STATISTICAL REVIEW AND EVALUATION

Date: February 13, 2000

Type: PLA 99-0279

Materials reviewed: PLA volumes; Part IV Clinical Vols. 01-33
Supplemental print materials submitted through 02-12-00
WLVP FAX information: (see communication file)
CD-ROM data submissions dated: 6-7-99, 9/15/99, 10-05-99, 12-17-99

Product: 7-Valent Pneumococcal Conjugate Vaccine
(Saccarhide CRM197 conjugate of serotypes 4,6B,9V,14,18C,19F,23F)

Sponsor: Wyeth-Lederle Vaccines and Pediatrics (WLVP)

Indication: Prophylactic immunization against invasive pneumococcal disease

From: Pamela R. Getson, Ph.D. (HFM-215)
Mathematical Statistician

To: Lydia Falk, Ph.D. (HFM-481)

Through: Peter A. Lachenbruch, Ph.D. (HFM-215)
Director, Division of Biostatistics

cc: R. Douglas Pratt, M.D., M.P.H. (HFM-475)
Susan Ellenberg, Ph.D. (HFM-210)
Chron

Background

Although a 23-valent pneumococcal vaccine has been licensed for several years for use in adults and children over 2 years of age, it is a polysaccarrhide congugate formulation which does not elicit an adequate immunologic response in infants and children under the age of two years. Approximately 80% of invasive pneumococcal disease occurs in children younger than two years of age, with a peak incidence around 18 months of life. Invasive disease carries a high risk of death or co-morbidity from a variety of pernicious sequella of the disease. After the successful eradication of Hib-induced disease following the introduction of the Hib vaccine (which uses the same protein conjugation to CRM197), major efforts were devoted to the use of this carrier protein in the development of a pneumococcal vaccine which would be safe and efficacious in infants and children under the age of two years.

The current license application involves the use of a heptavalent (7V) formulation of a pneumococcal vaccine in a 3 dose primary, plus fourth dose series administered to infants at 2,4,6 and 12-15 months of life. Serotypes included in the vaccine are 4, 6B, 9V, 14, 18C, 19F, and 23F. Three essential studies were submitted in support of licensure; a large-scale pivotal efficacy study P118-8), a manufacturing and bridging study (P118-16) and a lot consistency study (P118-12). Additional studies which provided information regarding overall safety, immune response and specialized assessments of "catch-up" data and concomitant vaccine administration (interference) are provided in Attachment 1. The application was received on June 1, 1999 and CBER accepted the PLA for filing on July 13, 1999 granting it priority review status for the conduct of an expedited review. Initially three indications were sought; one for prevention of invasive pneumococcal disease due to vaccine serotypes, one for reduction in rates of acute otitis media, and one for reduction in rates of pneumonia. Subsequent to the filing, the latter two indications were removed from the application.

The clinical section of the application consists of 33 volumes which contain study reports for 8 studies and information regarding 3 additional studies. A clinical summary of the efficacy trial is provided in Volume 13 and an integrated clinical summary including separate inclusion time points for cases in the efficacy trial, is included in Volume 33 of the application.

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; Safety and reactogenicity given with DTaP; Catch-up data; Compatibility with HbOC, DTaP;
	Infants	7, 9	None	
	Toddlers	15-18	None	
D118-P15	Infants	2, 4, 6, 12-15	MnCC	Ongoing efficacy study among Navajo and Apache; Only catch-up immunogenicity data provided
	Toddlers	Various	MnCC	
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 only
	Toddlers	12-15	None	
D124-P501	Toddlers	12-17	MnCC	9-valent immunogenicity data for catch-up presented.
		18+	MnCC	

All review of datasets and verification against printed materials has been conducted using primarily the CD-ROM materials included in October 4 (CBER receipt 10-05-99) and additional studies (especially those for "catch-up" immunization) with analyses submitted December 17 (CBER/DBE receipt 12-23-99).

Review (trial conduct/design):

Study 118-8: 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

The pivotal efficacy study was conducted at Kaiser-Permanente Northern California (NCKP) and involved an enrolled sample through August 24, 1998, of 37,868 infants. This study was a randomized, double-blind study conducted in 2-month old infants. The comparator arm used the WLVP experimental meningococcal C conjugate vaccine (MnCC). The primary endpoint was the per-protocol efficacy of heptavalent pneumococcal conjugate vaccine (7VPnC) against invasive disease due to the serotypes included in the vaccine. Secondary objectives included assessment of safety and tolerability , as well as immunogenicity of both the 7VPnC and MnCC vaccines, and determinations of: the ITT efficacy of the pneumococcal vaccine against vaccine serotypes, the PP and ITT efficacy of the pneumococcal vaccine against overall invasive pneumococcal disease, and assessments of the immunogenicity of the pneumococcal vaccine following both a primary series and a 4th dose ('booster').Initially, the application included secondary effectiveness endpoints for the reduction of vaccine serotype specific AOM and pneumonia. Subsequent to filing the application, the sponsor removed these last two indications from current consideration as part of this application.

Various times were used to provide information for the efficacy, safety and immunogenicity analyses. The efficacy analyses involved use of all 37,868 subjects receiving at least one dose of vaccine up through the time of the acquisition of the 17th case of invasive disease on August 24, 1998; when enrollment in the trial was terminated. The per-protocol data set included 30,291 subjects. The safety database included the 34,146 subjects enrolled through April 30, 1998 for ascertainment of ER visits, hospitalizations, clinical visits and deaths. An acute reactogenicity subset of approximately 7,500 subjects was used to assess acute local and systemic events. See Attachment 2 for summary and frequency validation of selected subset procedure. A description of the agreements related to a pre-planned set of interim analyses, and locking of the safety database at 4/30/98 follows, below.

The efficacy study was conducted using the integrated computer database systems of NCKP for which precise SOP protocols were submitted for review as regards issues of eligibility, enrollment/disenrollment, dose administration, safety, efficacy and follow-up. See Attachment 3. These databases were used to design tracking mechanisms for data collected for use in integrated care and utilization summaries from the three types of NCKP facilities (ER, out-patient clinic,

hospital), safety (AE) both short-term, longer-term and telephone for a subset and all immunogenicity data. A monitored telephone subset of patients were queried for AEs by parent telephone interview at 48-72 hours and 14 days post-immunization. Rates of utilization for specific diagnoses following vaccine receipt were monitored for ER visits within 3, 14, and 30 days, hospitalizations within 3,14,30 and 60 days and clinic visits for 3 days, with certain diagnoses to 30 days.

To determine the efficacy of the 7VPnC vaccine against invasive pneumococcal disease, surveillance for cases was performed in the study population during the follow-up period and rates were compared between treatment groups. Cases were identified by: weekly reporting by a nurse or clerk at each study center, weekly review of listings of all positive cultures for *S. pneumoniae* from a normally sterile body site for children less than 9 years of age generated from the NCKP Regional Microbiology laboratory database, and review of monthly listing of children discharged from NCKP hospitals with a diagnosis compatible with invasive pneumococcal disease. Computer programs which effected both clinical and commercial information capture, were submitted for review. (Vol.15). These commercial programs were assessed and validated. Of special importance for discussion of the calculation of follow-up proportions (person-years) below, is the validation of the programs for definition and accuracy of the HMO enrollment for members and their infants who were part of this pivotal study. Of similar importance is the validation of the electronic system used to continue both ascertainment of cases and follow-up of enrollees for issues of safety and subset inclusion in various data subsets for use in per-protocol (PP) vs intent-to-treat (ITT) types of analyses.

For submitted synopses of treatment methodology/duration, criterion for evaluation of efficacy (invasive disease, immunogenicity and safety), and statistical methods employed for such evaluations, see Attachment 4.

Randomization schedules for assignment to groups (PnC or MnCC) were prepared by a single NCKP statistician for distribution to each study site. Healthy infants were randomized to receive immunizations identified as **A** (MnCC), **B** (PnC), **C** (MnCC) or **D** (PnC) within the separately prepared schedules delivered to each site. The generation of these codes, assignments at the sites and subsequent blinding of personnel occurred as follows: the randomization was nested within each study site, block sizes were randomly chosen among 4,6,8,and 10 for each iteration, with treatment groups equally allocated. Treatment assignments were randomly permuted within each block. The vaccines were supplied in single dose vials labeled with one of the four group codes as described, above. All vials were visually identical. The subject randomization was not available to the study nurse until after the child had been enrolled and consent signed. The group code assignments were entered by the study nurse into the child's study casebook and the paper injection log, but were not recorded on the subject's chart, computer records or in any other documents. Color coded injection slips were entered in the patient chart. The correspondence of these color codes with a A,B,C,D codes were only known to the study nurse. Logs of study vaccine administration were FAXed on a daily basis to the project data manager. In addition to the study nurse, the group assignment codes were known to the nurse administering the vaccine,

NCKP data managers and study monitors from NCKP and WLVP. These codes were not known to any of the child's caregivers, the child's parents or anyone else involved in the trial; including telephone interviewers, study investigators and any other ancillary medical personnel. The randomization scheme employed, which utilized an additional step of randomly assigned block sizes for subsequent permuted group assignment, provided an additional level of confidence that biased assignment did not occur. Comprehensive knowledge of the four group codes was only known by the NCKP statistician and WLVP labeling personnel, all who signed confidentiality agreements. There was no unblinding for safety assessment during the trial through the time of the interim analysis. While unexpected unblinding is always a possibility in any study, the extra difficulty introduced by randomly varying block sizes, the minimization of personnel with knowledge of these codes, the cross use of colored slips, the lack of electronic capability for 'aggregation surveillance' by local personnel at the individual sites, and the lack of need for unblinding of the Study Advisory Group due to monitored safety concerns, seems to mitigate against this potential.

The overall design of the study was that of a group sequential design. Initially, the study was designed and powered to allow for two interim analyses, with early-stopping depending on a series of case splits. The first look would occur after 8 cases; the trial was proposed to end if the case split was 8:0 in favor of the PnC vaccine. If necessary, the second look would occur after 20 cases had accrued; a favorable case split as low as 15:5 was proposed. Full analysis would occur at 40 cases. CBER advised that stopping after 8 cases would be unacceptable due to insufficient safety data and that a case split of 15:5 was not advised due to a lower c.i. of .035. See Attachment 5. The sponsor was advised to adopt one interim analysis instead. The actual trial accrual rate of cases continued to proceed much slower than originally estimated, and the sponsor prepared a rationale for an interim analysis upon identification of a 17th case of invasive disease. A plan was then proposed based on an interim analysis at 17 cases and a final analysis upon the accrual of 26 cases. The stopping rule for this analysis was accepted as a case split of 15:2 or better in favor of the PnC vaccine.

118-8: Acceptable Case Splits for Stopping at Interim Analysis

Number of Cases		Vaccine Efficacy	95% Lower Conf. Limit	
Control	Vaccinated	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

The 17th case was acquired on August 20, 1998 and the case split was 17:0 in favor of PnC vaccine. See Attachment 6 for a complete description of the pre-planned interim analysis based on 17 cases.

A large number of subjects (approximately 22%) were excluded from the PP analysis of efficacy at the April 30, 1998; nearly 20% were excluded from the PP analysis conducted at the August 20, 1998 date. This large number of exclusions was investigated extensively. Attachment 7

provides a comprehensive listing of these reasons classified by treatment group, as well as the algorithm used to handle specific missing dose situations for the invasive disease analysis sets . The vast majority of such cases occurred for failure to receive the third (or 4th) dose by the time the analysis was conducted at either 4/30/98 or 8/20/98, respectively. Reasons for PP exclusions were remarkably similar between the groups across all categories for both intervals.

The possible effect that such exclusions could have on follow-up time was also examined in detail. Follow-up time proportions for both the PP and IIT analyses were nearly identical (.50, .50) at the April 1998 cut-off data for which complete information was available.

As of April 30, 1998, the cumulative follow-up times for the 7VPnC and MnCC groups were 10,047 and 10,098 child-years, respectively. Given that the estimate of vaccine efficacy (VE) is a function of the ratio of follow-up times between the two groups, precise knowledge of follow-up time is preferred. In this trial, initial lack of precision of the ratio of follow-up existed because the follow-up data available on April 30, 1998 (when the databases were locked for safety, OM, and pneumonia by agreement) was used to project the ratio of follow-up on August 20, 1998, the date of the primary analysis.

Responding to FDA inquiries, Wyeth-Lederle performed an analysis (received August 31, 1999), in which variations in follow-up times were assumed in order to assess effects on confidence limits around the efficacy estimate. 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 remained above 71%. Thus, any plausible difference between projected follow-up and actual follow-up is likely to have had a minimal effect on the lower bound of the confidence interval.

Calculation of the confidence interval for the point estimate was further complicated because 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, was included in the total follow-up time. In general, early termination from the health plan could be expected to decrease the probability that extra cases would be ascertained. However, this loss would not be expected to introduce a systematic bias in the relative group proportions of "missed case" ascertainment, given the sponsor's determination 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). It was suggested that 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 would not vary.

Based on a detailed estimate which accounted for the primary three categories for which exclusions would occur, it was demonstrated that the proportional follow-up times would not vary at the later August date and that the lower bound of the 95% c.i. for efficacy against invasive disease would not drop below 71% even in the most extreme case of disproportionate follow-up between groups over the interceding time interval from April 30, 1998 to August 20, 1998. On

December 22, 1999, a complete determination of follow-up time through August 20, 1998 was received and indicated the same proportional follow-up in both groups (.50), as was estimated in the October communication. The c.i. calculations do not differ through the hundredths decimal place. See Attachment 8.

Accurate and complete case ascertainment was very important for the trial results to be adequately assessed and for the sufficiency of the early stopping rule as described above. Less favorable case splits which might have occurred through differential non-ascertainment in the PnC group only, could have been highly detrimental. There is no direct way to address this point for patients excluded from analysis, but there are several indicators that provide some degree of assurance. First, all non-pneumococcal blood culture results were investigated through the period to August 20, 1998. All positive cultures were identified and there was no imbalance across treatment groups, with slightly more cultures ordered for the PnC group and nearly identical proportions of negative and non-pneumo positive cultures obtained. Thus, if missed, the cases would have been expected to remain proportional to final case group distribution. Nearly equal proportions of reasons for exclusion noted earlier, and the similarity of PP and ITT analyses would also support a premise of proportional case finding/missing.

Statistical critique (methods)

Demography: Demographic information was collected from the subset of subjects for which acute safety data were collected via telephone interview. Day care status, mother's education, subject race, and household income were collected, summarized, and compared between the 7VPnC and MnCC treatment groups using a Chi-Square test. There were no significant differences between the groups for any of the measured variables.

Efficacy Invasive Disease: The protective efficacy of 7VPnC against invasive pneumococcal disease was estimated as (1 - disease rate ratio). Exact binomial test was used to test the null hypothesis of no vaccine efficacy. Confidence interval for vaccine efficacy was determined using exact binomial distributions (Clopper-Pearson method). This trial incorporated a group sequential design with one interim analysis at 17 cases of primary endpoint - invasive pneumococcal disease due to vaccine serotypes during per-protocol follow-up period in immunocompetent children and the final analysis at 26 cases. The acceptance criteria set for the interim analysis had a type 1 error of 0.0024 and ensured that the overall type I error a for the group sequential design was below 0.05.

Immunogenicity: For the primary series, the endpoint was the IgG antibody concentration (ELISA) to each pneumococcal vaccine serotype at post dose 3. Comparisons were made between the 7VPnC group with the MnCC group. Post dose 3 bleeds were analyzed using ANCOVA with various treatment factors and pre dose 1 values as a covariate. All effects were correctly modeled, as needed. When significant non-normality was found, nonparametric tests

were employed. For the comparison of percent of subjects achieving defined antibody levels, Fisher's Exact test was employed.

For the booster dose, the endpoint was the antibody concentration (ELISA) to each pneumococcal vaccine serotype at post dose 4. Comparisons of pneumococcal antibody responses were made between the 7VPnC and MnCC treatment groups using an ANOVA. Paired t-tests were used to assess the booster response from post dose 3 to post dose 4 and from pre dose 4 to post dose 4. For the comparison of percent of subjects achieving defined antibody levels, Fisher's Exact tests were used.

Safety: To assess the difference in local reactogenicity between the 7VPnC (or MnCC) and DTP-HbOC (or DTaP) injection sites following each dose, a sign test was used. To assess the difference between the 7VPnC and MnCC injection sites following each dose, a Chi-Square test or Fisher's Exact test was used. For systemic events within 48 hours and from 3 to 14 days following each dose, the percent of children experiencing the events were compared between the 7VPnC and MnCC treatment groups using a Chi-Square or Fisher's Exact test. For hospitalizations within 3, 14, 30 and 60 days, emergency room visits within 3, 14 and 30 days, and outpatient clinic visits within 3 and 30 (seizures only) days, the rates per 1000 person-years were determined and the relative risk estimates, 95% confidence interval (Mid-Probability Method), and the p-values comparing the 7VPnC and MnCC treatment groups (two-sided exact binomial test) were calculated.

Of the 30,291 subjects in the per-protocol group, a total of 17 vaccine-serotype invasive disease cases were accrued in fully vaccinated children at the time of the interim analysis (August 20, 1998). All 17 cases were in MnCC group. The estimated incidence of vaccine-serotype invasive disease in children fully vaccinated with 7VPnC was 0 cases per 100,000 child-years compared to 116.5 cases per 100,000 child-years in MnCC recipients. The point estimate of the efficacy of 7VPnC against vaccine-serotype invasive disease was 100% with 95% lower confidence limit at 80.5% (one-sided 95% lower confidence limit, see the table below). The null hypothesis of no vaccine efficacy was rejected with a P-value of less than 0.0001 (two-sided exact binomial test).

Bacteremia was the most frequent diagnosis seen in these 17 cases (14 cases out of 17). The most prevalent serotype in these 17 cases was 19F . The other 3 cases were two of sepsis and one of pneumonia. No invasive disease due to serotype 4 was observed during the study. More than half of the cases were seen in children under the age of 12 months. However, the amount of follow-up was also the highest in children under the age of 12 months

Analysis of Vaccine Efficacy against Invasive Pneumococcal Disease - Cases Accrued Before Interim Analysis (August 20, 1998)

Invasive Pneumococcal Disease	Number of Cases		P-Values* of Significance between Groups	Vaccine Efficacy Estimate (VE)	95% Confidence Limits* of VE	
	7VPnC	MnCC			Two-Sided Limits	One-Sided Lower Limit
Vaccine Serotypes						
Per-Protocol Analysis	0	17	< 0.0001	100%	(75.4%, 100%)	80.5%
Intent-to-Treat Analysis	0	22	< 0.0001	100%	(81.7%, 100%)	85.4%
All Serotypes						
Per-Protocol Analysis	2	20	0.0001	90.0%	(58.3%, 98.9%)	64.590
Intent-to-Treat Analysis	3	27	< 0.0001	88.996	(63.896, 97.9%)	68.6%

* Two-sided P-Values and confidence limits were based on exact binomial distribution.

All statistical tests were validated for primary and secondary efficacy analyses, and immunogenicity analyses. Reverse cumulative distribution functions were not regenerated, but analyses were verified which utilized 'maximal discrimination thresholds' for each antibody. ANOVA and ANCOVA models which were specified in [redacted] were replicated using [redacted] In most cases, the model outputs were nearly identical. For two exceptions, later clarifications of misclassified group members, including an inaccurate PP-flag designation, allowed for correction. Such errors in the datasets are included in correspondence between the sponsor and CBER during the period of August 31, 1999 and December 10, 1999. Safety analyses were also verified, although more discrepancies occurred in count-type data which was largely due to difficulty encountered when calculating 'windows' for various intervals which occurred when portions of data were missing. Most discrepancies were correctable. The relative risks and p values could not be verified for a set of tables dealing with systemic events (Tables 56-73). Clarification regarding incorrect n's acquired through sponsor rounding errors and used in the tables was provided in correspondence on December 10, 1999. Corrected values in the new tables which accompanied this correspondence were verified. Additional analyses were conducted to verify count data for seizures/seizure-type diagnoses occurring throughout the trial, lots associated with certain serious AEs and the randomness of the medical record number as used for the telephone interview subset. Separate analyses were also conducted to assess the serial order of exclusion criteria using the conventions provided to CBER for use of the "first occurring" situation. Three types of inconsistencies were found, but only one was not clarified for the source of the difference in category. This only affected one subject code.

Overall, the statistical procedures proposed for their application purposes were all appropriate and correctly specified. The sponsor was careful to use the most accurate procedures and to check for all assumptions of normality, interaction/non-parallelism, centering for co-variates and various re-weighting and missing schemes. All point estimates included correctly specified c.i., GMCs were

evaluated with c.i. on the differences and paired tests were used where necessary. Correct interpretations of clinical vs statistical significance of safety findings, especially local reactogenicity, were also provided. For a detailed summary of results, see FDA Briefing Document for VRBPAC meeting November 5, 1999 (Pratt).

A series of additional subjects from four other protocols/studies (**118-9**; Ss 15-24 months, **118-12**; control Ss re-enrolled for 7,9,15-18 month assessment, **118-15**; 12-17, 18-23 month assessment in Native Americans, and **118-16**; 7-9,12-15 months control-7V only) and a separately designed open-label trial (**118-18**; 18-24,24-36,36-60 months, 5-10 years) have been used to recommend dosing schedules for 'catch-up' immunization of infants and young children unable to receive the PnC vaccine according to the schedule studies in the large efficacy trial (See Attachment 9; catch-up descriptions for each protocol included).

Demographic comparisons between and among groups were evaluated and assessed as non-significant in all except the 118-18 study, for which the comparisons were not evaluated. This is of no probable consequence, but is noted as a slight difference in method. The full range of antibody concentrations were also depicted as reverse cumulative distribution curves for visual inspection. The statistical method employed for testing were post/pre GMC ratios (GMR) evaluated with 95% c.i. for each serotype for each age strata. The significance of the difference of each GMR from 1, was evaluated by paired t-test, with McNemar's test employed to assess the significance of the paired changes in percentage seroresponders from pre to post-vaccination for each of the two pre-defined IgG thresholds of 0.15 and 0.50 μg/mL. Data were submitted on a new CD-ROM (dated 12-17-99; received 12-23-99). These calculations have been verified, as well as those added through a conservative adaptation for Wilcoxon tests.

Initial summarized tables were provided with this December submission which provided contrasted significance tests for each serotype by study against the efficacy study cohort receiving **either** DTP vaccination **or** to those receiving DtaP vaccinations. A GMC ratio comparison with appropriate c.i. for contrast **only** with the DtaP cohort from the efficacy trial was requested of the sponsor in January 2000. These tests were necessary to allow labeling which could support various 'catch-up' schedules with immunogenicity results contrasted only to those most currently appropriate and obtained in the efficacy trial. That is, in order for these schedule comparisons to be of practical clinical use, a decision was made to request the comparison against only those efficacy subjects who had received the concomitant standard-of- care vaccines (i.e. DtaP).These subjects comprise a small subgroup, but all contrasting levels from the efficacy trial for subjects who received DTP-containing vaccines, are also included in tables 2 and 3 of the proposed label, which preceded the one for catch-up immunization of "previously unvaccinated older infants and children." See Attachment 10; proposed label Table 4.

Summary

The new PnC vaccine showed 100% efficacy (c.i. 76-100% PP; 82-100% ITT) against invasive disease due to the vaccine serotypes and approximately 90% efficacy against all serotypes causing disease in the studied population. It must be assumed that the studied sample is representative of

the entire U.S. and that the geographic incidence and serotype prevalence would likewise be representative of that in the US overall. The vaccine was highly immunogenic and showed a significant response to a 4th dose in the series (called 'booster'). Given that follow-up was truncated in the manner specified above, efficacy post dose 3 must be viewed as that **until the fourth dose**, as it is not clear for what period the protective effect would have maintained without a fourth dose. Use of an investigational comparator arm (MnCC) does not allow full interpretation of the systemic safety profile in the efficacy study, but observations from amended supporting studies 118-12, 118-16 and 118-18 in which only concomitant vaccines as standard-of-care were used, provides a clearer understanding of the PnC safety. Thus, the PnC vaccine appears to be highly efficacious, with an acceptable safety profile for both local and systemic symptoms. Phase IV studies have been approved and contracted for performance to continue to assess both general and specific aspects of safety that may be of continuing importance to surveil.

Review (design/methods)

Study 118-12: A randomized, double-blind trial of the safety and immunogenicity of three lots of heptavalent (4,6B,9V, 14, 18C, 19F, 23F) pneumococcal conjugate vaccine administered to healthy infants at 2,4,6 month of age

This study was used to support the requirement for licensure regarding consistency of manufacture of 3 consecutively produced (pilot scale) lots using a comparison of immunogenicity and safety. Secondary objectives were for demonstrating the compatibility of the PnC vaccine with concomitantly administered HbOC(HibTITER), DtAP(ACEL-IMUNE) and OPV or IPV.

118-12: Study Design

Vaccine group	Vaccine lot (lower left thigh @ 2, 4, 6 mos)	N	Concurrent vaccines & schedule (all groups)
1	Lot A 7-5018-011A	75	ACEL-IMUNE (right thigh) @ 2, 4, 6 mos)
2	Lot B 7-5018-010A	75	HibTITER (upper left thigh) @ 2, 4, 6 mos)
3	Lot C 7-5018-006A	75	OPV @ 2, 4, and 6 mos, or IPV right thigh or upper extremity @ 2 and 4 mos
4	Control group (no control vaccine or placebo administered)	75	

Subjects in the control group were reenrolled and administered two does of the 7VPnC vaccine at 7 and 9 months of age, with a boost at 15 - 18 months of age. Serological data from these subjects contribute to the data to support regimens for "catch-up" immunizations.

Randomization and blinding were handled similarly to the 118-8 efficacy study, with the exception that the parents of control group infants were aware that they were not receiving the experimental 7VPnC vaccine. Specific design/method/statistical considerations are included in Attachment 11. A total of 342 infants were enrolled, with 311 randomized and receiving the first dose. Withdrawals and reasons were nearly identically distributed across the five sites.

All results have been verified using [redacted] statistical routines to match assumptions and model testing for effects as indicated in the sponsor's methods section, above. Decisions for including terms in each ANCOVA model or for model reduction receive concurrence due to similarity of the interpretation provided by each. As a minor point, Table 1, Vol 27 site #4 includes incorrect "randomized and received" counts displayed for two doses. These counts are correctly accumulated in the electronic dataset for the study.

No significant differences were noted in post dose 3 GMCs across the three lots for any of the pneumococcal antigens, nor for any of the other antigens measured for concurrently administered routine immunizations. Results of this lot consistency portion of the trial indicate that as regards immunogenicity evaluation, the lots are equivalent and may be pooled for further comparison of antibody responses as contrasted to a control group receiving only the routine immunization without concomitantly administered 7VPnC.

Although CBER concurs regarding the lot consistency assessment and the interpretation of all analyses as regards the immunogenicity comparisons for Lots A, B, and C, there are several important points which should be noted here for the purpose of better understanding and/or clinically interpreting the relevance of the combined lot "concomitant" vs non-concomitant comparisons which will be discussed below. First, independent comparisons among the three lots for pre-dose 1 or for post dose 3 are made using available samples for each of those independent time points. In addition, due to limited volume of each serum sample and the number of antigens assayed, the number of available assay results for each antigen is less than the number of subjects with eligible serum samples. The sponsor is careful to note that actually assayed totals may vary, and refers the reader to various Appendix I Tables in Volume 27. These are all important tables, because they include the highly specific subsets and ANCOVA models which were used to assess immunogenicity. Depending on which sets of samples one wishes to use (all evaluable post dose 1 AND post dose 3) or all evaluable, the results are slightly different, although all but one may be interpreted in the same manner. If a protective correlate is undefined, it is often preferred to assess the sufficiency of a post dose 3 value in terms of the 'paired' predose 1 value, thus requiring complete datasets for both values. When this is done, the covariate must be carefully assessed before choosing terms for the model. In one case, fimbriae, it can be shown that there is a significant predose 1 by site interaction and a different model which does not rely on a centered mean is appropriately selected. One should note that when predose 1 values are simply evaluated for interlot differences, no significant differences are noted from the ANOVA testing of GMCs for fimbriae. (Table 17). Indeed, both the predose 1 and postdose 3 values for this antigen, noted for each of the three lots, is nearly identical. The matching seroresponse table 18, shows no significant difference among the lots, but that on average fewer than half of the subjects achieve a 4-fold rise. It is difficult to discern if this is of clinical importance given the actual GMCs, but if there is no correlate, it must be considered.

To continue considering only fimbriae, when the lots are combined and contrasted to control of no 7VPnC, there is a predose 1 group difference, which is no longer noted postdose 3 and the post dose 3 GMC ratio comparisons with 90% c.i. (Table 20) indicate a concurrent to non-concurrent

ratio of .81 (.58-1.14) which passes the 2-fold test of .5 to 2.0 for bounds. It might also be noted some of the verified ratios are slightly different than those in Table 20 (for example fimbriae .789 vs .81), but that calculations of 90% c.i. for these ratios did not show any with lower bounds below .5. Responses to the tetanus antigen provide a summary for just the opposite of those noted in the separate tables discussed for fimbriae. This commentary is simply provided as a *caveat* to assessing the relationships of the pre-post changes for these antigens through inspection of any single table of simple GMC or % seroresponder changes. **Again, CBER statistical review concurs that immunogenicity data for the three lots A,B,C provide a demonstration of lot consistency in manufacture.** See attachment 12 for referenced tables.

Comparisons of postdose three immunogenicity responses for the combined pilot lots vs a control arm receiving no 7VPnc (referred to as "with concurrent vs w/o concurrent") were all verified with only a few differences in numeric value differences for GMRs, none which affected the interpretation of lower or upper bounds for the ratios. In general, the statistical review concurs with the sponsor's results and interpretation. The differences in seroresponse noted for pertactin and fimbriae when administered concurrently with 7VPnC deserve continued scrutiny given the extremely low bounds on the seroresponder proportional differences, in view of the concordant results in GMC differences; particularly for pertactin. Interpretations of differences in GMCs for antigens such as tetanus appear more straightforward when the seroresponse is at maximum for both groups. (See Attachment 13, Tables 20,21,22 vol. 27).

Review: design/methods/statistics

Study 118-16; Bridging Study Comparing the safety and immunogenicity of a full-scale manufacturing lot of heptavalent pneumococcal conjugate vaccine to a pilot lot in healthy infants immunized at 2,4 and 6 months of age

Similarity or bridging between the pilot lot used for the efficacy study and a manufacturing scale lot (Lot N) was a necessary component for licensure. This randomized double-blind controlled multicenter study was designed to compare the safety and immunogenicity of a pilot plant lot formulated with Adjuphos which was used in the efficacy trial 118-8 to that of the first manufacturing scale lot (Manufacturing N lot) formulated with a different aluminum phosphate owned by Lederle. Initially, the study was as designed below:

D118-P16: Study design and subject allocation

Vaccine group	Vaccine lot (lower left thigh @ 2, 4, 6 months)	N planned (evaluable)	Concurrent vaccines & schedule (all groups)
1	Pilot scale lot (Adjuphos adjuvant; blow-molded vials) Lot# 7-5018-013A	175 (150)	DTaP (right thigh) @ 2, 4, 6 mos) HbOC (upper left thigh) @ 2, 4, 6 mos) IPV (left upper deltoid) @ 2, 4 mos) Hepatitis B (upper right thigh) @2, 6 mos)
2	Full-scale manufacturing lot "P" (Adjuphos adjuvant; Blow-molded vials) Lot# 7-5018-016A	175 (150)	
3	Full-scale manufacturing lot "N" (w/Lederle AlPO4 adjuvant; single dose tubing vials) Lot# 7-5029-002A	175 (150)	
4	Control group (no control vaccine or placebo)	125 (100)	

Before unblinding the sponsor indicated that the study co-primary immunogenicity endpoints of GMCs and seroresponse rates would be contrasted only for the Pilot lot and Manufacturing N lot. Criteria for demonstrating acceptable bridging were no more than a 2-fold difference in GMCs between pilot and manufacturing lot N, and no more than a 10% difference in response rate between the pilot and N lot at pre-defined threshold values for each serotype determined from pooled data from studies 118-8 and 118-12 to provide for maximal differentiation between unimmunized and immunized subjects. Detailed discussions with CBER were held to substantiate the use of such thresholds and **the understanding that such thresholds were agreed for use only for the purpose of bridging of pilot to full scale lots in this specific trial.** Laboratory, clinical and statistical input regarding the sufficiency of these thresholds, which represent the post-dose 3, 7 month serology for infants enrolled in the efficacy study and the lot consistency study were held at length. Use of maximized differences between reverse cumulative distribution curves for the immunized and unimmunized samples were agreed upon. Additional agreement on proposed statistical considerations for multiplicity adjustments, use of correlational assumptions for cross-reactive antibodies, global power considerations and possible use of global "index" scores were reached. Essentially, only power considerations remained for determination regarding interpretation of any significant tests which may arise spuriously due to the number of multiple tests required; 14.

Concentration levels for maximal differences were accepted from numeric files and graphic plots provided by the sponsor, and were not reproduced from raw data. These values were:

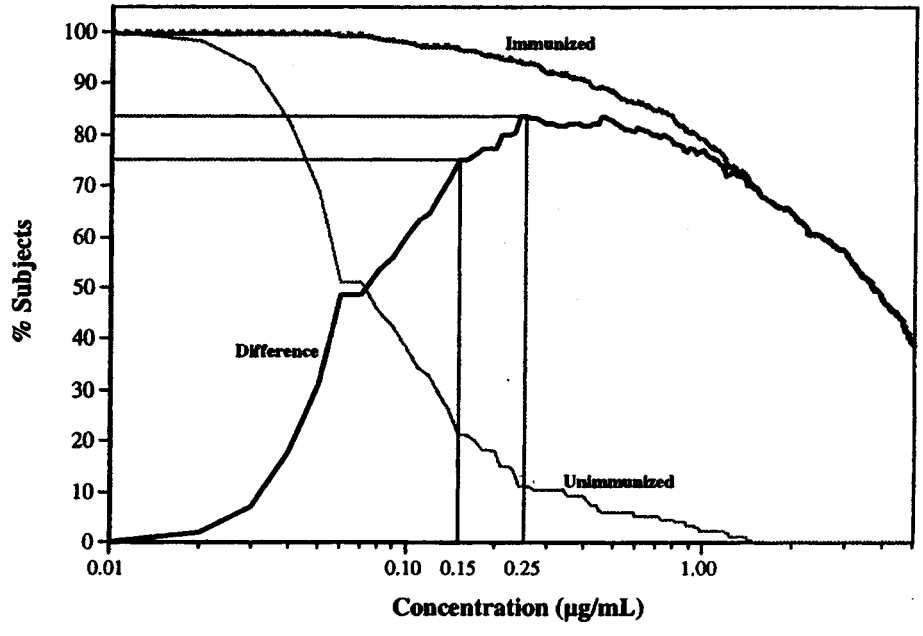
Concentration Level Where Maximum Difference Between the Immunized and Unimmunized Populations Seen							
	4	6B	9V	14	18C	19F	23F
Max. Diff Concentration	0.15	0.25	0.28	0.38	0.21	0.26	0.18

* Based on the combined data from study 118-8 and 118-12. The data of 118-8 are based on the population who received three doses of concurrent DTP-HbOC vaccine and the data from 118-12 are from population who received three doses concurrent DtaP+ HbOC vaccines.

An example of separately specified serotype threshold criteria is demonstrated for 6b below.

Difference between Reverse Cumulative Distributions of Immunized and Unimmunized Populations
Combined Data from Study 118-8 and 118-12

Serotype 6B



For immunogenicity comparisons, the lower limit of the 90% confidence interval for the ratio of the post dose 3 lot N/pilot lot GMCs were evaluated. The 90% c.i. used for the non-inferiority

test was derived from a simple 2 group ANOVA F-test since testing for model effects of clinic and interactions showed no significance for any of the serotypes. Post dose 3 GMCs for each serotype by lot and comparisons of seroresponders by lot are included as Attachment 14 (Tables 67-69 Volume 33). Reference to CBER's November VRBPAC briefing document (Pratt) is made for reviewing safety information.

All analyses were verified with assumptions, excepting the threshold value as noted, above. Both lots elicited good antibody responses to all 7 pneumococcal serotypes. Lot N was equivalent to the pilot lot when the two were compared for GMCs and percent who achieved specified antibody concentrations (both particular 'maximized' thresholds as well as $\geq .15$ μg/mL). The safety profile was acceptable to clinical reviewers. These data support the bridge of pilot to full scale manufacture. See November 1999 VRBPAC briefing document (Pratt) for detailed result summaries.

Attachment 1

Study Definitions

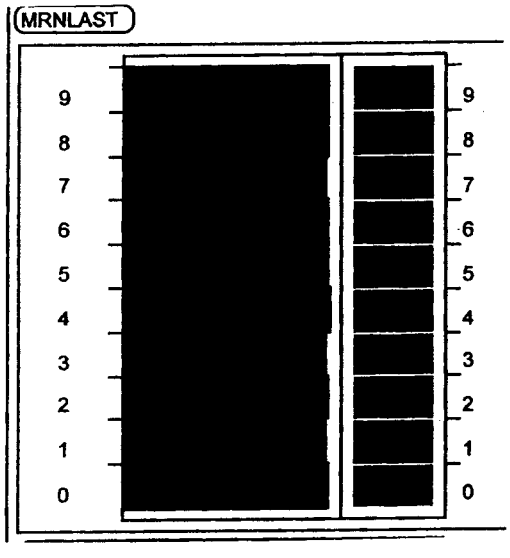
Study Number	Description
118-8	Evaluation of the Safety and Efficacy of Heptavalent Pneumococcal Vaccine and Safety of Meningococcal Group C Conjugate Vaccine in Infants at 2, 4, 6 and 12-15 Months of Age in the Northern California Kaiser Permanente Medical Care Program
118-12	A Randomized, Double-Blind Trial of the Safety and Immunogenicity of Three Lots of Heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) Pneumococcal Conjugate Vaccine Administered to Healthy Infants at 2, 4 and 6 Months of Age
118-16	Bridging Study Comparing the Safety and Immunogenicity of a Full-Scale Manufacturing Lot of Heptavalent Pneumococcal Conjugate Vaccine to a Pilot Plant Lot in Healthy Infants Immunized at 2, 3 and 6 Months of Age with an Open-Label Study of the Safety and Immunogenicity of a Booster Dose of Heptavalent Pneumococcal Conjugate Administered at 12 to 15 Months of Age
Catch-up	'Catch-up' is defined as vaccination of previously unvaccinated children 7 months of age or older. Catch-up data are from protocols 118-9, 118-12, 118-15 (Native American), and 124-501.
118-09	A Randomized, Double-Blind Trial Comparing the Safety and Immunogenicity of Two Lots of Heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) Pneumococcal Conjugate Vaccine in Toddlers 15-245 Months of Age
118-15	A Double-Blinded, Controlled Study of the Efficacy, Immunogenicity, Safety and Tolerability, and Effectiveness of a Pneumococcal Conjugate Vaccine Containing Seven Serotypes (6B, 14, 19F, 23F, 18C, 4 and 9V) Compared to a Control Meningococcal C Vaccine in Navajo and Apache Indian Infants.
124-501	A Randomized, Blinded, Controlled Trial Evaluating the Effect of Immunization with 9-Valent Pneumococcal Conjugate Vaccine on Nasopharyngeal Carriage of S. pneumoniae in Israeli Toddlers Enrolled in Day Care Centers
118-3	Original: A Randomized, Double-Blind, Trial of the Safety and Immunogenicity of Heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) Pneumococcal Conjugate Vaccine and Meningococcal Group C Conjugate Vaccine in Healthy Infants at 2, 4 and 6 Mos. of Age Amended: A Randomized Open-Label Study of the Safety and Immunogenicity of a Booster Dose of Heptavalent Pneumococcal Conjugate Vaccine Administered With Either a Combination Vaccine Composed of Diphtheria-Tetanus Toxoids Acellular Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (TETRACEL™) or DTaP (ACEL-IMUNE) and HbOC (HibTITER®) Administered Concurrently in Separate Syringes in Children 15-18 Months of Age.

Attachment 2

ALGORITHM FOR DETERMINING WHICH PATIENTS ARE SELECTED FOR TELEPHONE INTERVIEW:

The following three groups were interviewed:

- Subjects receiving the first dose of study vaccine prior to January 6, 1997, AND having MRNs ending in 2, 4, 6 or 8
- Subjects receiving a first dose of study vaccine and having concomitant HibTITER and AcelIMUNE between April 28, 1997, and May 5, 1998, AND having MRNs ending in 2 or 4 (per Amendment 2 to the 118-08 protocol)
- In order to obtain comparative reference data, parents who declined study participation but had children who were receiving AcelIMUNE and HibTITER were approached for similar safety evaluation. A total of 500 children were consented and subsequently interviewed by telephone after each dose of AcelIMUNE, HibTITER, as well as other concomitant vaccinations. This began in July of 1997 (per Amendment 5 to the 118-08 protocol)



Frequencies

Level	Count	Probability	Cum Prob
0	3441	0.10077	0.10077
1	3387	0.09919	0.19996
2	3413	0.09995	0.29992
3	3380	0.09899	0.39890
4	3448	0.10098	0.49988
5	3435	0.10060	0.60048
6	3412	0.09992	0.70040
7	3394	0.09940	0.79980
8	3420	0.10016	0.89996
9	3416	0.10004	1.00000
Total	34146		

10 Levels

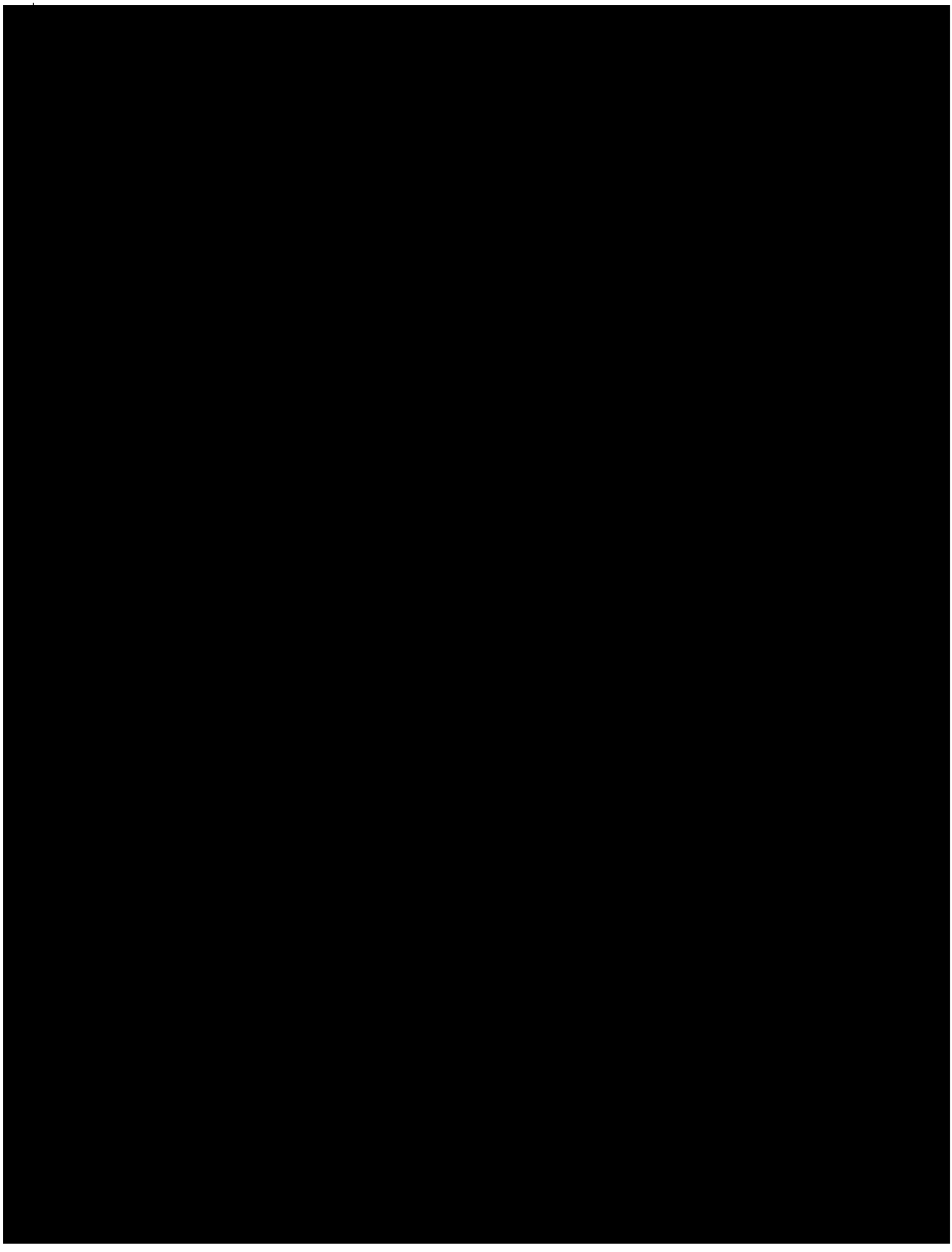
Attachment 3

Overview of Databases Used at NCKP

As mentioned in the PLA submission for study 118-08, the Kaiser Permanente Vaccine Study Center in Northern California Kaiser Permanente uses several different databases. The medical record number (MRN), a unique KP identifier assigned to each health plan member upon joining or being born into the health plan is the [redacted]. A description of the databases, the variables contained therein, and algorithms used for the various functions they perform will be helpful in understanding how these databases are utilized.

Kaiser Immunization Tracking System (KITS)

[redacted]



[redacted]

ALGORITHM USED WITHIN 'KITS' FOR FINDING STUDY AND CONCOMITANT VACCINES

[redacted]

Patient Demographics Database (PATDEM)

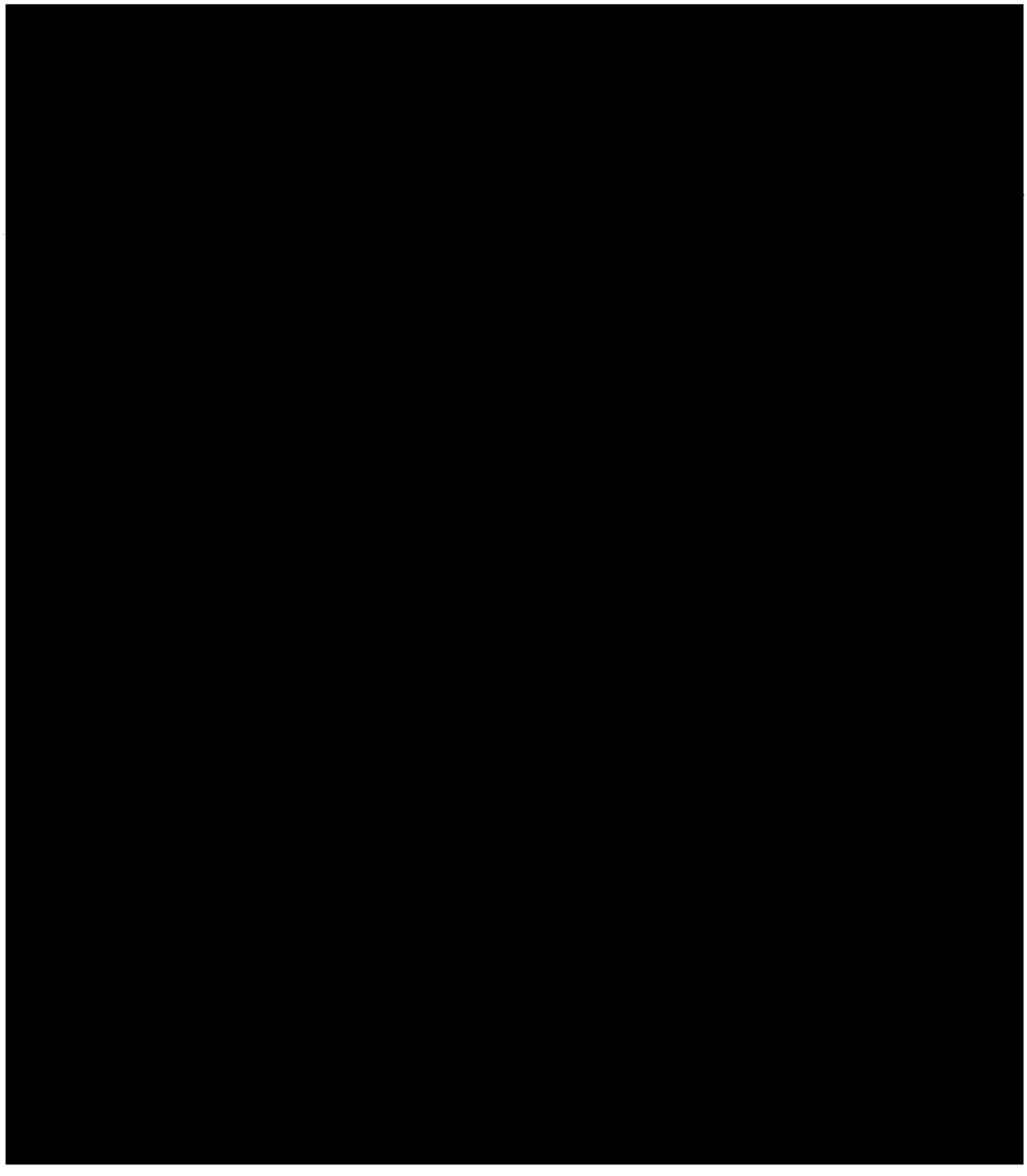
[redacted]

[redacted]

ALGORITHM USED WITHIN PATDEM IN DATA PULLS FOR KAISER PERMANENTE VACCINE STUDY CENTER:

[redacted]

[redacted]



[redacted]

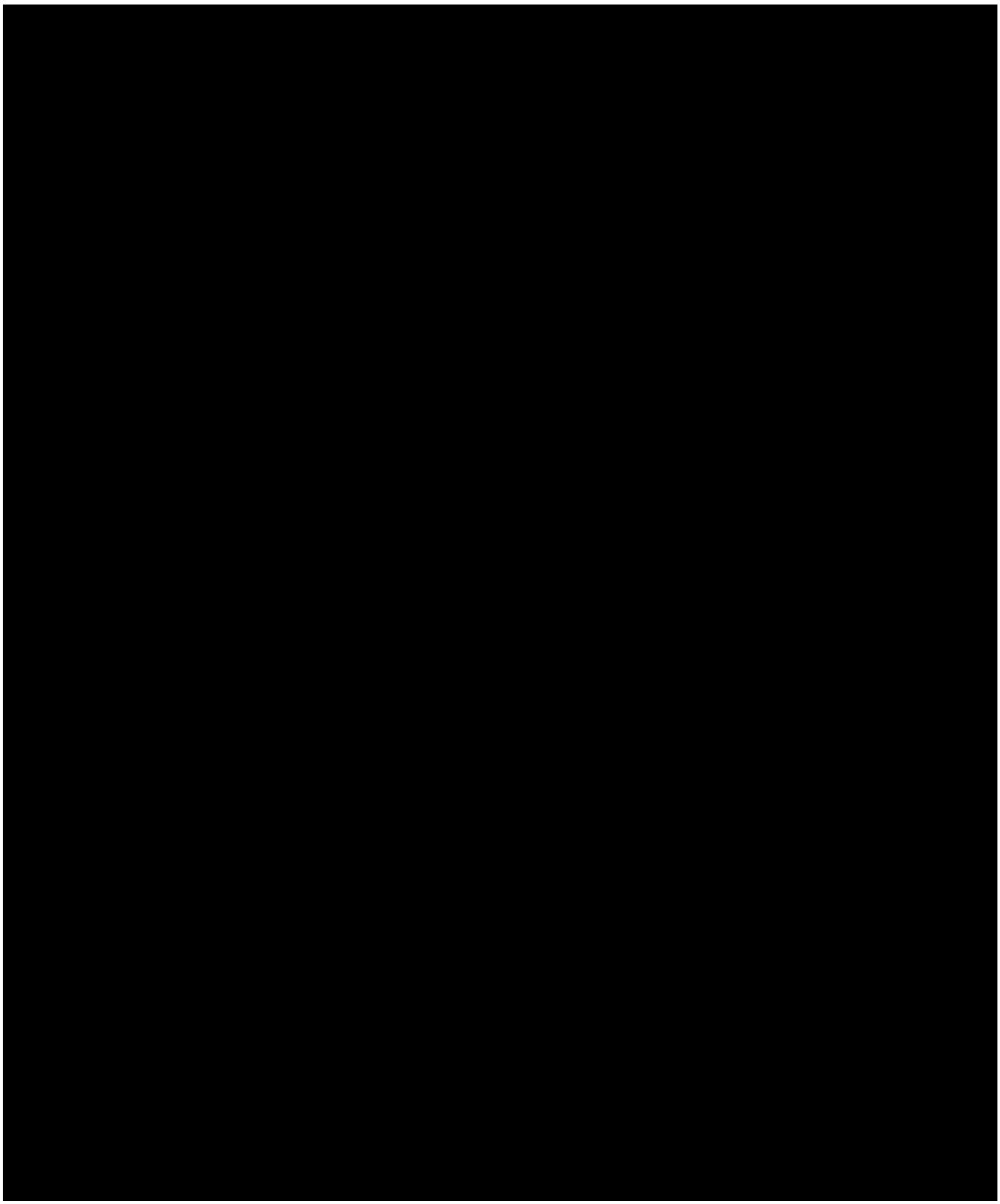
ALGORITHM USED FOR LABORATORY DATA FOR REPORTING TO KAISER PERMANENTE VACCINE STUDY CENTER:

[redacted]

ALGORITHM FOR HOSPITALIZATIONS PULLED FOR D118-P8 TRIAL:

[redacted]

ALGORITHM FOR CLINIC VISITS PULLED FOR D118-P8 TRIAL:



[redacted]

[redacted]

ALGORITHM FOR OUT OF PLAN VISITS PULLED FOR D118-P8 TRIAL:

[redacted]

Telephone Safety Information

Safety data in the 118-08 trial was partially monitored via parental interview. These parents were given Parent Diary Cards created to help them answer the questions of telephone interviewers who contacted them 48-72 hours post-injection and 14 days post-injection. The trained interviewers used forms specifically designed for consistent interviewing and ease of data entry (these forms are included as part of the PLA for this trial). Specifically, local reactions at the injection sites were monitored on the day of immunization and for 48 hours. Fever was recorded on the day of immunization, for 2 days after, and at any other time within the 14 day period. Other systemic events were monitored for 14 days. Once this information is collected it is double entered and error-

checked by Division of Research personnel. Any information meeting certain criteria were reported directly to the Principal Investigator. These criteria are enumerated here:

- Fever of 103° F or higher
- Redness or swelling of the left thigh which is greater than the size of a half dollar
- Tenderness of the left leg which interferes with the movement of the leg
- Raised, red, itchy rash or hives
- Grey, ashen, or blue skin color (pale only if combined with other reportable symptoms)
- Limpness or floppiness
- Convulsions/seizures
- Twitching (shaking, jerking, shivering)
- Loss of consciousness
- Wheezing or asthma
- Severe allergic reactions
- Hair loss
- Hospitalizations for any reason
- ER visits unless clearly unrelated and not meeting the definition of a serious adverse event as defined
- Serious Adverse Events: Any event which is fatal, life threatening, permanently or temporarily disabling or incapacitating or results in hospitalization, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional)

The KITS and PATDEM regional databases were accessed daily to identify and obtain telephone numbers of study population members who received study vaccine 48 hours earlier that were eligible for telephone interviews based on the criteria below. Information from these electronic sources was supplemented and confirmed by examination of injection logs faxed daily by all study nurses.

[redacted]

ALGORITHM FOR DETERMINING WHICH PATIENTS ARE SELECTED FOR TELEPHONE INTERVIEW:

The following three groups were interviewed:

- Subjects receiving the first dose of study vaccine prior to January 6, 1997, AND having MRNs ending in 2, 4, 6 or 8
- Subjects receiving a first dose of study vaccine and having concomitant HibTITER and AcelIMUNE between April 28, 1997, and May 5, 1998, AND having MRNs ending in 2 or 4 (per Amendment 2 to the 118-08 protocol)
- In order to obtain comparative reference data, parents who declined study participation but had children who were receiving AcelIMUNE and HibTITER were approached for similar safety evaluation. A total of 500 children were consented and

Attachment 4

2. SYNOPSIS

Name of Sponsor/Company: Wyeth-Lederle Vaccines and Pediatrics	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: 7-valent pneumococcal conjugate vaccine, meningococcal group C conjugate vaccine	**Volume:**	
Name of Active Ingredient: saccharide-CRM_{197} conjugates of pneumococcal serotypes 4,6B,9V,14,18C,19F,23F, saccharide - CRM_{197} conjugate of mening C	**Page:**	

Title of Study: 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 the Northern California Kaiser Permanente Medical Care Program.

Investigators: Steve B. Black, M.D., Henry Shinefield, M.D.

Study center: Kaiser Hospital (22 Clinics within NCKP)
280 West MacArthur Blvd.
Oakland, CA 94611

Publication (reference): Black S, Shinefield H, et al. Efficacy of Heptavalent Conjugate Pneumococcal Vaccine (Wyeth Lederle) in 37,000 Infants and Children: Results of the Northern California Kaiser Permanente Efficacy Trial. Abstract LB-9, 38th ICAAC, San Diego, CA, September 24 - 27, 1998.

Studied period (years): **date of first enrollment:** October 1995 **date of last enrolled:** August 1998 **Study currently ongoing**	**Phase of development:** Phase III

Objectives: The primary objective of this study was to determine the protective efficacy of heptavalent pneumococcal conjugate vaccine (7VPnC) against invasive disease due to serotypes included in the vaccine. Secondary objectives included the following:

- To assess the safety and tolerability of heptavalent pneumococcal conjugate vaccine administered as a primary series in infants at 2, 4, and 6 months of age with a booster dose at 12 to 15 months of age.
- To assess the safety and tolerability of meningococcal group C conjugate vaccine (MnCC) in infants immunized at 2, 4, 6, and 12 to 15 months of age.
- To determine the protective efficacy of heptavalent pneumococcal conjugate vaccine in an intent-to-treat analysis.
- To evaluate the effectiveness of vaccination with heptavalent pneumococcal conjugate vaccine on overall invasive pneumococcal disease in the study population.
- To assess the effectiveness of vaccination on rates of acute otitis media and pneumonia in the study population as determined from computerized data sources.
- To assess the immunogenicity of pneumococcal conjugate vaccine following a primary series and booster dose.

Methodology:
This was a randomized, double-blinded study in 2-month-old infants. Subjects qualified for enrollment if they met all inclusion criteria and none of the exclusion criteria. Eligibility was determined by performing a medical history prior to each immunization. Parents or guardians of subjects were asked to read and sign the informed consent. Subjects were then equally randomized into one of four treatment groups (Groups A-D), two treatment groups assigned for each vaccine. Subjects were recruited into the one of the four treatment groups and received the appropriate vaccine according to the protocol at 2 months (42-120 days), 4 months (35-120 days after dose 1), 6 months (35-120 days after dose 2), and 12 to 15 months (defined as the first day the child turns 12 months to the day before the child turns 16 months) of age. Subjects were to have completed the primary series by one year of age and

Name of Sponsor/Company: Wyeth-Lederle Vaccines and Pediatrics	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: 7-valent pneumococcal conjugate vaccine, meningococcal group C conjugate vaccine	**Volume:**	
Name of Active Ingredient: saccharide-CRM_{197} conjugates of pneumococcal serotypes 4,6B,9V,14,18C,19F,23F, saccharide - CRM_{197} conjugate of mening C	**Page:**	

to have received the fourth dose at least two months after the third dose. As the immunization schedule at 2, 4, and 6 months of age coincides with those of Hib, DTP, and poliovirus vaccines, initially all subjects received DTP-HbOC (TETRAMUNE®) from a separate syringe into the opposite leg and oral poliovirus vaccine (ORIMUNE®) concurrently. As recommendations changed during the course of the study to include DTaP and then a sequential IPV schedule, the protocol was amended to allow administration of these vaccines. Subjects also received hepatitis B vaccine when appropriate. For the booster dose, all subjects received a fourth dose at 12-15 months of age of the same investigational vaccine that they had received for the primary series. DTP-HbOC or DTaP and HbOC, MMR, OPV, and varicella vaccine could be given concurrently but were not required at the booster dose visit.

To determine the efficacy of the 7VPnC vaccine against invasive pneumococcal disease, surveillance for cases was performed in the study population during the follow-up period and were compared between treatment groups. Cases were defined as a positive culture of *Streptococcus pneumoniae* from a normally sterile body fluid obtained from a child with an acute illness consistent with pneumococcal disease. To determine the efficacy of the 7VPnC vaccine against otitis media, clinical diagnoses of acute otitis media for the study population were determined from computerized data sources and compared between treatment groups.

Blood samples were drawn prior to the first dose, one month following the third dose, prior to and one month following the fourth dose, and at approximately 24 months of age in a volunteer subset of subjects, for determination of antibody response to the 7 pneumococcal serotypes contained in the vaccine.

Following each injection with study vaccine, all subjects were observed at the study site by a physician or a study nurse for a period of 15 minutes for any signs or symptoms of intolerance to the vaccine. Acute adverse events occurring after the 15-minute period were monitored in a subset of infants through telephone interviews of the parents. Approximately 7400 subjects were interviewed after receipt of study vaccine, at 48-72 hours and 14 days postimmunization. Approximately 3000 of these subjects had received 7VPnC vaccine concurrently with DTP-HbOC, 3000 had received MnCC concurrently with DTP-HbOC, 700 had received 7VPnC concurrently with DTaP and HbOC, and 700 had received MnCC vaccine concurrently with DTaP and HbOC. Acute safety was assessed in these subsets of subjects following doses 1, 2 and 3. Acute reactions following dose 4 were assessed in subsets of subjects who received DTP-HbOC concurrently, DTaP concurrently, and no vaccines concurrently with study vaccine. Detailed safety data were also collected following each dose on an additional 500 subjects who declined study participation, but agreed to be interviewed by telephone regarding any adverse events the child experienced following DTaP and HbOC. These data will not be presented in this report. The parent or guardian of the subject was instructed to monitor signs and symptoms of local reactions and systemic events and any untoward effect for 14 days after each vaccination. This information was recorded by the parent or guardian onto a special form and collected by trained study personnel during telephone interviews of parents at 48-72 hours and 14 days following receipt of each dose of vaccine.

Additionally, the frequency of relatively rare events requiring medical attention after vaccination were evaluated for all study participants. This was accomplished through the use of comprehensive hospitalization, emergency room, and outpatient clinic utilization databases within NCKP. These databases were used to obtain rates of utilization for specific diagnoses within specific time frames following receipt of study vaccine: emergency room visits within 3, 14, and 30 days of vaccination; hospitalizations within 3, 14, 30 and 60 days of vaccination; and outpatient clinic visits for diagnoses of interest within 3 and 30 (seizures only) days of immunization. Line listings of all the adverse events were reviewed by the principal investigators

Name of Sponsor/Company: Wyeth-Lederle Vaccines and Pediatrics	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: 7-valent pneumococcal conjugate vaccine, meningococcal group C conjugate vaccine	**Volume:**	
Name of Active Ingredient: saccharide-CRM_{197} conjugates of pneumococcal serotypes 4,6B,9V,14,18C,19F,23F, saccharide - CRM_{197} conjugate of mening C	**Page:**	

and the sponsor on a monthly or bimonthly basis and were classified as to severity, recovery, and relationship to vaccine. In addition, any clinically significant illness/event documented from the telephone interview was reviewed in the same manner.

In this report, only safety events collected through April 30, 1998 will be reported.

Number of subjects (planned and analyzed):
Total Planned: Approximately 31,200
Total Enrolled: 37,868 (Through August 24, 1998, when enrollment was terminated.)
34,146 (Through April 30, 1998, cut-off date for otitis media and safety databases)
Analyzed for Efficacy: Invasive Disease Intent-to-Treat: 37,868, Per-Protocol: 27,118 (estimate)
Otitis Media Intent-to-Treat: 34,146, Per-Protocol: 23,746
Analyzed for Immunogenicity: Primary Series Intent-to-Treat: 303, Per-Protocol: 180
Booster Dose Intent-to-Treat: 203, Per-Protocol: 130
Analyzed for Safety: For ER visits, hospitalizations, outpatient clinic visits, and deaths- approximately 34,146.
For acute local reactions and systemic events-approximately 7400.

Diagnosis and main criteria for inclusion:. Healthy 2-month-old infants were enrolled in the study. Infants with any serious chronic disease, progressing neurological disease, uncontrolled epilepsy, known or suspected impairment of the immune system, a previous anaphylactic reaction, a hypersensitivity reaction to any vaccine component, a history of pneumococcal infection of a normally sterile body site or pneumococcal pneumonia, a history of meningococcal infection of a normally sterile body site, a history of idiopathic thrombocytopenic purpura, a contraindication to OPV, had received any prior vaccination with the exception of hepatitis B, or with sickle cell disease, functional or anatomic asplenia, Down Syndrome, or nephrotic syndrome were excluded.

Test product, dose and mode of administration, lot number:
Dose and Mode of Administration: 0.5mL Intramuscular
7VPnC Lot Numbers: [redacted]
MnCC Lot Numbers: [redacted]

Duration of treatment: Subjects were immunized at 2, 4, 6, and 12-15 months of age. For invasive disease efficacy, subjects are continuing to be followed for invasive disease caused by *S. pneumoniae*. For efficacy against otitis media, diagnoses were considered until April 30, 1998. For immunogenicity, blood samples were drawn from a subset of subjects at 2, 6, 12, 13, and 24 months of age. For safety, hospitalizations were assessed for 60 days after each dose, emergency room visits were assessed for 30 days after each dose, and outpatient clinic visits were assessed for 3 and 30 (seizures) days after each dose.

Reference therapy, dose, mode of administration, and lot number:
None

Name of Sponsor/Company: Wyeth-Lederle Vaccines and Pediatrics	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: 7-valent pneumococcal conjugate vaccine, meningococcal group C conjugate vaccine	**Volume:**	
Name of Active Ingredient: saccharide-CRM_{197} conjugates of pneumococcal serotypes 4,6B,9V,14,18C,19F,23F, saccharide - CRM_{197} conjugate of mening C	**Page:**	

Criteria for evaluation:

Efficacy:

Invasive Disease: A case of invasive pneumococcal disease was defined as a positive culture of *S. pneumoniae* from a normally sterile body fluid obtained from a child presenting with an acute illness consistent with pneumococcal disease. A subject was considered vaccinated per protocol if the following criteria were met: first dose ≥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. Per-protocol follow-up started 14 days after dose 3 and continued until the earliest of the following: onset of invasive pneumococcal disease, 480 days (16 months) without receipt of booster dose, termination of trial. Intent-to-treat follow-up occurred in all subjects who were randomized into the study and began immediately following randomization. The primary efficacy variable was cases of invasive disease due to a serotype contained in the vaccine during the per-protocol follow-up period in children immunized per-protocol. Secondary efficacy variables were 1)cases of invasive pneumococcal disease due to a vaccine serotype in the intent-to-treat population, 2)cases of any invasive pneumococcal disease, regardless of serotype, during the per-protocol follow-up period in children immunized per-protocol, and 3)cases of any invasive pneumococcal disease, regardless of serotype, in the intent-to-treat population.

Otitis Media (OM): A subject was immunized per-protocol if the following criteria were met: first dose ≥42 days of age, interval of 35-120 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. Per-protocol follow-up began 14 days after dose 3 and continued until either dropout from the health plan, age 16 months without receipt of booster dose, or April 30, 1998. Intent-to-treat follow-up occurred in all subjects who were randomized into the study and began immediately following randomization. The primary outcome was the overall incidence of OM episodes ("new visits") in the per-protocol follow-up. A child experienced a "new visit" if they had not had a visit for OM in the preceding 21 days. Secondary outcome variables included overall incidence of OM episodes in intent-to-treat population, and the risk of first OM episode, frequent OM episodes, tympanostomy tube placement, and all OM clinic visits in per-protocol and intent-to-treat follow-up. Cases of spontaneously-ruptured ear drums were also assessed.

Immunogenicity: Antibodies (IgG) to the 7 pneumococcal serotypes included in the 7VPnC vaccine were determined by ELISA on samples drawn at 2, 7 12-15, and 13-16 months of age. GMCs and % of subjects achieving defined values (i.e.≥0.15µg/mL and ≥0.50µg/mL for pneumococcal assays) were determined.

Safety: In a subset of subjects, prompted local reactions (erythema, induration, tenderness) were assessed for 2 days following each dose and prompted systemic events (irritability, change in sleep patterns, loss of appetite, vomiting, diarrhea, hives, change in skin tone, fever) and other systemic events (wheezing, convulsions, lethargic/limp, loss of consciousness, twitching) were assessed for 14 days after each dose. Emergency room visits within 3, 14 and 30 days of each dose, hospitalizations within 3, 14, 30 and 60 days of each dose, and outpatient clinic visits for seizures within 3 and 30 days and allergic reactions including hives as well as wheezing, asthma, breath holding and shortness of breath within 3 days were also assessed. All subjects who received a dose of study vaccine were included in the assessment of hospitalizations, ER visits, and outpatient clinic visits.