BOB used data from immunogenicity studies to help determine the efficacy of pneumococcal vaccine before, during, and after it was used in clinical trials. Its rationale for using such studies is this: If a vaccine does not produce good antibody response, it most likely will not protect an individual from a target disease.

Correlation between a quantifiable immunogenic response and a predictable level of protection has not yet been fully established for pneumococcal vaccine. For some vaccines, certain patterns of antibody responses can be correlated with some level of protection, but the minimum level of circulating antibodies necessary for protection against the target disease is not known. This situation applies to pneumococcal vaccine. Immunogenicity studies were included in some clinical trials of pneumococcal vaccine, and using data from these trials, BOB did attempt to correlate levels of pneumococcal antibody production with protection against pneumococcal disease. BOB's attempts at correlation continue today.

Clinical Trials

By law, BOB must require manufacturers to submit data from clinical trials to be used in its prelicensing evaluation of the safety and efficacy of new vaccines. The purpose of clinical trials of pneumococcal vaccines was to test the experimental vaccines' clinical safety and efficacy in defined human populations. The eight premarketing clinical trials on which BOB based its evaluation of the new polyvalent pneumococcal vaccine altogether involved about 43,000 U.S. and foreign subjects, including about 18,767 vaccinees (7,120 domestic, 11,647 foreign).3

[3]For a description of the methods and results of these premarketing clinical trials and other studies of experimental pneumococcal vaccine (excluding epidemiologic and immunogenicity studies), see app. 3.6.

Each clinical trial study population was divided into at least two groups: 1) an experimental group, which received the pneumococcal vaccine that was being evaluated; and 2) one or more control groups, which received either a placebo vaccine or a type of vaccine that differed substantially from the one being tested. In some studies, subjects were assigned to the experimental or control group on a random basis. Additionally, in some studies, subjects were paired on the basis of certain characteristics before being assigned to the experimental or control group. Furthermore, in some double blind clinical trials, neither the investigators nor the test subjects knew which vaccine was being administered to a given subject. The most ideal clinical trials were randomized, controlled, and double blind (Hales, 1979).

In clinical trials of pneumococcal vaccines, investigators observed subjects during a designated time period for adverse reactions and the presence or absence of disease. They then tabulated and analyzed data regarding the vaccine's safety and efficacy. Pneumococcal vaccine's relative safety was evaluated by measuring and comparing the incidence of acute adverse reactions in the experimental group with the incidence of similar reactions in the control group(s). Similarly, the vaccine's efficacy in most studies was determined primarily by measuring and comparing the incidence of pneumococcal pneumonia in the experimental group with the incidence in the control group(s).[4] To help assess efficacy in some trials, investigators also measured vaccinees' antibody responses to pneumococcal vaccine. Data generated in the trials were subjected to various types of statistical analysis.

[4]In one study, investigators measured the incidence of LRTI rather than pneumococcal pneumonia.

Appendix 3.6
REVIEW OF PREMARKETING CLINICAL TRIALS AND STUDIES BOB USED TO EVALUATE THE SAFETY AND EFFICACY OF POLYVALENT PNEUMOCOCCAL VACCINE

INDUSTRY-SPONSORED TRIALS

Merck Sharp and Dohme—Two South African Trials, 1973-76

From 1973 to 1976, Merck Sharp and Dohme (MSD) conducted two major clinical trials of pneumococcal vaccines among gold miners in South Africa (Smit, 1977). In the first trial, No. 315, investigators assessed the safety and efficacy of a 6-va]ent **polysaccharide vaccine (Types** 1, 2, 4, 8, 12, 25); in the second, No. 315A, they tested a 12-valent vaccine (Types 1,2,3,4,6,8,9,12,25, 51,56, 73).

Study No. 315.—In study No. 315, 983 subjects were given the 6-valent pneumococcal vaccine; 1,051 were given meningococcal A vaccine, and 985 were

given a saline (placebo) vaccine. The latter two groups served as controls. Subjects were randomly assigned to study groups, and all subsequent testing was done blindly, that is, without knowledge of the subjects' group assignment.

Researchers watched for the occurrence of pneumococcal pneumonia for about 24 months after immunization. Among subjects receiving pneumococcal vaccine who were studied for more than 2 weeks after vaccination, the attack rate of pneumococcal pneumonia was 9.2 cases per 1,000 persons. Among control subjects, the attack rate was 38.3 cases per 1,000 persons. The protective efficacy rate, that is, the percent reduction in type-specific pneumococcal pneumonia among those receiving pneumococcal vaccine, was 76 percent ($p < .001$).

Investigators also measured antibody responses to the pneumococcal vaccines. At least 74 percent of a subgroup of 40 subjects receiving pneumococcal vaccine developed antibodies to each type of pneumococcus represented in the vaccine.

To assess the incidence and nature of adverse reactions, investigators in study No. 315 observed vaccinees for 3 days following vaccination. Reported adverse reactions were minor. [1]

Study No. 315 A.—Study No. 315A was conducted in much the same manner as study No. 315. In study No. 315A, ***540*** subjects received a 12-valent pneumococcal polysaccharide vaccine; 585 received meningococcal A-C vaccine, and 550 persons received a saline (placebo) vaccine. Among subjects receiving the 12-valent pneumococcal vaccine, the attack rate of pneumococcal pneumonia was 1.8 cases per 1,000 persons, as compared to 22.0 cases per 1,000 persons in the control group. Thus, the protective efficacy rate was 92 percent ($p < .004$). At least 83 percent of those receiving pneumococcal vaccine developed antibodies to each of the 12 types of pneumococci represented in the vaccine. Again, the reported incidence of adverse reactions was low. [2]

In both of these Merck studies, informed consent was obtained from each participant. Miners who reported to the dispensary for medical attention were evaluated clinically for pneumococcal pneumonia, and if the clinical findings were positive, they were followed-up with chest X-rays and laboratory diagnostic work on serum and sputum samples. When indicated, medical treatment was provided.

Merck/Papua (Riley)—New Guinea Highlands Trial, 1973-76

From 1973 to 1976, I. D. Riley conducted a study of Merck's 14-valent vaccine (Types 1, 2, 3, 4, 5, 6, 7, 8, 12, 14, 18, 23, 25, and 46) in the New Guinea Highlands surrounding Papua (Riley, 1977). This study was cosponsored by Merck Sharp and Dohme, and the Papua Department of Public Health.

A total of 5,946 persons in Riley's study received the 14-valent pneumococcal vaccine; another 6,012 persons received a saline (placebo) vaccine and served as controls. Subjects' consent to participate was verified by thumbprint.

To assess morbidity in this study, investigators conducted bimonthly household surveys of half of the study subjects. Vaccinees were observed for the onset of pneumonia, which was diagnosed mostly clinically and, when possible, by X-ray.

Criteria used in this study to measure the difference in the incidence of pneumococcal pneumonia between vaccinees and controls were not as well defined as in Merck's two South African studies. To assess the incidence of morbidity, researchers in Riley's study used pneumonia or lower respiratory tract infection (LRTI) instead of type-specific pneumococcal pneumonia. Among the 5,373 people observed for morbidity for 16 months, 138 of the 2,660 observed control subjects developed LRTI, as did 114 of the 2,713 observed vaccinees. The difference in the incidence of LRTI between vaccinees and controls, therefore, was only 18 percent ($p < .05$).

In general, there was very little difference in vaccine-type pneumococcal isolation rates from among vaccinees and controls. Antibody responses were measured in 22 ,recipients of pneumococcal vaccine. A twofold increase in serum antibody titers, using prevaccination vs. postvaccination geometric mean titers, was demonstrated for 10 of **14** serotypes.

In the 3 years of this study, 303 subjects died—133 vaccinees and 170 control subjects. This was a 22 percent difference ($p < 0.05$). Forty-two percent (68) of the vaccinees and 55 percent (94) of the control subjects died from respiratory illnesses.

Vaccine-related side effects were studied only in the first 133 subjects receiving the pneumococcal vaccine; side effects were not reported for the control subjects. Of the 133 vaccinees observed for adverse reactions, 75 percent (98) reported no side effects, 42 percent (31) complained of a sore arm, 7 percent (9) complained of fever, and 3 percent (4) complained of a swollen arm. [3]

Merck Sharp and Dohme (Weibel)—Five Small U.S. Studies, 1967-77[4]

The results of five small studies that Merck conducted in the United States were reported by Robert

[1] See tables 7 and 8 in ch. 3.
[2] See tables 7 and 8 in ch. 3.
[3] See tables 7 and 8 in ch. 3.
[4] Merck studies reported by Weibel, No 384, No. 431, No. 454, No. 482, and No. 497, were not controlled clinical trials.

Weibel and associates (Weibel, 1977). Collectively, these five Merck studies, No. 384, No. 431, No. 454, No. 482, and No. 497, involved a total of 104 subjects.

All five were designed: 1) to measure the incidence of vaccine-related side effects to 12-valent (Types 1, *3, 4, 6, 8, 9, 12, 14, 19, 23, 51, 56)* or 14- valent (Types 1, 2, 3, 4, 6, 8, 9, 12, 14, 19, 23, 25, 51, 56) pneumococcal vaccines; and 2) to measure antibody titer responses.

In general, vaccine side effects observed in these studies were mild and local (redness, swelling or pain at injection site), but also quite common. Nearly all of the *42* vaccinated children and *86* percent of the 50 vaccinated adults reported some type of reaction. Most reactions began 4 hours after vaccination, About 40 percent of the children and 14 percent of the adults reported a mild fever (99° to 100.9° F). One child experienced headache, myalgia (muscle pain), and a maximum temperature of 104°F for 1 day; her local reactions lasted 5 days. [s]

[s]See tables 7 and 8 inch. 3.

FOREIGN-SPONSORED TRIALS

Chamber of Mines of South Africa (Austrian) —Three South African Trials, 1972-76

From 1972 to 1976, the Chamber of Mines of South Africa financed clinical testing of polyvalent pneumococcal vaccines among newly recruited workers in the East Rand Preparatory Mines in Boksburg, South Africa (Austrian, et al., 1976). Three major trials were conducted under the guidance of Robert Austrian, University of Pennsylvania, who tested two pneumococcal polysaccharide vaccines produced under NIAID contract by Eli Lilly: a 6-valent vaccine (Types 1,3,4,7, 8, 12) and a 13-valent vaccine (Types 1,2,3, 4, 6,7,8,9,12,14, 18,19, 25).

The three trials involved a total of 12,000 mine workers, assigned randomly to groups. About 4,000 received a pneumococcal vaccine; another 4,000 received a Group A meningococcal vaccine, and yet another 4,000 received a saline (placebo) vaccine. The major purpose of these trials was to assess the efficacy and safety of Lilly's 6- and 13-valent pneumococcal vaccines, using the meningococcal and saline vaccine groups as controls.

In one study, 1,493 subjects received the 13-valent pneumococcal vaccine; 1,527 received the Group A meningococcal vaccine, and 1,480 received the saline placebo. Vaccine recipients were observed for several months, and the incidence of putative pneumococcal pneumonia or pneumococcal bacteremia among them was recorded. Seventeen cases of pneumococcal pneumonia or bacteremia were diagnosed among recipients of the pneumococcal vaccine; 77 cases were diagnosed among recipients of the meningococcal vaccine, and 83 cases among recipients of the placebo. Based on these findings, the efficacy rate of the 13-valent pneumococcal vaccine was calculated to be 78.5 percent ($p < .0001$.)

Analyses of combined data from all three trials indicated that the vaccines tested had an overall *82.3* percent rate of efficacy against pneumococcal bacteremia caused by vaccine types of pneumococci, In other words, the incidence of pneumococcal bacteremia caused by serotypes of pneumococci represented in the vaccine was 82.3 percent lower among pneumococcal vaccinees than the incidence of such bacteremia among controls. The reported incidence of vaccine-related side effects was very low.[b]

[b]See tables 7 and 8 inch. 3.

U.S. GOVERNMENT-SPONSORED TRIALS

The National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) funded two major clinical trials of pneumococcal vaccine. In addition, NIAID Partially supported other small trials. Data from at least the two of NIAID-sponsored trials discussed below were used by BOB to evaluate the safety and efficacy of pneumococcal vaccine.