.4	0.0801	**0.001**
> 2.4cm	1.3	1.7	0.6250	0.4	1.0	0.2500	0.180[3]
Tenderness	19.4	17.3	0.0801	15.0	15.6	0.6776	0.069
Interferes with Leg Movement	4.1	3.3	0.2188	2.5	2.5	>.999	0.168
Dose 3	N=422	N=422		N=377	N=377		
Erythema	13.8	11.4	0.1433	9.3	8.2	0.5572	**0.049**
> 2.4cm	1.4	1.0	0.6250	2.4	1.9	0.7266	0.308
Induration	10.4	10.4	>.999	6.9	8.3	0.4731	0.066
> 2.4cm	2.4	1.9	0.6875	0.8	2.1	0.1250	0.082
Tenderness	14.7	13.1	0.2649	12.3	12.0	>.999	0.280
Interferes with Leg Movement	2.9	1.9	0.2188	1.6	0.5	0.1250	0.240

Adapted from Tables 48, 49, and 50 of Study Report, volume 13, Part IV of PLA.
[1] P-value, calculated using the sign test, assesses the difference between 7VPnC injection sites and DTaP injection sites in 7VPnC recipients, and between MnCC injection sites and DTaP injection sites in the MnCC recipients.
[2] P-value, calculated using the Chi-Square test, assesses the difference between 7VPnC and MnCC injection sites in all subjects for which data were available (Sponsor's analysis).
[3] P-value, calculated using Fisher's exact test (Sponsor's analysis)
Total N may vary depending on available data.

Local reactions following the 4th dose of 7VPnC or MnCC when given concurrently with DTaP were assessed in the NCKP efficacy trial. In the summarized data, subjects could have received either DTP-HbOC or DTaP and HbOC with the primary series, thus complicating the assessments. Erythema and induration were reported more frequently for 7VPnC injection sites than for DTaP in pairwise comparisons within subjects, and more frequently than for MnCC injection sites in control subjects.

Table 17: Efficacy Study 118-8
Local Reactions within 48 Hours of Injection,
Children Vaccinated with DTaP vs. 7VPnC or MnCC Vaccine, Dose 4

	7VPnC N=165 %	DTaP N=165 %	p-Value[1]	MnCC N=178 %	DTaP N=178 %	p-Value[1]	p-Value[2] 7VPnC vs. MnCC
Erythema	10.9	3.6	**0.0042**	4.5	4.0	>.9999	**0.043**
> 2.4cm	3.6	0.6	0.1250	0.0	0.0		**0.005**[3]
Induration	12.1	5.5	**0.0127**	4.5	3.4	0.6875	**0.005**
> 2.4cm	5.5	1.8	0.0703	0.0	0.0		**<0.001**[3]
Tenderness	23.3	18.4	0.0963	15.4	14.9	>.9999	0.052
Interferes with Leg Movement	9.2	8.0	0.7539	1.7	1.7		**0.002**

Adapted from Table 55 of Clinical Study Report, Volume 13, Part IV of PLA
[1] P-value, calculated using the sign test, assesses the difference between 7VPnC injection sites and DTaP/HepB injection sites in the 7VPnC recipients, and between MnCC injection sites and DTaP/HepB injection sites in the MnCC recipients.
[2] P-value, calculated using the Chi-Square test, assesses the difference between 7VPnC and MnCC injection sites in all subjects for which data were available.
[3] P-value calculated with Fisher's Exact Test.
Subjects may have received mixed pertussis vaccine regimens concurrently in the primary series.

10.3.2 Local reactions in supporting studies

Local reactions following concurrent administration of 7VPnC and DTaP with the primary series were also assessed in the lost consistency study, 118-12, and the manufacturing bridging study, 118-16 (See attachment B for description of study designs). In both of these studies, local reactions for 7VPnC and HbOC in the left leg were compared pairwise within subjects to reactions in the right leg, inoculation site of DTaP +/- Hep B.

Erythema, induration and tenderness were more common in the leg receiving 7VPnC. Severe reactions were uncommon.

Table 18: Manufacturing Bridging Study 118-16
Local Reactions Within 72 hours of Injection, Within Subject Comparisons,
7VPnC and HbOC Vaccine vs. DTaP and HepB

Local Reaction	Dose 1: All 7VPnC Lots (N=487)			Dose 2: All 7VPnC Lots (N=440)			Dose 3: All 7VPnC Lots (N=440)		
	7VPnC Site %	DTaP Site %	p-value[1]	7VPnC site %	DTaP Site %	p-value[1]	7VPnC site %	DTaP site %	p-value[1]
Erythema	10.9	6.2	**0.0002**	11.6	8.6	0.053	4.3	10.9	**0.049**
>2.4 cm	0.6	0.6	>.9999	0.7	0.5	>.999	0.9	0.2	0.250
Induration	9.9	5.6	**0.0015**	10.5	6.8	**0.036**	10.0	6.6	**0.028**
>2.4 cm	1.2	1.0	>.9999	0.9	0.2	0.375	1.1	0.2	0.125
Tenderness	22.3	17.2	**0.0001**	17.0	13.3	**0.029**	15.8	13.2	**0.043**
Interferes w/ Movement	2.9	2.9	>.9999	3.5	1.8	0.065	1.8	2.1	>.999

Adapted from Tables 17, 18, and 19, pages 68, 69, and 71, Volume 29, Part IV of PLA
Controls received DTaP and HbOC at age 2, 4, and 6 months. All groups received Hepatitis B at age 2 and 6 months. IPV was administered in the arm at ages 2 and 4 months.
[1] P-value, calculated using the sign test, assesses the difference between 7VPnC injection sites and DTaP/HepB injection sites in recipients of a 7VPnC lot.

Table 19: Lot Consistency Study 118-12
Local Reactions within 72 hours Injections,
HbOC with 7VPnC Versus DTaP, Within Subject Comparisons

	Dose 1			Dose 2			Dose 3		
Local Reaction	HbOC+ 7VPnC L thigh N=256 %	DTaP R thigh N=256 %	P-value*	HbOC+ 7VPnC L thigh N=245 %	DTaP R thigh N=245 %	P-value*	HbOC+ 7VPnC L thigh N=239 %	DTaP R thigh N=239 %	P-value*
Erythema	11.2	4.4	**0.001**	12.9	5.6	**0.002**	16.7	6.9	**0.001**
> 2.4 cm	1.6	0.8	0.414	0.4	0	1.000	1.7	0.9	0.414
Induration	10.7	3.6	**0.001**	17.2	7.3	**0.001**	14.2	7.4	**0.003**
> 2.4 cm	2.0	0	0.063	2.1	0	0.063	0.9	0.4	0.564
Tenderness	19.8	13.1	**0.001**	15.2	7.6	**0.001**	13.2	8.1	**0.005**
Interferes w/ Movement	2.4	2.4	1.000	2.5	1.3	0.083	3.0	1.3	**0.046**
Any Reaction	27.9	16.4	**0.001**	28.2	15.1	**0.001**	28.4	15.7	**0.001**
Any Signific. Reaction	5.2	3.2	0.166	4.7	1.3	**0.005**	5.6	2.2	**0.021**

Adapted from Table 33, page 61, Volume27, Part IV of PLA.
The number of children with available reaction data may be smaller and vary from reaction to reaction.
Combined data of three 7VPnC lot groups.
* P-value based on McNemar test for within-subject comparison. In the cases where the frequencies in one or both groups are zero, Wilcoxon signed rank test was used.

In study 118-12, it was also possible to separate out rates of local reactions attributable to 7VPnC + HbOC vs. HbOC alone, as subjects in the control group did not receive 7VPnC or other active control vaccines. Rates of local reactions in legs inoculated with both 7VPnC and HbOC were significantly greater than in control subjects. Induration and tenderness were reported more frequently after each dose of the primary series for 7VPnC recipients. Severe reactions were uncommon.

Table 20: Lot Consistency Study 118-12
Comparisons of Local Reactions, HbOC + 7VPnC vs. HbOC Alone

	Dose 1			Dose 2			Dose 3		
Local Reactions at Left Thigh	HbOC with 7VPnC N=256 %	HbOC N=86 %	P-value*	HbOC with 7VPnC N=245 %	HbOC N=82 %	P-value*	HbOC with 7VPnC N=239 %	HbOC N=80 %	P-value*
Erythema	11.2	1.2	**0.003**	12.9	1.3	**0.002**	16.7	5.2	**0.012**
>2.4 cm	1.6	0	0.576	0.4	0	1.000	1.7	0	0.575
Induration	10.7	3.6	**0.048**	17.2	2.6	**<0.001**	14.2	5.2	**0.041**
>2.4 cm	2.0	0	0.337	2.1	0	0.336	0.9	1.3	1.000
Tenderness	19.8	10.6	0.068	15.2	10.1	0.348	13.2	3.9	**0.021**
Interfering Limb Movement	2.4	2.4	1.000	2.5	0	0.343	3.0	0	0.200
Any Reactions	27.9	11.9	**0.003**	28.2	10.1	**<0.001**	28.4	11.7	**0.003**
Any Significant Reaction	5.2	2.4	0.373	4.7	0	0.072	5.6	1.3	0.202

Adapted from Table 32, page 67, Volume 27, Part IV of PLA.
Pilot lots were combined for these comparisons.
The number of children with available reaction data may be smaller and vary by reaction.
* P-value based on Fisher's exact test.

10.3.3 Review Comments Regarding Local Reactogenicity of 7VPnC

Local reactions due to 7VPnC were less frequent and less severe than reactions attributable DTP-HbOC, but more frequent than local reactions due to DTaP, HbOC and the investigational vaccine, MnCC. It appears that local reactions at the 7VPnC site were potentiated by concurrent DTP-HbOC in the opposite leg, but not by concurrent DTaP. Tenderness interfering with leg movement was reported by nearly 8% of subjects at each dose of the primary series when given with DTP-HbOC, but approximately 3% or fewer subjects when given with DTaP across studies.

Local reactogenicity attributable to 7VPnC did not appear to increase sequentially with the first 3 doses. But at the 4th dose, when given concurrently with DTaP in opposite legs, severe induration and pain occurred more commonly than with the primary series, and more commonly that at the DTaP site.

It should be noted that no data are presented in the PLA addressing local and systemic reactions of 7VPnC when administered with DTaP for all 4 doses.

10.4 Systemic Reactions in NCKP Efficacy Trial (118-8)

10.4.1 Systemic Reactions with Concurrent DTP-HbOC

Against a background of concurrently administered DTP-HbOC, fever ≥38°C and irritability were reported significantly more frequently in the 7VPnC group than in the MnCC group after each of the first 3 doses. Rates of fever >39°C increased with subsequent doses (1.3%, 3.0%, and 5.3%), and were significantly more frequent after doses 2 and 3 in the 7VPnC group, compared to the MnCC control group. Other systemic reactions, such as prolonged crying, restless sleep, loss of appetite and vomiting were also significantly more common in the 7VPnC group for 1 or more doses of the primary series.

Convulsions within 48 hours of a study vaccine inoculation were reported among subjects in the actively monitored subset for 2 children in the 7VPnC (1 each after doses 1 and 2), and 1 child in the MnCC group (after dose 3).

The entire list of events solicited by telephone interview in the NCKP trial is shown in the following table, with results for the first 3 doses.

Table 21: Efficacy Study 118-8
Systemic Events Within 48 Hours of Injection by Dose
Among Infants Receiving DTP-HbOC, OPV, Hepatitis B[1], and 7VPnC or MnCC

Systemic Reaction	Dose 1			Dose 2			Dose 3		
	7VPnC N[1]=2996 %	MnCC N=2976 %	p-value[2]	7VPnC N=2784 %	MnCC N=2758 %	p-value[2]	7VPnC N=2590 %	MnCC N=2588 %	p-value[2]
Fever ≥38°C	33.4	28.7	**0.001**	34.7	27.4	**0.001**	40.6	32.4	**0.001**
Fever >39°C	1.3	1.3	0.934	3.0	1.6	**0.001**	5.3	3.4	**0.001**
Irritability	71.3	67.9	**0.004**	69.4	63.8	**0.001**	68.9	61.6	**0.001**
Cry 3+ Hours	0.6	0.8	0.510	0.7	0.3	**0.029**	0.5	0.4	0.391
Restless Sleep	18.1	17.9	0.868	27.3	24.3	**0.009**	33.3	30.1	**0.012**
More Sleep	49.2	50.6	0.294	32.5	33.6	0.393	25.9	23.4	**0.040**
Loss of Appetite	24.7	23.6	0.358	22.8	20.3	**0.022**	27.7	25.6	0.083
Vomiting	17.9	14.9	**0.002**	16.2	14.4	0.067	15.5	12.7	**0.005**
Diarrhea	12.0	10.7	0.095	10.9	9.9	0.212	11.5	10.4	0.169
Hives	0.7	0.6	0.651	0.8	0.8	0.974	1.4	1.1	0.379
Wheezing	0.1	0.1	>.999[3]	0.2	0.2	0.987	0.2	0.3	0.779
Blue Skin Tone	0.03	0.1	0.624[3]	0.1	0.0	0.500[3]	0.04	0.04	.999[3]
Gray/Ashen Skin	0.03	0.0	>.999[3]	0.04	0.0	.999[3]	0.0	0.0	–
Weak/letharg/limp	0.1	0.1	0.687[3]	0.1	0.1	0.686[3]	0.0	0.1	0.249[3]
Twitching	0.1	0.1	>.999[3]	0.1	0.1	0.687[3]	0.04	0.1	0.625[3]
Convulsions	0.3	0.0	>.999[3]	0.04	0.0	.999[3]	0.0	0.04	0.500[3]
Loss of Consc.	0.0	0.0	–	0.0	0.0	–	0.0	0.0	–

Adapted from Tables 56, 57, and 58, Volume 13, Part IV of PLA.
Number of subjects reporting may vary with systemic reaction reported.
[1] 91%, 58%, and 52% of infants received hepatitis B vaccine, and 91%, 93%, and 94% received OPV at doses 1, 2, and 3, respectively.
[2] Chi-Square test.
[3] Fisher's Exact test

10.4.2 Systemic Reactions with Concurrent DTaP + HbOC

Systemic reaction rates observed among the actively monitored subset of infants who received concurrent DTaP with the first 3 doses are most relevant to current practice in the U.S. In the NCKP efficacy trial, rates of febrile reactions were significantly greater in the 7VPnC group than in the MnCC group when administered with DTaP with the first 3 doses (See table below).

Rates of fever >39°C and irritability were significantly greater in the 7VPnC group after the 2nd dose. Hives were reported more commonly in the 7VPnC group after the first dose; however, no trend was apparent for subsequent doses. Loss of appetite occurred more frequently in the 7VPnC group after each dose; the difference was significant at the 3rd dose.

The list of systemic events solicited through telephone interviews in the NCKP trials are also shown in the following table. No convulsions were reported in either vaccine group. One event, possibly consistent with a hypotonic hyporesponsive episode, was reported in the 7VPnC group after the 2nd dose.

Table 22: Efficacy Study 118-8
Reported Systemic Events Within 48 Hours of Injection by Dose Among Infants Receiving DTaP, HbOC, OPV or IPV, Hepatitis B, and 7VPnC or MnCC

Systemic Reaction	Dose 1			Dose 2			Dose 3		
	7VPnC N=710 %	MnCC N=710 %	p-value[1]	7VPnC N=556 %	MnCC N=507 %	p-value[1]	7VPnC N=460 %	MnCC N=414 %	p-value[1]
Fever ≥38°C	**15.1**	**9.4**	**0.001**	**23.9**	**10.9**	**0.001**	**19.1**	**11.8**	**0.003**
Fever >39°C	0.9	0.3	0.178[2]	**2.5**	**0.8**	**0.029**	1.7	0.7	0.180
Irritability	48.0	48.2	0.936	**58.7**	**45.3**	**0.001**	51.2	44.8	0.059
Cry 3+ Hours	0.1	0.3	>.999[2]	0.4	0.0	0.501[2]	0.2	0.5	0.606[2]
Restless Sleep	15.3	15.1	0.914	20.2	19.3	0.705	25.2	19.0	**0.030**
More Sleep	40.7	42.0	0.637	25.6	22.8	0.296	19.5	21.9	0.380
Loss of Appetite	17.0	13.5	0.064	17.4	13.4	0.073	**20.7**	**13.8**	**0.008**
Vomiting	14.6	14.5	0.974	16.8	14.4	0.278	10.4	11.6	0.568
Diarrhea	**11.9**	**8.4**	**0.029**	10.2	9.3	0.611	8.3	9.4	0.539
Hives	**1.4**	**0.3**	**0.020**	1.3	1.4	0.857	0.4	0.5	>.999[2]
Wheezing	0.4	0.3	0.687[2]	0.0	0.6	0.108[2]	0.0	0.7	0.106[2]
Blue Skin Tone	0.1	0.0	0.500[2]	0.0	0.0	–	0.0	0.2	0.473[2]
Gray/Ashen Skin	0.0	0.0	–	0.0	0.0	–	0.0	0.0	–
Weak/letharg/limp	0.0	0.0	–	0.2	0.0	>.999[2]	0.0	0.0	–
Twitching	0.1	0.0	0.500[2]	0.2	0.2	>.999[2]	0.0	0.0	–
Convulsions	0.0	0.0	–	0.0	0.0	–	0.0	0.0	–
Loss of Consc.	0.0	0.0	–	0.0	0.0	–	0.0	0.0	–

Adapted from Tables 64, 65, and 66 of Clinical Study report, Volume 13, Part IV of PLA.
[1] Chi-Square test (Sponsor's analysis).
[2] Fisher's Exact test (Sponsor's analyss)
Number of subjects reporting may vary with systemic reaction reported.

After a 4th dose of 7VPnC administered concurrently with DTaP, rates of fever ≥38°C, and >39°C, within 48 hours were 21% and 1.3%, respectively. Fever rates in the MnCC group did not differ significantly. The subsets of subjects who received DTaP with study vaccine as a 4th dose may have received mixed regimens of pertussis vaccines with the first 3 doses. With the 4th dose, 90% of subjects received HbOC, 88% received MMR, and 49% received VZV.

Table 23: Efficacy Study 118-8
Reported Systemic Events Within 48 Hours of Injection Among Infants Receiving DTaP, HbOC, MMR, Varicella[1], and 7VPnC or MnCC, Dose 4

	7VPnC N=224 %	MnCC N=230 %	p-value[2]
Fever >39°C	1.3	1.7	>.999[3]
Fever ≥38°C	21.0	17.0	0.274
Irritability	44.2	42.6	0.733
Restless Sleep	20.2	19.1	0.779
More/Sounder Sleep	17.0	16.5	0.883
Loss of Appetite	20.5	23.1	0.502
Vomiting	4.9	4.8	0.949

Excerpted from Table 67 of Clinical Study Report, page 242, Volume 13 of PLA.
[1] 90% of DTaP recipients also received HbOC, 88% received MMR, and 49% received VZV.
[2] Chi-Square test. [3] Fisher's Exact test.

As allowed by the study protocol, some subjects received a 4th dose of study vaccines without any concurrent immunizations. Fever and common systemic reaction rates for these subjects are shown below. Irritability was reported significantly more often in the 7VPNC group. Fever rates did not differ appreciably between study groups.

Table 24: Efficacy Study 118-8
Reported Systemic Events Within 48 Hours of Injection
Among Infants Receiving 7VPnC or MnCC Only, Dose 4

	7VPnC N=644		MnCC N=627		p-value[1]
	n	%	n	%	
Fever ≥38°C	88	13.7	76	12.1	0.412
Fever >39°C	9	1.4	6	1.0	0.467
Irritability	294	45.6	221	35.1	**0.001**
Cry 3+ Hours	1	0.2	0	0.0	>.999[2]
Restless Sleep	133	20.7	133	21.3	0.806
More/Sounder Sleep	102	15.9	94	15.0	0.676
Loss of Appetite	125	19.4	115	18.3	0.617
Vomiting	44	6.8	39	6.2	0.653
Diarrhea	79	12.3	71	11.3	0.588

Adapted from Table 72, Clinical Study Report, Volume 13, Part IV of PLA
N may vary with systemic reaction
[1] Chi-square test
[2] Fisher's Exact test.

10.4.3 Systemic Reactions in Supporting Studies 118-12 and 118-16

In studies 118-12 and 118-16, the control groups did not receive MnCC or other investigational vaccines, and all infants received DTaP with the primary series. Safety data from these trials provide the clearest view of systemic reactions attributable to 7VPnC. In both studies active monitoring for fever and systemic events within 72 hours of injections were reported, rather than 48 hours as in the NCKP efficacy study.
Rates of systemic reactions in study 118-12 were similar between the pooled 7VPnC pilot lot groups and controls. Rates of fever ≥38°C were numerically greater in the 7VPnC groups after doses 2 and 3, however comparisons to control were not statistically significant.

Comment: Fever rates may have been spuriously low due to use of antipyretics, which were used significantly more often in the 7VPnC group after dose 2.

Table 25: Lot Consistency Study 118-12
Percent of Infants Reporting Systemic Event Within 72 Hours of Injection

Systemic Reaction	Dose 1			Dose 2			Dose 3		
	7VPnC N=256 %	Control N=86 %	p-value[3]	7VPnC N=245 %	Control N=82 %	p-value[3]	7VPnC N=239 %	Control N=80 %	p-value[3]
Fever ≥38°C	4.9	8.6	0.271	19.3	12.8	0.230	16.3	12.0	0.457
Fever >39°C	0.8	0.0	1.000	1.8	1.3	1.000	0.9	0.0	1.000
Drowsiness	48.6	38.8	0.132	31.5	22.8	0.156	27.4	9.1	**<0.001**
Fussiness	39.9	31.8	0.198	39.1	37.5	0.895	37.6	31.2	0.340
Decreased Appetite	17.8	15.3	0.740	12.7	16.5	0.448	13.2	14.3	0.848
Any Event	68.1	58.5	0.140	61.4	50.0	0.088	56.9	39.5	**0.011**
Use of Antipyretics	27.3	20.0	0.198	39.1	24.1	**0.021**	28.6	26.0	0.770

Adapted from Table 27, page 55, Volume 27, Part IV of PLA
* P-value based on Fisher's exact test (Sponsor's analysis).

In study 118-16, conducted at Kaiser Permanente centers, two manufacturing lots and one pilot lot were compared for safety and immunogenicity. Systemic events for the pooled 7VPnC groups versus control were provided in the clinical summary of the PLA. Fever ≥38°C was reported more frequently after each dose; differences relative to control were statistically significant after doses 1 and 2. Fever >39°C was reported more frequently after the 2nd dose (3.8%). Use of antipyretic agents was not reported in this study.

Table 26: Manufacturing Bridging Study 118-16
Percent of Infants Reporting Systemic Event Within 72 Hours,
7VPnC (All Lots) vs Control

Systemic Reaction	Dose 1			Dose 2			Dose 3		
	7VPnC N=498 %	Control N=108 %	p-value[1]	7VPnC N=452 %	Control N=99 %	p-value[1]	7VPnC N=445 %	Control N=89 %	p-value[1]
Fever ≥38°C	21.9	10.2	**0.005**	33.6	17.2	**0.001**	28.1	23.6	0.44
Fever >39°C	0.8	0.9	1.00	3.8	0.0	0.053	2.2	0.0	0.38
Irritability	59.7	60.2	1.0	65.3	52.5	**0.021**	54.2	50.6	0.56
Drowsiness	50.8	38.9	0.026	30.3	31.3	0.90	21.2	20.2	1.0
Decreased Appetite	19.1	15.7	0.49	20.6	11.1	**0.033**	20.4	9.0	**0.011**

Adapted from Table 30 of Integrated Clinical Summary, Volume 33, Part IV of PLA.
All subjects received DTaP+HbOC at each dose, Hep B at dose 1 and 3, and IPV at dose 1 and 2.
Pilot lot and 2 Manufacturing lots data pooled.
[1] P-value for comparison of pooled data to control (Sponsor's analysis).

10.4.4 Review Comments Regarding Systemic Reactogenicity

Assessment of systemic reaction rates and adverse events attributable to 7VPnC in the NCKP efficacy trial is complicated by concurrent recommended immunizations, including DTP-HbOC for most of the subjects, and use of an investigational vaccine (MnCC) in the comparator group.

In the NCKP efficacy trial, fever and systemic reactogenicity due to 7VPnC were detectable above background rates due to DTP-HbOC and other concurrent vaccines, as determined by comparisons to the MnCC group. Some systemic reactogenicity is likely due to MnCC. Therefore, comparisons to systemic reaction rates for MnCC may mask excess reaction rates attributable to 7VPnC.

In both the NCKP efficacy study, and in the supporting study 118-16, when 7VPnC was administered with DTaP and other concurrent vaccines with the first 3 doses, increased rates of fever ≥38°C, and fever >39°C were associated with 7VPnC, compared to control groups. Increased use of antipyretic agents was reported in study 118-12. Irritability, decreased appetite, and drowsiness were also associated with 7VPnC, but without consistent pattern.

Rates of fever increased with sequential doses when 7VPnC were administered with DTP-HbOC. When administered with DTaP and HbOC, rates of fever and systemic reactions did not appear to increase with sequential doses of 7VPnC.

Across studies, when 7VPnC was administered against a background of the concurrent vaccines most relevant to current practice (DTaP, HbOC, IPV, Hep B), rates of fever ≥38°C, and >39°C, were reported most frequently after dose 2. By dose, rates of fever ≥38°C ranged from 5%-22% after dose 1, 19%-34% after dose 2, and 19-28% after dose 3. Fever >39°C was reported for 0.6%-0.9% after dose 1, 1.8%-3.8% after dose 2, and 0.9%-2.2% after dose 3.

True associations of adverse events with study vaccines may be masked if the same adverse event occurs in both study groups. The similar composition of these two study vaccines, which are both polysaccharide conjugates using identical carrier proteins, may increase the likelihood that such true associations are missed.

Nevertheless, the absolute rates of mild and severe febrile reactions and other systemic reactions that have been observed in the Prevnar treatment groups across trials, appear to fall within a range of what has been acceptable historically in the U.S.

10.5 Adverse Events

10.5.1 Adverse events in the NCKP Efficacy Study (118-8)

All subjects in the NCKP efficacy trial were followed for adverse events through the use of automated databases used within the NCKP health care system. All hospitalizations within 60 days, and emergency room visits within 30 days, of each study vaccine dose were recorded with an accompanying diagnosis and reported in the PLA. Numbers and rates of outpatient clinic visits for specific diagnoses of interest (i.e. seizures, allergic reactions, including hives, and

wheezing, shortness of breath and asthma) occurring within 30 days of a vaccine dose were also recorded and provided in the PLA.

Events resulting in study termination were also reported. Incidence of SIDS in the study population was to be evaluated and compared to the SIDS rate in the entire NCKP population and to the overall state-wide rate. Diagnoses of neurologic disorders and anaphylactic reactions were to be followed for outcome.

10.5.1.1 Deaths

Eighteen deaths (8 in 7VPnC recipients and 10 in MnCC recipients) occurred in the NCKP efficacy trial on or prior to April 30, 1998. None of the deaths were considered by the investigators or the sponsor to be related to study vaccines.

Sudden Infant Death Syndrome (SIDS) was listed as the cause of 9 deaths (5 in the MnCC group, and 4 in the 7VPnC group). All of the deaths attributed to SIDS occurred ≥ 5 days after study inoculations.

Other causes of deaths were accidental (n=2), homicide (n=2), congenital anomalies (n=2), complications of prematurity (n=1), and bacterial leptomeningitis (n=1), Leigh's syndrome (1).

An additional 12 deaths (2 in 7VPnC, 10 in MnCC) were reported in a planned safety update, received September 13, 1999, for the period May 1,1998, through December 31, 1998. Causes of death in the 7VPnC group were diabetic ketoacidosis (1) and traumatic asphyxia (1). Causes of death in the MnCC group were SIDS (3), drowning (2), pneumococcal meningitis (1), SCIDS (1), glioblastoma (1), metachromatic leukodystrophy (1), and pneumonia in a child with Werdnig-Hofffman disease (pneumococcal meningitis and SCIDS case were discussed among case characteristics, above, and in attachment A). None of the deaths were judged related to study vaccines by the investigators.

The rate of SIDS for cases through December 31, 1998, were compared to State of California rates for 1996 and 1997.

Table 27: Efficacy Study 118-8
Rate of SIDS in Study Groups Compared with California SIDS Rates

	7VPnC	MnCC	State CA 1996	State CA 1997*
Number of SIDS cases	4	8		
Number vaccinated[1]	18,927	18,941		
Rate per 1000	0.2	0.4	0.6	0.6

Reproduced from October 18, 1999 submission to PLA
* 1997 rate is provisional
[1]Number of subjects receiving at least 1 dose

Note: FDA sought clarification that the SIDS rates calculated for the state of California had been adjusted to omit cases which occurred in the first 2 months

of life to assure that the California-wide rate was an appropriate comparator for the study population. At the advisory committee meeting, Dr. Black presented the SIDS rate for California to be 0.5 per 1000 for the period 1996-1997, after appropriate adjustment. Additional age and season adjusted SIDS rates were presented by Dr. Black at the VRBPAC meeting, comparing expected rates based on California state data, to observed rates within periods of 1 week, 2 weeks, 1 month, and 1 year of the most recent vaccine dose. For each period examined, the SIDS rate in the 7VPnC group was less than the expected SIDS rate (statistical comparisons and confidence intervals not provided).

Table 28: Efficacy Study 118-8
SIDS Rates, Age & Season Adjusted,
Comparison with SIDS Expected from the California State Data**

	< 1 week		≤ 2 weeks		≤ 1 month		≤ 1 year	
	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs
7VPnC	1.06	1	2.09	2	4.28	2	8.08	4
MnCC	1.06	2	2.09	3*	4.28	3*	8.08	8*

Adapted from November 5, 1999 VRBPAC presentation of Dr. Steve Black.
* plus one additional case classified as compatible with SIDS but occurring at 448 days of age.
** 1995-1997 data

10.5.1.2 Hospitalizations

Rates of hospitalizations occurring within 3, 14, 30 and 60 days of a vaccine dose were calculated for all recorded diagnoses, and comparisons made between treatment groups. At least 92 separate hospitalization diagnoses were recorded. Comparisons between treatment groups for each diagnosis were provided, based type of concomitant pertussis vaccine received (DTP or DTaP), and on occurrence after any of the first 3 doses ("primary series"), after the 4th dose, or all doses combined. Among the multiple comparisons made, significantly increased ($p<0.05$, uncorrected for multiple comparisons) hospitalization rates were observed for certain comparisons for the diagnoses of seizures, asthma, gastroenteritis, and epilepsy, as described below.

Febrile Seizures: Rates of hospitalizations for febrile seizures within 30 days and 60 days of a study vaccine dose were significantly greater in 7VPnC group than the MnCC group during the primary series, and across all doses, when given concurrently with whole cell pertussis containing vaccine (DTP-HbOC). Hospitalizations for febrile seizures during the intervals more proximal to the vaccine doses (3 and 14 days), were not significantly increased.

Hospitalization rates were not significantly increased in the 7VPnC group for any interval when administered with acellular pertussis containing vaccine (DTaP).

Asthma: Hospitalizations for asthma within 60 days of a vaccine dose were significantly greater in the 7VPnC after doses of the primary series when administered concurrently with DTaP (11 events in 7VPnC group vs. 3 in the MnCC group).

Comparisons after the 4th dose, and across all doses combined, did not show increased rates in the 7VPnC group. When administered with DTP-HbOC, all comparisons across all observation intervals, and across all doses, showed no significantly increased hospitalization rates for asthma.

Gastroenteritis: Hospitalizations for gastroenteritis within 14 days of a vaccine dose were significantly greater in the 7VPnC group, after doses of the primary series and for all doses combined, regardless of concomitant pertussis vaccine. Hospitalization for gastroenteritis within 3 days, 30 days, and 60 days were not significantly elevated for any comparison, regardless of concomitant pertussis vaccine type or dose series.

(**Note:** 9 cases of intussusception were reported in the trial, 5 in the 7VPnC group and 4 in the MnCC group; rotavirus vaccination was not allowed by protocol).

Epilepsy: Hospitalizations for epilepsy within 30 days of a vaccine dose were significantly more frequent in the MnCC group. All other comparisons for epilepsy showed no differences between groups.

10.5.1.3 Emergency Room Visits

Rates of emergency room visits occurring within 3, 14, and 30 days of a vaccine dose were calculated for all recorded diagnoses, and comparisons made between treatment groups. Comparisons between treatment groups of ER visit rates by diagnosis were made in a manner similar to that used to compare hospitalization rates. At least 80 ER diagoses were listed; comparisons were provided for each diagnosis based on type of concomitant pertussis vaccine received (DTP or DTaP), and on occurrence after any of the first 3 doses ("primary series"), after the 4th dose, or all doses combined. Among the multiple comparisons made, significantly increased ($p<0.05$, uncorrected for multiple comparisons) ER visit rates were observed for certain comparisons.

Croup: ER visits for croup within 3 days of a vaccine dose were significantly more common in the 7VPnC group after doses of the primary series when subjects receiving concomitant DTP and DTaP were combined. ER visits for croup after the 4th dose, and for all doses combined, were not significantly elevated.

Breath holding: ER visits for a diagnosis of breath holding were increased in the 7VPnC group for the 30 day post-vaccination period, when all doses were combined. ER visit rates for breath holding were not increased for the periods more proximal to the vaccine dose (3 and 14 days).