

# APPENDIXES

## Appendix 1.1

### PNEUMOCOCCAL VACCINE RESEARCH AND DEVELOPMENT (1881-1966)

#### Early Pneumococcal Research (1881-1931)

The pneumococcus was successfully isolated for the first time in 1880 by two researchers working independently, Sternberg in the United States, and Pasteur in France (White, 1938). For the next 5 years, several investigators, notably Friedländer and Fraenkel, debated the association between pneumococcus and lobar pneumonia, but this debate ended in 1886, with confirmation of the association by Weichselbaum.

Lobar pneumonia was a major “killer disease” in the latter part of the 19th century. Several investigators at the time, therefore, attempted to develop ways of protecting humans from the pathogenicity of pneumococci. In 1891, the Klemperers demonstrated the therapeutic value of pneumococcal serum therapy both in animals and in humans (White, 1938). These researchers withdrew blood from recovered patients, refined pneumococcal serum, and injected it into rabbits or other humans. The Klemperers found that in some rabbits, the serum conferred protection against pneumococcal disease; in others, it lessened the severity of disease. In humans, the Klemperers obtained similar, though somewhat less convincing, results with the serum.

At first, researchers believed that pneumococcal serum contained an antitoxin that could neutralize the hypothetical “toxins” of Pneumococci, thus conferring protection against pneumococcal disease. Later, however, investigators such as Metchnikoff, Mosny and Washburn, demonstrated an agglutination reaction, whereby pneumococci were aggregated by a protein substance in pneumococcal serum and thus rendered less able to produce disease (White, 1938).

The discovery of this agglutination phenomenon was an important one, because it contributed to the understanding of the basic immunologic antigen-antibody concept that ultimately led to a method of classifying different types of pneumococci. Neufeld and Haendel, who administered pneumococcal serum to counteract two distinct types of pneumococci, were among the first investigators to use the agglutination test to establish serotypes of pneumococci that produce pneumonia (White, 1938).

Researchers using Neufeld’s serological system of classification were better able: 1 ) to determine which types of pneumococci produce pneumonia and other

infections, 2) to conduct epidemiologic studies associating pneumococcal types with disease outbreaks in different geographical locations, and 3) to assess the severity of infections produced by specific types of pneumococci. Classification of pneumococcal types was also a prerequisite to the partially successful treatment of humans with type-specific antiserum, prepared initially in horses and later in rabbits.

#### Whole Cell Pneumococcal Vaccine Trials (1911-38)

Prevention of pneumococcal infections through the use of whole cell vaccines was initiated in 1911 in South Africa. In 1914, Wright and coworkers attempted to assess the prophylactic value of whole cell pneumococcal vaccines among South African gold miners (Wright, 1914). Pneumococcal pneumonia was a major endemic killer of these miners, and Wright’s team vaccinated over **50,000** workers. Data from this trial, the first major test of a pneumococcal vaccine in that country, did suggest the possible effectiveness of a whole cell vaccine, but nonetheless were felt to be inconclusive (Wright, 1914).

Following Wright’s clinical experiment, Lister was able to identify specific types of pneumococci found in South Africa (Lister, 1917). Using a whole cell vaccine containing five specific types of pneumococci identified by Lister, Maynard demonstrated a 20 percent reduction in the incidence of pneumococcal pneumonia among South African gold miners, but no significant reduction in the mortality rate (Maynard, 1915). Lister himself also demonstrated a significant protective value of this vaccine, but the design of his studies—he selected control groups from separate mines with different attack rates—was questionable (Heffron, 1939), and some scientists refused to accept his results as valid.

Based on the outcome of Lister’s trials, however, in 1930, one South African mining company began vaccinating all new worker recruits. The rates of morbidity and mortality associated with pneumococcal pneumonia dropped significantly among vaccinees, and although still somewhat controversial, the idea of vaccinating against pneumococcal infection gained greater acceptance (Heffron, 1939).

In general, early trials of whole cell pneumococcal vaccines among South African gold miners lacked: 1 ) adequate control populations, 2) rigorous bacteri-

ologic assessment of the causes of pneumonia among miners and the general population, and 3) observations of specific antibody production among vaccinated subjects. Despite these limitations, however, early studies did demonstrate the potential value of a pneumococcal vaccine in protecting a population against pneumococcal disease. They also gave some indication of the areas in which further research was needed.

### **Early Public Efforts to Control Pneumococcal Pneumonia (1931-46)**

Before the 1940's, patients with pneumococcal disease in the United States generally were treated with type-specific pneumococcal antiserum (Cole, 1929). Immune serum, obtained from animals immunized with pneumococci, was high in pneumococcal antibody content, and it was injected into patients with pneumococcal infection in hopes that the pneumococcal antibodies would reduce the severity of their disease or cure them.

In spite of the demonstrated effectiveness of pneumococcal antiserum, physicians in this country did not use it extensively. Some were unconvinced of, or confused about, the safety of the antiserum and its effectiveness against some types of pneumonia. The correct use of the serum required physicians to isolate the patient's infecting pneumococcus, an endeavor which could delay treatment for 1 or 2 days. Maybe most importantly, the antiserum was expensive, and its administration required expertise not found in many hospitals.

In 1931, Bigelow and White initiated a statewide pneumococcal pneumonia control program in Massachusetts (Dowling, 1973). The program included the following activities: 1) typing pneumococci in specimens collected in State laboratories; 2) training technicians to type specimens in small hospitals; 3) appointing consultants to verify diagnoses and administer the serum; 4) educating physicians to diagnose and treat pneumonia; and 5) providing free pneumococcal antiserum.

Under this program, the distribution of pneumococcal types in Massachusetts was studied, and better antisera were developed. Furthermore, the program may have contributed to a decline in the case fatality rate of pneumococcal pneumonia. During the first 5 years of its operation, the fatality rate in Massachusetts dropped from 33 percent to 17 percent (Heffron, 1937).

In 1936, the New York State Health Department established a pneumonia control program modeled after the one in Massachusetts. Under this program antisera were developed for five types of pneumococci, reports were made on 13,540 cases of pneumonia,

and the fatality rate of pneumonia was reduced (Stebbins, 1940).

By 1938, eight States were operating programs to diagnose pneumococcal disease and to distribute free serum. Because so few States were adopting pneumonia control programs, in 1938, then Surgeon General Thomas Parran asked Congress to appropriate Federal funds to establish more State pneumonia control programs. Congress obliged by allocating about \$1.1 million for such programs for fiscal years 1940 and 1941 (U.S. Ex. Br., PHS, 1941). Many States initiated programs in order to obtain a share of these funds.

The antibacterial drug, sulfapyridine, was introduced in 1939 and rapidly replaced pneumococcal antiserum as the standard treatment for pneumonia. Possible reasons for physicians' accepting sulfapyridine and other sulfonamides, and discarding pneumococcal antiserum include the following (Dowling, 1973):

1. Sulfonamides were equally effective against all types of pneumococci, thus apparently eliminating the need for time-consuming typing of pneumococci in patients' specimens.
2. The physician needed merely to write a sulfonamide prescription. The costly and time consuming procedures of intravenous administration of the antisera and hypersensitivity testing were eliminated.
3. Sulfonamides appeared to be safer than the serum.

As the widespread use of sulfonamides essentially eliminated the market for type-specific pneumococcal antisera, Federal funding for State pneumonia control programs in which pneumococcal antisera were used was cut dramatically. In 1945, all Federal funding for these programs was terminated. Soon thereafter, the control programs faded away. Sulfonamides were inexpensive, and most States discontinued all components of their pneumonia control programs, including pneumonia surveillance and physician education.

As the widespread use of sulfonamides essentially eliminated the market for type-specific pneumococcal antisera, Lederle Laboratories, which had been a major producer, stopped its investment in pneumococcal antisera products. The company also abandoned the production of diagnostic antisera for typing pneumococci.

According to Dowling (Dowling 1973):

Obsolescence eventually triumphed completely, and pneumococcal antiserum, the end-product of a series of technological innovations, was itself displaced because of technological innovation. It was thrown in the scrap heap along with the bustle, the pot-bellied stove, and the one-horse shay.

The total impact of early State pneumonia control programs cannot be comprehensively assessed, but certain observations are noteworthy (Dowling, 1973):

1. These programs were originally designed to work within the prevailing system of rendering medical care and gained appreciable support from local medical societies. The programs enhanced the professional or economic status of practicing physicians.
2. Initially these programs were funded primarily through private agencies, such as the Commonwealth Fund and an insurance company. Substantial State funds were allocated only after the initial programs were working. Federal funds were provided later, and these stimulated increased State financing.
3. Publicity for these programs was limited out of concern that public demand for the serum might surpass the level of its use among physicians.
4. These programs educated physicians about the diagnosis and treatment of pneumonia and provided free treatment to patients who, in the absence of such programs, would not have been treated at all.

### **Polysaccharide Pneumococcal Vaccine Trials and Product Development (1930-54)**

Francis and Tillett demonstrated the ability of pneumococcal capsular polysaccharides to stimulate the production of antibodies in humans (Francis, 1930). In subsequent investigations, researchers gained a fuller understanding of the chemistry and biology of the pneumococcal organism and developed an extensive system for classifying types of pneumococci on the basis of their capsular polysaccharides.

After 1930, researchers continued to expand on the theory that the pneumococcus, or more likely, certain chemical components of the pneumococcus, elicited an immunologic reaction in humans who had been stricken by pneumococcal disease. The objectives of their investigations were these: 1) to explain more fully the nature of human antibody reactions, 2) to isolate from pneumococci the specific components (antigens) responsible for eliciting human antibody reactions, and 3) to purify these antigens and prepare a vaccine that could protect humans from pneumococcal diseases.

Researchers during the 1930's began using, and demonstrated respective immunogenicity from, vaccines comprised of capsular polysaccharides extracted from pneumococcal cells (Felton, 1938). Fel-

ton and coworkers, over a 5-year period in the 1930's, conducted a number of studies of the safety and efficacy of Types 1 and 2 pneumococcal polysaccharide vaccines among West Coast Civilian Conservation Corps volunteers (Felton, 1938). In one study, individuals in a group of 3,126 volunteers were given 1 mg each of Type 1 and Type 2 polysaccharides, and then monitored for adverse reactions. Of these volunteers, 60 percent (1,881) had no adverse reaction, 32 percent (1,010) had a local reaction without systemic symptoms, 7.3 percent (214) experienced a local reaction with slight malaise, and 0.7 percent (21) had a severe local or systemic reaction.

In another of Felton's trials, 13,829 volunteers received 0.5 mg each of Types 1 and 2 capsular polysaccharides from a different source. Of these individuals, 43 percent (5,959) experienced no reaction, 35 percent (4,845) had a local reaction, 18 percent (2,476) experienced a local reaction with malaise, and 3.9 percent (549) had a severe reaction. Felton interpreted these results as evidence of the relative safety, compared to that of other vaccines, of the pneumococcal polysaccharide vaccines used in his tests.

In a third study, Felton attempted to assess the efficacy of Types 1 and 2 pneumococcal polysaccharide vaccines by measuring vaccine-induced antibody responses. Type 1 vaccine was administered to 281 individuals, and Type 2, to another 276. Most vaccinees over the age of 1 year did demonstrate a rise in antibody titer, and Felton interpreted this response as preliminary evidence of the efficacy of these two vaccines. Felton also attempted to account theoretically for the large variation among vaccinees' antibody responses to both vaccines.

Ekwurzel and coworkers, including Felton, also conducted large-scale clinical trials of a polysaccharide vaccine over a 5-year period in the 1930's. This team immunized 61,000 adult males with a vaccine containing 1 mg each of Types 1 and 2 capsular polysaccharides (Ekwurzel, 1938). The results were regarded as inconclusive because of incomplete bacteriologic studies by the investigators, but did strongly suggest that a pneumococcal polysaccharide vaccine might help reduce the incidence of pneumonia caused by the types of pneumococci represented in the vaccine.

During the 1940's, the use of antibiotic therapy to treat bacterial pneumonia gained widespread acceptance by physicians, and generally such therapy appeared to be quite effective. Nevertheless, some researchers did continue efforts to develop effective pneumococcal polysaccharide vaccines. Three major research efforts subsequent to the introduction of antibiotics provided some clinical evidence of the safety and efficacy of 2-, 3-, 4-, and 6-valent pneumococcal capsular polysaccharide vaccines in humans.

In 1945, MacLeod and associates showed that a 4-valent (Types 1, 2, 5, **7**) pneumococcal capsular polysaccharide vaccine could provide immunity against type-specific pneumococcal infections (MacLeod, 1945). In this study, conducted at an Army Air Force Technical School, approximately 8,500 men received the 4-valent vaccine, and an equal number of control subjects received a placebo (saline) injection. During a 7-month followup period, 4 cases of pneumococcal disease caused by types in the vaccine occurred in the vaccinated group, while 26 cases occurred in the control group. This was a highly statistically significant difference. The number of type-specific cases occurring in the group that was not immunized, however, was significantly lower than had been expected. This outcome was attributed to herd immunity, whereby individuals who have not been immunized gain some protection from a disease because of a reduction in its spread among individuals who have been immunized. All reported adverse reactions to the vaccine used in this study were mild and disappeared promptly.

In 1947, Kaufman demonstrated the safety and efficacy of 2-valent (Types 1 and 2) and 3-valent (Types 1, 2, and 3) pneumococcal polysaccharide vaccines (Kaufman, 1947). In Kaufman's 6-year study, a random group of 5,750 persons was immunized, and another group of 5,153 was observed as controls. All subjects in this study were civilians age **40** or over; more than 70 percent were age 60 or over. Among vaccinees, there occurred 99 cases of pneumonia, an incidence rate of **12.2** per 1,000; among controls, there developed **227** cases of pneumonia, an incidence rate of 44 per 1,000. Among immunized subjects, the mortality rate was 6.2 per 1,000 compared to 19.0 per 1,000 among controls. It should be noted, however, that a decrease in rates of pneumococcal disease caused by types not in the vaccine was also observed among the vaccinated groups (Fraser, 1979). Approximately 5 percent of those vaccinated experienced minor adverse reactions, such as pain at injection site and redness of skin, but all such reactions subsided within **48** hours.

In 1948, Heidelberger, et al., reported that a majority of study subjects receiving a single injection containing six types of pneumococcal capsular polysaccharides (Types 1, 2, 3, 5, 7, and 8) had demonstrated an antibody response to each type comparable to that observed following injection of one polysaccharide at a time (Heidelberger, 1948). Heidelberger reported further in 1950 that when these six polysaccharides were injected in a single immunizing dose, antibody levels in those injected persisted at

half maximal levels for 5 to **8** years (Heidelberger, 1950).

Based on the results of these early investigations, in the late 1940's, one U.S. pharmaceutical manufacturer, E. R. Squibb & Sons, developed and marketed two 6-valent pneumococcal capsular polysaccharide vaccines. One vaccine was for adults and contained capsular polysaccharide Types 1, 2, 3, 5, 7, and 8; and the other was for children and contained Types 1, **4**, **6**, **14**, **18**, and 19. With increasing emphasis on antibiotic treatment of pneumococcal diseases, however, neither of Squibb's pneumococcal vaccines ever gained widespread acceptance; so, in 1954, the company discontinued their production.

### Research on Pneumococcal Pneumonia and Bacteremia (1952-62)

Perceptions of a need for the development of a polysaccharide pneumococcal vaccine generally diminished following the introduction of antibiotics until Austrian and Gold produced data, between **1952** and 1962, showing that, despite the prevalent use of antibiotics to treat it, bacteremic pneumococcal pneumonia remained a significant cause of illness and death (Austrian, 1964). These researchers found in their study at Kings County Hospital in Brooklyn, N. Y., that 10 types of pneumococci accounted for at least **70** percent of bacteremic cases of pneumococcal pneumonia. Overall, 17 percent of those patients treated for bacteremic pneumococcal pneumonia with penicillin or other antibiotics died. In patients over 50 years of age, the mortality rate was 28 percent, and among individuals with complicating illnesses such as heart disease, stroke, and pulmonary emphysema, the mortality rate was **30** percent. These findings, combined with evidence of antibiotic-resistant strains of pneumococcal organisms, sparked renewed interest in the development of a pneumococcal vaccine.

### Pneumococcal Research After 1966

Research on the pneumococcus, pneumococcal diseases, and pneumococcal vaccine was renewed in 1967 primarily because of a substantial public effort launched, at the strong urging of Robert Austrian, by the National Institute of Allergy and Infectious Diseases (NIAID). The details of these research activities after 1966 are presented in chapter 2. The clinical trials that were used by the Bureau of Biologics (BOB) to assess the safety and efficacy of the currently licensed pneumococcal vaccine are discussed in chapter 3 and are described in detail in appendix 3.6.