Clinical Review of New Product License Application

PLA 92-0279

Prevnar™

Seven Valent Pneumococcal Conjugate Vaccine

Date Application Received: June 1, 1999
Date Review Completed: February 14, 2000

1.0 General Information

Product Names: Prevnar™
Pneumococcal 7-valent Conjugate Vaccine
(Diphtheria CRM_{197} Protein)

Manufacturer: Wyeth-Lederle Vaccines and Pediatrics

Proposed Indication: Prevention of invasive disease caused by *Streptococcus pneumonia*

Dosage Form: Liquid, single use vials, preservative-free

Adjuvant: Aluminum phosphate

Route of Administration: Intramuscular

Review committee:

Carl Frasch	Chairperson
Douglas Pratt	Clinical review
Lydia Falk	Regulatory review/DVRPA
Carolyn Deal	Carolyn Deal/DBP
Pamela Getson	Biostatistics
Robert Lee	Product manufacturing & physical-chemical characterization
C.J. Lee	Product manufacturing and QC for release testing
Nelydia Concepcion	Immune response, including assay validation
Kirsten Vadheim	ELA/facilities
Mary Andrich	Bioresearch monitoring
Patrick Swann	Pre-clinical/toxicology review

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3.0 Introduction and Background

3.1 Epidemiology of pneumococcal infections in children

Streptococcus pneumoniae is a common bacterial cause of pneumonia, otitis media, bacteremia, and meningitis. Children under the age of 2 years and individuals with abnormalities in host defense are most susceptible to pneumococcal disease. Active Bacterial Core Surveillance (ABCs) data from 1998 showed that invasive pneumococcal infection (bacteremia, meningitis, or infection of a normally sterile site) rates in U.S. children aged <12 months and 12-23 months were 165 and 203 cases per 100,000 population, respectively. The peak incidence rate occurred among children 6-11 months of age (236 per 100,000). Higher rates of invasive pneumococcal disease were found among certain racial/ethnic groups (i.e., African-Americans, Alaskan Natives, and specific American Indian groups).

In a retrospective analysis within Northern California Kaiser Permanente, 554 culture-confirmed cases were identified in children 0-4 years of age from 1988 to 1991. The highest incidence was for children less than 18 months of age (241/100,000 in those 12-17 months of age, 177/100,000 in those 6-11 months of age).

3.2 Rationale for chosen formulation

Two 23-valent unconjugated polysaccharide vaccines are currently licensed for use in adults, and for use in some children over the age of 2 years who are at high risk of invasive pneumococcal disease. Efficacy of these polysaccharide vaccines against invasive disease caused by pneumococci has not been demonstrated for infants and young children. Unconjugated polysaccharide antigens have been shown to be poorly immunogenic in infants and very young children.

Chemical linkage, or conjugation, of bacterial capsular polysaccharides to certain proteins produces antigens capable of stimulating antibody production in infants. This strategy was highly successful in the development vaccines against Haemophilus influenza type B (HIB) infections in infants and small children. Wyeth-Lederle has marketed conjugate HIB vaccine based on the same carrier protein (CRM_{197}) used in Prevnar.

Prevnar contains conjugated polysaccharides of the 7 most prevalent pneumococcal serotypes (types 4, 6B, 9V, 14, 18C, 19F, and 23F) which account for approximately 80% of invasive pneumococcal disease in infants and young children in the U.S. In a surveillance study conducted at Northern California Kaiser Permanente, these 7 serotypes accounted for 83% of invasive disease among the 136 cases identified between 1992 and 1994 in children less than 4 years of age.

3.3 Regulatory background

Wyeth-Lederle Vaccines and Pediatrics submitted a Product License Application (PLA) to FDA/CBER on June 1, 1999, for Prevnar™, a 7-valent, polysaccharide-protein conjugate vaccine for prevention of disease caused by *Streptococcus pneumoniae*. FDA/CBER granted priority review status to the application, and committed to an expedited review, based on the severity of disease for which the vaccine would be indicated, i.e., "invasive pneumococcal disease (meningitis and bacteremia)", lack of alternative licensed vaccines for use among infants and small children, and preliminary results indicating substantial evidence of efficacy. Preliminary efficacy data were presented to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) at the November 19,1998 meeting.

With submission of this PLA, regulatory approval was requested to market Prevnar:

"For active immunization of infants and children beginning as early as 6 weeks of age to help protect against invasive diseases caused by *Streptococcus pneumoniae* due to the capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, 23F)"

At the VRBPAC meeting of November 5, 1999, FDA/CBER sought advice from the committee about the adequacy of the safety and efficacy data provided in the PLA to support the indication for prevention of invasive pneumococcal disease.

Although efficacy of Prevnar in preventing acute otitis media and pneumonia was examined among the secondary and tertiary endpoints in the large pivotal efficacy study, these potential indications were not the focus of the initial license application and were only briefly discussed in the sponsor's presentation at VRBPAC.

An abbreviated chronology of some key elements in the clinical development and review of Prevnar is presented below:

Chronology of Clinical Development

IND 5832 filed (7-valent)	November 1994
NCKP efficacy study initiated	October 1995
Safety data base of efficacy trial locked	April 30, 1998
Primary efficacy analysis	August 20, 1998
Otitis media analysis plan finalized	November 1998
Pneumonia analysis plan finalized	March 3, 1999
Efficacy trial unblinded, case ascertainment ends	April 20, 1999
Manufacturing-bridging study complete	May 17, 1999
PLA Submitted	June 1, 1999
FDA/CBER accepts PLA as complete	July 13, 1999
Advisory committee meeting	November 5, 1999
Major amendment: Additional "catch-up" data received	December 17, 1999
Phase 4 protocols received	January 31, 2000

4.0 Product characteristics

Prevnar is a liquid formulation. Each 0.5 mL vaccine dose contains 15-26 μg of CRM_{197} carrier protein, a non-toxic variant of diphtheria toxin. Total pneumococcal saccharide content of 16 μg; serotype specific saccharide content for each component is:

- 2 μg of polysaccharide for serotypes 4, 9V, 14, 19F, and 23F,
- 2 μg of oligosaccharide for serotype 18C,
- 4 μg of polysaccharide for serotype 6B

Each dose of 7VPnC also contains 0.5 mg of aluminum phosphate adjuvant. The formulation contains no thimerosal or other preservatives.

The control vaccine used in several of the clinical studies, including the pivotal efficacy study, is an investigational meningococcal C vaccine (MnCC), also manufactured by Wyeth-Lederle Vaccines and Pediatrics. Each 0.5 mL dose of liquid formulation of MnCC contains 10 μg of group C oligosaccharides coupled to CRM_{197}. MnCC also contains 0.5 mg of aluminum phosphate adjuvant.

The two study vaccines vials are identical in appearance.

For detailed description and evaluation of manufacturing methods, please refer to review of Dr. Robert Lee.

5.0 Pre-clinical and toxicology studies

Please refer to the review of Dr. Patrick G. Swann.

6.0 Clinical Studies Reviewed

The clinical section of the application contains study reports for 8 clinical studies and supporting data from 3 additional studies. An integrated clinical summary is also provided.

In the tables and summaries that follow, Prevnar, 7-valent pneumococcal conjugate vaccine, is referred to as 7VPnC, meningococcal group C conjugate vaccine is referred to as MnCC.

Table 1: Clinical Studies in the Product License Application

Study Number	Population	Schedule (Months)	Control	Regulatory Objective/ Other Information
D92-P5	Infants	2, 4, 6	No 5VPnC	Saccharide model and dose selection
	Toddlers	15-18	None	PNU-IMUNE®23 Boost
D118-P2	Adults	18-60 yr	PNU-IMUNE®23	Safety, immunogenicity in adults
D118-P3	Infants	2, 4, 6, 12-15	MnCC	Safety and Immunogenicity Support MnCC as control for Phase 2 and 3
D118-P7	Infants	2, 4, 6, 12-15	MnCC	Pilot for Efficacy Study; Safety and Immun. Compatibility with Hep B
D118-P8	Infants	2, 4, 6, 12-15	MnCC	Efficacy: invasive disease, AOM, pneumonia; Large safety data base for adverse events; Safety when given with DTP or DTaP
D118-P9	Toddlers	15-24	7VPnC	2 Lots of 7VPnC;
D118-P12	Infants	2, 4, 6	No vaccine	Pilot Lot Consistency;
	Infants	7, 9	None	Safety and reactogenicity given with DTaP;
	Toddlers	15-18	None	Catch-up data; Compatibility with HbOC, DTaP;
D118-P15	Infants	2, 4, 6, 12-15	MnCC	Ongoing efficacy study, Navajo and Apache;
	Toddlers	Various	MnCC	Only catch-up immunogenicity data provided
D118-P16	Infants	2, 4, 6	No vaccine	Bridging from pilot to manufacturing; Safety and reactogenicity given with DTaP; Compatibility with HbOC, HepB, IPV;
D124-P2	Infants	2, 4, 6	7VPnC	Compatibility with MMR, immunogenicity data
	Toddlers	12-15	None	obtained with 9-valent formulation
D124-P501	Toddlers	12-17	MnCC	Immunogenicity data for catch-up obtained
		18+	MnCC	with 9-valent formulation

All data supporting efficacy data, and the bulk of the safety data in the application, derive from the Northern California Kaiser Permanente (NCKP) efficacy trial, Study 118-8.

Other studies considered essential for licensure include:

- 118-12, the lot consistency study
- 118-16, which provided clinical evidence of ability to scale up production by bridging lots produced at the pilot scale to manufacturing scale lots.

Summaries and comments regarding non-pivotal supporting studies are found in Attachment B.

As shown in the table above, MnCC was used as a control vaccine for some studies, including the large-scale efficacy trial. Only two infant studies (118-12 and 118-16) compared the safety profile of 7VPnC against a 'no additional vaccine' control.

Safety and immunogenicity data, intended to support vaccination schedules for previously unvaccinated older children, so-called catch-up schedules, were submitted from studies 118-16 and 118-18; these studies were completed and study reports submitted as a major amendments to the PLA after the November 5, 1999 advisory committee meeting. However, because of the importance of these data in guiding catch-up in the immediate period post-licensure, the data were reviewed expeditiously for possible inclusion in the initial package insert.

Not included in the application are data from studies addressing safety and immunogenicity among children from some high-risk populations, such as children with sickle cell disease, HIV infection, Hodgkin's disease, and nephrotic syndrome. Also not included in the application are data from a trial conducted in Finland to evaluate the effectiveness of 7VPnC in preventing otitis media.

7.0 Analysis of Efficacy

Protective efficacy of Prevnar against invasive pneumococcal disease was studied in a single, large-scale trial.

Pivotal Efficacy Study 118-08: Evaluation of the Safety, Immunogenicity and Efficacy of Heptavalent Pneumococcal Conjugate Vaccine and Safety of Meningococcal Group C Conjugate Vaccine in Infants at 2, 4, 6 and 12-15 Months of Age in Northern California Kaiser Permanente (NCKP) Medical Care Program

7.1 Timetable of Study Events

The study was initiated in October 1995; enrollment ceased August 24, 1998, after results of the planned interim analysis demonstrated substantial evidence of efficacy. The safety database had been locked on April 30, 1998, in order to verify data and prepare the study report in anticipation of imminent accrual of sufficient cases to conduct the interim efficacy analysis. Follow-up of infants for invasive pneumococcal disease and serious adverse events continued through April 20, 1999, at which time vaccine assignments were unblinded to all study personnel and families of subjects. The 7VPnC vaccine was then offered to subjects in the control group.

7.2 Objectives

7.2.1 Primary objective

To determine the protective efficacy of 7VPnC against invasive pneumococcal disease caused by serotypes represented in the vaccine.

A case of invasive pneumococcal disease was defined as a positive culture of *S. pneumoniae* from a normally sterile body site (e.g. blood, CSF, joint fluid) obtained from a child presenting with an acute illness consistent with pneumococcal disease.

7.2.2 Secondary objectives

Multiple secondary objectives relevant to the licensure of Prevnar were also specified:

- To assess the safety and tolerability of 7VPnC
- To determine the protective efficacy of 7VPnC among all enrolled subjects (intent-to-treat)
- To evaluate the effectiveness of 7VPnC on overall invasive pneumococcal disease, regardless of serotype
- To assess the effectiveness of 7VPnC on rates of acute otitis media and pneumonia using computerized data sources
- To assess the immunogenicity of 7VPnC following after a 3 dose series administered at 2, 4, and 6 months of age, and after a 4th dose given at 12-15 months of age.

7.3 Study Vaccines, dose and administration

7.3.1 Vaccines used

During the efficacy study, 11 different pilot lots of 7VPnC, and 12 different pilot lots of MnCC were used.

Licensed vaccines used in the study were: DTP-HbOC (Tetramune), OPV (Orimune), DTaP (Acel-imune), HbOC (HibTITER), MMR, Varicella, Hepatitis B (Recombivax HB), and IPV (IPOL).

In the original protocol, DTP-HbOC (Tetramune) and OPV (Orimune) were given concurrently with study vaccine at 2, 4, and 6 months of age. Subjects could also receive one or more doses of hepatitis B vaccine concurrently.

Amendment # 2, implemented August 1996, allowed for the substitution of DTaP and HbOC for DTP-HbOC, and for the substitution of inactivated poliovirus vaccine (IPV) for OPV for immunization of infants at 2, 4, and 6 months of age.

7.3.2 Schedule and Dose Administration

Subjects received 0.5 mL i.m. injections of either 7VPnC or MnCC vaccine at 2, 4, 6 and 12-15 months of age.

Allowable time frames for study vaccine administration were:

- Dose 1: 42-120 days after birth,
- Dose 2: 35-120 days after the first dose
- Dose 3: 35-120 days after the second dose
- Dose 4: 12 to 15 months of age, and at least 60 days after dose 3.

At 12-15 months of age, DTP-HbOC or DTaP and HbOC (HibTITER), MMR, and varicella vaccine could be given concurrently.

Study vaccines were given in the left thigh. Other concurrently administered injectable vaccines were to be inoculated into the right thigh or deltoid, as appropriate.

7.4 Study Design and Conduct

This was a randomized, double-blind, controlled, multi-center trial.

7.4.1 Randomization and Blinding

Healthy infants were randomly assigned to receive 7VPnC or MnCC, identified by A, B, C, or D in the following way: randomization was nested within each study site, block sizes were randomly chosen among 4, 6, 8, and 10, with treatment groups equally allocated. Treatment assignments (A, B, C, or D) were randomly permuted within each block. The group code assignments were entered by the study nurse into the child's study casebook and the injection log, but were not recorded on the subject's chart, computer records or in any other documents. Group assignment was known to the study nurse and dedicated nurse vaccinator at each site, to the NCKP statistician, and to the NCKP and Wyeth-Lederle clinical monitors. Group assignments were not to be disclosed to parents of children in the study, others involved with the child's care or involved in the trial, including pediatricians, study investigators, and telephone interviewers.

7.4.2 Study population

Healthy male and female infants age 2 months (range 42-120 days) enrolled in the NKKP health care system were eligible to participate.

It was originally estimated that 60% of ~24,000 eligible infants per year at the NCKP would be enrolled over a period of 26 months, at a rate of 1200 subjects/month for a total anticipated enrollment of 31,200. The minimum duration of subject participation was to be 10-14 months.

7.4.2.1 Inclusion criteria

- Infants (42-120 days of age) who were in good health as determined by medical history, physical examination and clinical judgment
- Availability of legal caretakers by telephone for follow-up during the entire study period (10-14 months)
- At least one parent who could understand and sign the informed consent

7.4.2.2 Exclusion criteria

- Known or suspected disease of the immune system including HIV infection, or those receiving immunosuppressive therapy
- Progressive neurological disease
- Uncontrolled epilepsy/infantile spasms or history of seizures
- Any serious chronic disease (such as signs of cardiac or renal failure, or failure to thrive
- Sickle cell disease, functional or anatomic asplenia, Down syndrome, or nephrotic syndrome
- Known hypersensitivity to any of the components of the vaccines used in the study
- History of invasive pneumococcal disease
- History of idiopathic thrombocytopenic purpura
- Prior receipt of any vaccine other than vaccine for hepatitis B.
- History of meningococcal disease (defined as a positive culture of *N. meningitidis* from a normally sterile body site)
- If inactivated poliovirus immunization is indicated

Notes:

1) The last of the exclusion criteria was deleted with Amendment #2, which allowed the administration of IPV according to current immunization recommendations.

2) No specific exclusion was made for infants born prematurely. Premature infants could be enrolled if they were judged to be in good health.

7.5 Case definition: Invasive disease

A case of invasive pneumococcal disease was defined as a positive culture of *S. pneumoniae* from a normally sterile body fluid (e.g. blood, CSF, joint fluid) obtained from a child presenting with an acute illness consistent with pneumococcal disease.

Isolates of *S. pneumonia* were identified by standard microbiological techniques at the NCKP Regional Microbiology laboratory. Isolates were serotyped by the Quellung reaction using specific antisera by Dr. Robert Austrian at U. of Penn. School of Medicine and in the reference laboratory of [redacted]

7.6 Case Surveillance and Ascertainment: Invasive disease

Surveillance for cases of invasive pneumococcal disease was conducted weekly at each study site by review of all positive cultures for pneumococcus from normally sterile body sites among children < 9 years of age, generated from the NCKP Regional Microbiology database. Listings of children discharged from NCKP hospitals with diagnoses compatible with invasive pneumococcal disease were conducted monthly.

7.6.1 Per-protocol follow-up: Invasive disease

The per-protocol follow-up period started 14 days after dose 3. A subject was considered vaccinated per-protocol if the following criteria were met:

- first dose administered after 42 days of age minimum 35 days between primary series doses
- third dose given by 365 days of age
- booster dose administered between 365 days (12 months) and 480 days (16 months), and ≥ 60 days between primary series and booster dose
- subject did not have acquired or congenital immune deficiency; children who developed invasive disease were to be requested to undergo screening to rule out immune deficiency

7.6.2 Intent-to-treat follow-up: Invasive disease

Intent-to-treat follow-up began immediately following randomization, and included all subjects who were randomized into the study.

7.6.3 Termination of follow-up for efficacy against invasive disease

Follow-up for subjects in the primary efficacy analysis ended with:

a) onset of invasive pneumococcal disease of any serotype not vaccinated according to protocol

b) declaration of efficacy at early or primary analysis

7.7 Efficacy Endpoints: Invasive disease

7.7.1 Primary endpoint

The primary efficacy outcome was prevention of invasive disease caused by one of the 7 targeted pneumococcal serotypes among subjects vaccinated according to protocol during the per-protocol follow-up period.

7.7.2 Additional efficacy endpoints

Other prospectively defined study endpoints were:

7.7.2.1 Efficacy against invasive disease under intent-to-treat

7.7.2.2 [redacted]

7.7.2.3 [redacted]

7.7.2.4 [redacted]

Comment: Endpoints for evaluating vaccine effectiveness against acute otitis media and pneumonia, as ascertained from clinical diagnoses in computerized data sources, were also specified prior to unblinding. However these results are not the focus of the present expedited review, as the indication currently sought is for prevention of invasive disease.

7.8 Efficacy analysis plan

The final analysis plan for invasive disease at the time of unblinding differed from that proposed in the original protocol. The original analysis plan had included group sequential procedures for as many as 3 analyses at the 3 respective case accruals of 8, 20, and 40 cases, with stopping rules for case splits at each look. FDA did not recommend the earliest look at 8 cases. As the trial progressed, the sponsor requested a determination for a minimum number of cases for which an interim analysis might be conducted, with specific case splits which would be acceptable to FDA for termination of enrollment and a claim of efficacy. Agreement was reached in a meeting between representatives of Wyeth-Lederle and FDA on November 3, 1997, to modify the sequential analysis plan, by eliminating the look at 8 cases. Instead one interim analysis would occur after 17 cases of invasive pneumococcal disease due to vaccine serotypes had accrued among children who were vaccinated per protocol.

The test criterion at the interim analysis was specified as follows: If no more than 2 cases, out of a total of 17, were observed in the vaccinated group (7VPnC group), the vaccine was to be considered efficacious and the trial was to be stopped for evidence of efficacy. Exact confidence limits derived from exact binomial distributions.

Table 2: Efficacy Study 118-8
Acceptable Case Splits for Stopping at Interim Analysis

Number of Cases		Vaccine Efficacy	95% Lower Conf. Limit	
Vaccinated	Control	Estimate	one-sided	two-sided
0	17	100	80.7	75.7
1	16	93.8	66.6	59.7
2	15	86.7	51.5	42.6

Adapted from Table 2, page 84, Volume 13 of PLA

Protective efficacy against invasive pneumococcal disease was estimated as

$$e = 1 - r$$

where r is the ratio of attack rate in the 7VPnC group versus that in the MnCC group. Given that more than 30,000 children were randomized at a 1:1 ratio to the two vaccine groups, the amount of follow-up time in the two groups were expected to be nearly equal. The rate ratio estimate r, then, equals the ratio of the number of cases in the 7VPnC group versus that in the MnCC group.

8.0 Results of efficacy analysis

8.1 Subject disposition

Enrollment into the efficacy trial was terminated August 24, 1998. At that time, nearly 38,000 infants had been randomized and received at least one dose of study vaccines. Exact follow-up times for all subjects were not available at the time of the primary analysis in August. 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. 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, and therefore the confidence intervals would not change.

Table 3: Efficacy Study 118-8
Invasive Disease Primary Analysis,
Number of Subjects and Follow-up Time (Aug 20, 1998)

	7VPnC	MnCC	Total
Per protocol			
Subjects	15,161	15,115	30,276
Follow-up (child-year)	16,834	16,828	
Intent-to-treat			
Subjects	18,906	18,910	37,816
Follow-up (child-year)	26,773	26,757	

Approximately 7,500 randomized subjects were not included in the per-protocol analysis, but were included in the intent-to-treat analysis.

Reasons for exclusion from the per protocol analysis and protocol violations were provided as supplemental to the PLA. The most common reasons for exclusions were: failure to receive the 3rd dose by the data cut-off and, and 3rd dose not given within the first year of life. Children were also excluded for failure to receive

study vaccines in the designated time frames, receipt of incorrect vaccines, failure to meet entry criteria, receipt of immunoglobulin, invasive disease, and death.

Loss of health plan membership did not result in exclusion from the per protocol analysis, unless a dosing violation occurred.

Children who did not receive all doses because of adverse events were listed among dosing violations in the table of per protocol exclusions. Adverse events resulting in termination of dosing are listed in the safety review section.
Note: The number of subjects randomized as shown in the following table, differs from the number of subjects evaluated at the efficacy analysis as shown in the previous table, because the data cut-off for determining follow-up was April 30, 1998 while the primary analysis took place 4 months later.

Table 4: Efficacy Study 118-8, Per Protocol Exclusions

	7VPnC	MnCC
Number of subjects randomized	17,070	17,076
Number excluded from per protocol	3696	3723
Reasons for exclusion		
Dose 3 not given by data cut-off	2859	2877
Dose 3 not given by age 1 year	629	607
Dose 1 given <42 days, or > 120 days	35	35
Interval between doses 1 & 2 < 35 d.	15	19
Interval between dose 2 & 3 < 35 d.	32	36
Received incorrect vaccine	29	48
Other	97	101
Follow-up time truncated	1300	1289
Dose 4 not given by 16 months of age	1213	1171
Age at dose 4 < 12 months	41	69
Other	46	49

Excerpted from Tables 6 and 7 of September 29, 1999 submission to PLA

Comments:

1) The number of subjects excluded appears to be fairly well balanced between study groups by reason for exclusion.
2) Receipt of incorrect vaccine would be expected to reduce any observed treatment effect by narrowing differences between groups.

8.2 Demographics

Demographic information was collected for a randomly selected subset of about 7500 subjects from whom local reaction and systemic event data were collected via telephone interview. The subset was selected based on the last digit of the subject's medical record number.

Comment: The two study vaccine groups appear to be well balanced with respect to race/ethnicity.

Table 5: Efficacy Study 118-8,
Race/Ethnicity As Reported at 48 Hour Interview After Dose 1

	Asian %	Black %	Hispanic %	White %	Multi-ethnic %	Other/ Unknown %	p-value[2]
7VPnC (N=3708)	13.4	7.7	19.6	39.3	19.4	0.6	0.123
MnCC (N=3693)	13.0	8.4	17.9	40.5	19.3	1.0	

Reproduced from Table 11, page 89, Volume 13 of PLA
1 Telephone interviews conducted October 16, 1995 – April 30, 1998
2 Chi-Square Test (sponsor's analysis)

8.3 Efficacy

The planned interim analysis following accrual of the 17th case of invasive pneumococcal disease due to vaccine serotype, which took place on August 20, 1998, is considered the primary efficacy analysis.

8.3.1 Primary efficacy analysis

A total of 17 cases of invasive disease due to vaccine serotypes accrued among fully vaccinated children during the per-protocol follow-up period at the time of the interim analysis. All 17 cases were in the MnCC group. The point estimate of vaccine efficacy for the primary analysis was 100% (95% CI: 75.4%, 100%)

Results of the intent-to-treat analysis were consistent with vaccine efficacy observed in the per-protocol analysis. No cases of invasive disease were observed among children either fully or partially immunized with 7VPnC.

Table 6: Efficacy Study 118-8
Efficacy Against Invasive Pneumococcal Disease -Primary Analysis

Invasive Pneumococcal Disease (Cases through August 20, 1998)	Number of Cases		Vaccine Efficacy Estimate (VE)	95% Confidence Limits* of VE
	7VPnC	MnCC		
Vaccine Serotypes				
Per-Protocol	0	17	100%	(75.4%, 100%)
Intent-to-Treat	0	22	100%	(81.7%, 100%)
All Serotypes				
Per-Protocol	2	20	90.0%	(58.3%, 98.9%)
Intent-to-Treat	3	27	88.9%	(63.8%, 97.9%)

Adapted from Tables 17 page 105 , Volume 13 of PLA, and Table 5, page 25 of June 8, 1999 submission to the PLA.
* Two-sided P-values were determined based on exact binomial distributions and confidence limits were also determined based on exact binomial distributions (Sponsor's analysis).

8.3.2 All serotype invasive pneumococcal disease

Eight additional cases of invasive disease due to non-vaccine serotypes had accrued by the time of the primary analysis. Three cases occurred in the 7VPnC group and five cases in the MnCC group. Vaccine efficacy for all serotypes in the intent-to-treat analysis was 88.9% (95% CI: 63.8%, 97.9%).

8.3.3 Serotype Distribution of Cases

The proportion of all invasive disease due to vaccine serotypes at the time of the primary analysis was 81.5% (22/27). The most common vaccine serotype was 19F. No invasive disease cases due to pneumococcal serotype 4 were observed.

Table 7: Efficacy Study 118-8
Serotype Distribution of Cases of Invasive Pneumococcal Disease, Cases Accrued Through August 20, 1998

	Number of Cases (Percentage* due to Each Serotype)			
	Fully Vaccinated Children		All Randomized Children	
Vaccine Serotypes	7VPnC	MnCC	7VPnC	MnCC
19F	0	7 (35.0%)	0	8 (29.6%)
18C	0	4 (20.0%)	0	4 (14.8%)
6B	0	2 (10.0%)	0	3 (11.1%)
9V	0	2 (10.0%)	0	2 (7.4%)
14	0	1 (5.0%)	0	2 (7.4%)
23F	0	1 (5.0%)	0	3 (11.1%)
4	0	0 (0%)	0	0 (0%)
Total	0	17 (85.0%)	0	22 (81.5%)
Non Vaccine Serotypes				
38	1	1 (5.0%)	1	1 (3.7%)
3	0	1 (5.0%)	0	1 (3.7%)
19A	0	1 (5.0%)	0	1 (3.7%)
10F	1	0 (0%)	1	0 (0%)
18B	0	0 (0%)	0	1 (3.7%)
11A	0	0 (0%)	0	1 (3.7%)
23A	0	0 (0%)	1	0 (0%)
Total	2	3 (15.0%)	3	5 (18.5%)
All Serotypes Total	2	20	3	27

Adapted from Table 18, Clinical Study Report, Volume 13 of PLA.
* Percentage of the number of all invasive pneumococcal disease cases in MnCC group.

8.3.4 Vaccine Efficacy by Dose

At the time of the primary analysis, 10 cases of invasive disease had accrued between the 3rd and 4th doses, and 7 additional cases occurred after the 4th dose. Vaccine efficacy was calculated for cases accrued up to each of the 4 doses, as shown in the table below:

Table 8: Efficacy Study 118-8
Efficacy Against Invasive Disease by Dose,
(Cases Accrued Through August 20, 1998)

Invasive Pneumococcal Disease	Number of Cases		Vaccine Efficacy Estimate (VE)	95% Lower CI* of VE
	7VPnC	MnCC		
Vaccine Serotypes				
≤ 2 doses	0	5	100%	-9.2%
3 doses	0	10	100%	55.3%
4 doses	0	7	100%	30.6%
All doses	**0**	**22**	**100%**	**81.7%**
All Serotypes				
≤ 2 doses	1	7	85.7%	-11.2%
3 doses	2	10	80.0%	6.1%
4 doses	0	10	100%	55.3%
All doses	**3**	**27**	**88.9%**	**63.8%**

Adapted from Table 20, Clinical Study Report, Volume 13 of PLA.
* Two-sided P-values were determined based on exact binomial distributions and confidence limits were also determined based on exact binomial distributions.

In the primary (per protocol) analysis, 10 cases of invasive disease accrued in the control group vs. 0 cases in the 7VPnC group after 3 doses (lower 95% CI, 55%). Including the 7 additional cases that accrued after the 4th dose into the analysis as planned, the 95% lower bound of the CI for efficacy is 75%, a result which may be characterized as "highly efficacious".

Comment:

While 3 doses of 7VPnC resulted in 100% efficacy (lower 95% confidence interval above 50%), the trial design did not allow for an assessment of the durability of protection beyond 12 months of age. The efficacy study could have been conducted in such a way that children would receive only the 3 doses at 2, 4, and 6 months of age, with subsequent surveillance and accrual of cases over an extended period. Consistent with traditional infant vaccine schedules in the U.S., and the successful experience with Hib vaccines, the sponsor chose to administer a 4th dose of 7VPnC at 12-15 months of age, with continued follow-up for cases into the 2nd year of life and beyond. This study design might be expected to increase the chance of a favorable outcome. However, it is not possible to know what would have occurred past 12 months of age if children had received only the 3 doses. Whether a 4th dose is essential to assure long term protection to infants previously immunized with 3 doses, or simply provides a supplementary "boost" of protective insurance, has not been determined. Therefore, unless additional data indicate that 3 doses are sufficient for protection beyond 1 year of age, the 4th dose should be considered an essential dose in the vaccine series.

8.3.5 Invasive Disease Case Characteristics

Case narratives for each of the invasive disease cases were provided upon FDA request. Pneumococcus was isolated from the blood of all cases; those with meningitis also had CSF isolates.

Among the 22 vaccine serotype cases at the time of the primary analysis, no deaths were reported. Two infants < 6 months of age developed meningitis. One infant, who was diagnosed with meningitis, had residual hearing loss; all other children recovered fully.

Hospitalizations for invasive disease were uncommon, but more likely in the younger children. One child older than 1 year of age (14.5 mo) was hospitalized, while 3 infants less than 6 months of age (3.0, 4.5, and 4.6 mo) were hospitalized for invasive disease.

Pneumococcal isolates with decreased susceptibility to penicillin accounted for 41% (9/22) of the pneumococcal isolates.

Table 9: Efficacy Study 118-8
Characteristics of Cases of Invasive Disease at Primary Analysis, All Cases in the MnCC Group (N=22)

	Subjects in Per Protocol Efficacy Analysis (Fully Vaccinated)*	Additional Subjects in the Intent-to-Treat Efficacy Analysis (Partially Vaccinated)	Total
Characteristic	N=17	N=5	N=22
Age < 12 months	7	5	12
Age ≥ 12 months	10	0	10
Source of isolate			
Blood	17	5	22
Spinal fluid	0	(2)**	(2)
Antibiotic susceptibility of isolate			
Penicillin sensitive	10	3	13
Penicillin intermediate	4	1	5
Penicillin resistant	3	1	4
Hospitalized	1	3	4
Treated outpatient	16	2	18
Clinical Diagnoses			
Bacteremia	17	5	22
Meningitis	(0)	(2)	(2)
Septicemia/sepsis	(2)	(1)	(3)
Pneumonia	(1)	(1)	(2)
Periorbital cellulitis	(1)	(0)	(1)
Immunocompromised	0	0	0
Outcome			
Complete recovery/"Doing well"	17	4	21
Residual deficit	0	1 (hearing)	1
Deaths	0	0	0

Compiled from case narratives provided in July 7, 1999 submission to PLA.
* Fully vaccinated denotes those subjects who received at least 3 doses of vaccine within the acceptable time (Section 7.3.2)
** () n of cases for non-unique characteristics

Comment: Two children were diagnosed with sepsis. According to the case narratives provided, neither child with sepsis was hospitalized. Thus, as used in this study, the diagnosis of clinical sepsis appears to be of little value in assessing severity of disease, and illustrates the desirability of having common diagnostic criteria.

8.3.6 Analysis of cases accrued in extended follow-up

8.3.6.1 Vaccine serotypes

Enrollment ceased on August 24, 1998. Partially vaccinated subjects completed the vaccine schedule, and follow-up of such subjects was added to the continuing surveillance of efficacy outcomes and safety. A summary and analysis of invasive disease cases accrued through April 20, 1999, were provided with the PLA.

Results of the analysis of cases accrued through extended follow-up are consistent with results of the primary analysis. One case of invasive disease due to vaccine serotype occurred among fully vaccinated subjects in the 7VPnC group, and 39 cases were observed in the MnCC group.

Table 10: Efficacy Study 118-8
Efficacy Against Invasive Disease- Extended Follow-up Analysis

Invasive Pneumococcal Disease (Cases through April 20, 1999)	Number of Cases		Vaccine Efficacy Estimate (VE)	95% Confidence Limits* of VE
	7VPnC	MnCC		
Vaccine Serotypes				
Per-Protocol	1	39	97.4%	(84.8%, 99.9%)
Intent-to-Treat	3	49	93.9%	(81.0%, 98.8%)
All Serotypes				
Per-Protocol	3	42	92.9%	(77.6%, 98.6%)
Intent-to-Treat	6	55	89.1%	(74.7%, 96.2%)

Adapted from Tables 17 page 105 , Volume 13 of PLA, and Table 5, page 25 of June 8, 1999 submission to the PLA.
* Two-sided P-values and confidence limits based on exact binomial distributions (Sponsor's analysis).

The single invasive disease case of vaccine serotype (19F) among the fully vaccinated 7PnC cohort presented no unusual characteristics. Two additional cases of invasive disease due to vaccine serotype (6B, 19F) occurred among 7VPnC recipients accrued during extended follow-up analysis under intent-to-treat. One child received a single dose of 7VPnC. The other child was fully vaccinated, but had been diagnosed with leukemia (Case narratives for breakthrough cases are provided in Attachment A).

8.3.6.2 All serotype pneumococcal invasive disease

A total of 9 cases of invasive disease due to non-vaccine serotypes had accrued throughout the study until extended follow-up for invasive disease was terminated, 3 in the 7VPnC group and 6 in the MnCC group. Vaccine efficacy

for all serotypes in the follow-up intent-to-treat analysis was 89.1% (95% CI: 74.7%, 96.2%).

Vaccine serotypes accounted for 85% (52/61) of all cases of invasive disease in the study at the time case accrual was terminated.

Comment: Only 1 additional case of invasive disease due to non-vaccine serotypes had accrued from the time of the primary analysis (August 1998) until extended follow-up was terminated (April 1999). During the same interval an additional 30 cases due to vaccine serotypes were identified. Thus, replacement of prevalent serotypes chosen for representation in the vaccine by non-vaccine serotypes was not apparent during the study period.

8.3.6.3 Characteristics of invasive disease cases, extended follow-up

Narratives were provided for all 61 cases of invasive pneumococcal disease accrued until extended follow-up was terminated in April 1999. Pneumococcus was isolated from the blood of all but one case; a non-vaccine serotype (23A), penicillin-resistant pneumococcus was isolated from a thyroglossal duct cyst to account for the remaining case.

Four deaths occurred among children with invasive disease, 3 in the MnCC group and 1 in the 7VPnC group. Two of the deaths were attributable to invasive pneumococcal disease, and both of these occurred in the MnCC group. The remaining 2 deaths can be attributed to underlying disease or immunocompromising conditions (see Attachment A for case narratives).

The study protocol provided for an assessment of immunocompetence for all children with positive cultures for *S. pneumoniae* from a normally sterile body site. Assays for immunocompetence for the initial 22 cases included CBC, quantitative immunoglobulins (IgG, IgA, IgM), total hemolytic complement, and T-cell subsets for most cases. Results of tests of immunocompetence were provided upon FDA/CBER request, for the initial 22 cases in the intent-to-treat analysis (received August 31, 1999).

Two cases of invasive disease in the follow-up analysis occurred among children who were clearly immunocompromised; both subsequently died. One child with severe combined immunodeficiency in the MnCC group was included in the intent-to-treat analysis of all vaccine serotypes. A child with leukemia in the 7VPnC group was originally omitted from the follow-up intent-to-treat analysis. It was stated that this child did not meet the case definition because of the immunocompromised status of the child, but the case was listed for completeness. FDA requested that the case be analyzed under intent-to-treat.