Chapter 3

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Since 1979, Federal activities regarding the research, development, and use of pneumococcal vaccine have related to refining information on its appropriate use and developing a vaccine with broader coverage of pneumococcal disease. In coordination with international activities, the Food and Drug Administration (FDA) promoted the development of a new 23-valent vaccine. Two institutes of the National Institutes of Health—the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute on Aging (NIA)—have sponsored studies on efficacy among high-risk groups. At the same time, the Centers for Disease Control (CDC) and its Immunization Practices Advisory Committee (ACIP) have evaluated the efficacy of the vaccine for certain high-risk people and made recommendations regarding its use.

TESTING AND LICENSURE OF PNEUMOCOCCAL VACCINE

Postmarketing Surveillance

Within FDA, the Office of Biologics (formerly the Bureau of Biologics) of the National Center for Drugs and Biologics is responsible for the licensure of new vaccines to ensure that manufacturers comply with established requirements governing their manufacture and distribution. Manufacturers are required to maintain and submit reports of adverse reactions experienced during prelicensure testing as part of product license applications to FDA. FDA does not currently have the authority to mandate reporting of adverse reactions by physicians. Once a product license is issued, the system for monitoring adverse reactions becomes passive. Pharmaceutical manufacturers are required to maintain reports of adverse reactions that are voluntarily submitted to them. Although manufacturers are not required to transmit those reports of adverse reactions to FDA or any other Federal agency, they must make them available to FDA inspectors during annual inspections of establishments.

The detection of adverse reactions to the marketed vaccine thus relies primarily on individuals and organizations external to FDA. For example, a problem with the manufacture of one vaccine was discovered as a byproduct of independent researchers' investigating whether pneumococcal vaccine would induce protective immunity against group B streptococcus serotype **3** (11,71). The problem was solved by subsequent changes in manufacturing procedures.

Formulation of the 23-Valent pneumococcal Vaccine

The formulation of the 14-valent vaccine was based on epidemiologic studies conducted in the United States, Europe, and South Africa. Additional knowledge gained since the licensure of that vaccine in 1977 enabled the development of a 23-valent vaccine designed to be more efficacious. The development of the new vaccine was based on the following types of new information **(62,81,82):**

1. A worldwide surveillance system of type-specific pneumococci isolated from blood and cerebrospinal fluid conducted by the World Health Organization, the Centers for Disease Control, and the laboratory of Robert Austrian.
2. Studies of cross-reactivity within types using rabbit antisera and small-scale studies of healthy adults to address specific cross-reactivity questions.

3. Reported data on the emergence of pneumococcal types and subtypes with resistance to multiple antibiotics.
4. Increased information on the stability of component antigens of the pneumococcal vaccine.
5. Limited testing of dose-response relationships on healthy adults to determine the adequacy of the 25 µg dose per antigen compared to the 50 µg dose used in the 14-valent vaccine.

Representatives of the Office of Biologics and the CDC participated as members of the World Health Organization's (WHO) Expert Committee on Biological Standardization, which developed proposals for a pneumococcal vaccine with greater worldwide applicability. That committee considered the development of a vaccine to supplement the 14-valent vaccine (i. e., a vaccine that would not include any of the types in the 14-valent vaccine) to provide protection against other pneumococcal types (92). However, there was concern that with multiple vaccines on the market, confusion might result about which pneumococcal vaccine had been administered to a patient and revaccination might occur inadvertently. The WHO Committee ultimately recommended that a single formulation be developed and accepted as an international standard (92). The Committee also recommended that new types be added to that formulation if the World Health Organization identifies them as public health problems.

WHO organized laboratories worldwide to identify the frequency with which the 83 known pneumococcal types cause pneumococcal disease. More than 13,000 isolates of blood and cerebrospinal fluid, including some from the CDC, were analyzed to provide data for the development of the reformulated vaccine (62). Based on these data, the WHO Committee proposed a new polyvalent vaccine formulation containing 23 polysaccharide types. Table 4 summarizes the formulations of both pneumococcal vaccines and the rank order of the frequency of the pneumococcal types in the specimens that were analyzed. After reviewing WHO's recommendation, FDA's Vaccines and Related Biological Products Advisory Committee concurred with the suggested reformulation of the vaccine, and FDA advised the two manufacturers licensed to sell pneumococcal vaccine in the United States of the changes (81,82).

Table 4.—Pneumococcal Types in the 14-Valent and 23-Valent Vaccines

pneumococcal type	14-valent vaccine	23-valent vaccine	Rank order in worldwide specimens
1	X	X	3
2	X	X	23
3	X	X	5
4	X	X	2
5	X	X	15
6A	X		4[a]
6B		X	4[a]
7F	X	X	7
8	X	X	6
9N	X	X	14
9V		X	11
10A		X	20
11A		X	21
12F	X	X	12
14		X	1
15B		X	19[b]
17F		X	22
18C	X	X	9
19F	X	X	10
19A		X	13
20		X	17
22F		X	16
23F	X	X	8
25F	X		24
33F		X	18

[a]The ranks for 6A and 6B are based on the frequency Of the observations for both types together.
[b]The rank for 15B is baaed on the frequency of observations for both 15B end 15C.

SOURCE: J. B. Robbins, R. Austrian, C. J. Lee, et al., "Considerations for Formulating the Second-Generation pneumococcal Capsular Polysaccharide Vaccine With Emphasis on the Cross-Reactive Types Within Groups," *J. Infect. D/s.* 148(6):1136-1159, 1963.

Testing and Licensure of the 23-Valent Vaccine

Subsequent to notification of the recommended formulation of the 23-valent vaccine by FDA, Merck Sharpe & Dohme and Lederle Laboratories both submitted product license applications for reformulated vaccines. The Lederle application included the 23-valent formulation that was agreed upon internationally. The Merck Sharpe & Dohme application, which called for a 22-valent vaccine (excluding type 33 F), was subsequently amended to conform to the recommended 23-valent formulation.

Subsequent approval of these vaccines was based on the following studies performed by the manufacturers (81,82):

- manufacturing and control tests to verify the identity and purity of the inoculum and polysaccharides and to demonstrate the consistency of production of the 23 types of pneumococcal capsular polysaccharides,
- immunogenicity studies to assess adverse reactions and antibody response to the vaccine, and
- stability studies to determine the rate of degradation of the individual pneumococcal capsular polysaccharide types.

The immunogenicity studies performed by Merck Sharpe & Dohme used three separate groups of healthy volunteers (81,82). One group of 23 adults (ages 21 to 64) was vaccinated with a 22-valent vaccine (excluding type 33f) containing 50 µg per antigen, and a second group of 29 adults (ages 21 to 64) was vaccinated with a 22-valent vaccine containing 25 µg of each antigen. Since the studies used a 22-valent vaccine, Merck Sharpe & Dohme performed a third immunogenicity study of type 33F polysaccharide alone. In that study, 25 adult volunteers (ages 22 to 29) received a single injection of 0.5 ml of the 23-valent vaccine containing 25 µg of each antigen. The results of these studies showed that the level of immune response was acceptable in all cases (a twofold or greater rise of antibodies for all pneumococcal types in 87 to 100 percent of the recipients) and that the immune response to the 25 µg dose was essentially the same as the response to the 50 µg dose.

Lederle Laboratories used a 23-valent vaccine with 25 µg per type for its immunogenicity studies (81,82). Thirty-one healthy subjects between the ages of 45 and 65 were vaccinated with the vaccine. The results showed a twofold or greater rise of specific antibody levels in 93 to 100 percent of the subjects. Another study performed by Lederle using a 14-valent vaccine containing 10, 25, or 50 µg of the 14 types showed acceptable and essentially the same immune responses for the 25 and 50 µg doses.

It is disturbing that no prelicensure immunogenicity studies for the 23-valent vaccines involved people who were older than **65** or members of other high-risk groups. The small sample sizes also raise concerns about whether the study group is representative of the larger population and whether the results can be reproduced among larger numbers of people. FDA notes, however, that recent data compiled by the CDC suggest reasonable levels of efficacy for the 14-valent vaccine (see ch. 2).

Studies of the stability of the vaccines were based in part on studies of the stability of the two manufacturers' 14-valent vaccines. Since the 23-valent vaccines were newly developed at the time the applications were submitted, studies of the long-term stability of the vaccines could not be completed and are still ongoing.

Based on the results submitted by the manufacturers, FDA determined the vaccines to be safe. The adverse reactions (e.g., swelling or soreness at the sight of the injection, low-grade fever) observed in the recipients were not considered serious (81,82).

FDA approved PNEUMOVAX-23 (Merck Sharpe & Dohme) on June 30, 1983, and PNU-IMUNE 23 (Lederle Laboratories) on July 15, 1983. The approved indications for use of the vaccine specified on the package insert follow the recommendations for use of the 14-valent vaccine that were made by the ACIP in 1981 (see below).

RESEARCH ON pneumococcal VACCINE

The National Institutes of Health has been a major sponsor of pneumococcal vaccine research through NIAID and NIA. NIAID initiated a program to develop a polysaccharide pneumococcal vaccine in 1967. Its involvement in the early stages of pneumococcal vaccine development included providing support for Robert Austrian of the University of Pennsylvania, recognized as the leader in the development of this vaccine (85).

Two major studies of the efficacy of pneumococcal vaccine in the United States were also conducted under contract to NIAID: one that involved more than 13,000 essentially healthy

volunteers at the Kaiser-Permanante Medical Center in San Francisco, and the other of more than 1,300 long-term institutionalized patients at the Dorothea Dix Hospital in Raleigh, N.C. Neither of these studies demonstrated significant differences between vaccine and placebo recipients in the attack rates of radiographically documented pneumonia. During the Kaiser-Permanente trial, the incidence of pneumococcal pneumonia was very low. The results from Dorothea Dix Hospital were interpreted as suggesting that either the efficacy of the vaccine was low for the groups studied or the attack rate of pneumonia due to vaccine-susceptible pneumococci was very low (13).

NIAID is currently supporting basic research into the development of conjugated polysaccharide vaccines (coupling polysaccharide antigens to protein carriers). It is hoped that these vaccines will achieve greater efficacy for children and people with immunological deficiencies **(30).** Numerous clinical trials in infants and young children have been conducted. Although the initial work in the development of conjugated vaccines is being performed with *Hemophilus influenza* type b, the basic research is expected to be relevant to the development of other conjugated polysaccharide vaccines, such as pneumococcal vaccine.

NIAID has supported a large number of studies of the immunogenicity of pneumococcal vaccine through a contract with Gerald Schiffman of the State University of New York, who conducts assays to measure the levels of antibody stimulated by pneumococcal vaccine (44). Through that contract, NIAID is supporting the clinical trial of pneumococcal vaccine in the Veterans Administration (see ch. 2).

NIA has expressed concern about the absence of acceptable data on the effectiveness of pneumococcal vaccine for elderly people. Proceedings of a 1981 conference cosponsored by NIA and NIAID note that there are no published randomized placebo-controlled trials that conclusively show the efficacy of the vaccine in elderly people (65). NIA is supporting a study by Bentley and Schiffman, which is extending their preliminary findings on the immune response of elderly people to pneumococcal vaccine.

Concluding that more definitive studies were needed to determine the efficacy of pneumococcal vaccine in elderly people, NIA together with NIAID in 1982 issued an announcement calling for research and grant applications on the subject. The announcement specifically called for studies on the efficacy of pneumococcal vaccine in various subpopulations of the elderly and on the presence of nonvaccine serotypes of pneumococci in the immunized and nonimmunized elderly (84).

SURVEILLANCE ACTIVITIES

Since licensure of pneumococcal vaccine in 1977, CDC's activities have related to refining information on the vaccine's effectiveness and appropriate use for specific high-risk groups. The only surveillance system for pneumococcal infection in the United States is the CDC's Pneumococcal Surveillance System in the Center for Infectious Disease, Division of Bacterial Diseases. Since 1978, a group of hospitals (currently 37) have submitted subcultures of all pneumococci isolated from blood and cerebrospinal fluid to the CDC for serotyping (14). This sample of hospitals was nonrandomly chosen to include hospitals of different types in 22 different States. Most of the hospitals (25 of the original 37) were also participants in the CDC National Nosocomial Infection Study **(15).**

The original purpose of the pneumococcal Surveillance System was to examine the distribution of pneumococcal types and any change in that distribution with vaccine use. CDC data indicate that no shift in the distribution of pneumococcal serotypes has occurred since the introduction of the 14-valent vaccine (15). The CDC has also used information from its Surveillance System to estimate the type-specific efficacy of the 14-valent vaccine for elderly and other high-risk people (16). The methodology entailed comparing pneumococcal types associated with disease in vaccinated and unvaccinated people (see ch. 2).

RECOMMENDATIONS FOR USE OF PNEUMOCOCCAL VACCINE

The ACIP, an advisory group to the Public Health Services, is responsible for making recommendations on the use of new vaccines and for periodically revising recommendations on existing vaccines. ACIP members are selected from nominations made by professional and academic societies and represent experts in relevant disciplines (e.g., epidemiology, microbiology, public health, immunology) **(20).** Representatives of the FDA Office of Biologics and NIAID serve as ex-officio members. The ACIP also has liaison members from professional organizations such as the American Academy of Pediatrics and the American Medical Association.

The ACIP has issued two sets of recommendations on the use of pneumococcal vaccine: one in January 1978, shortly after a 14-valent vaccine was licensed, and the second in August 1981. The ACIP reviewed additional information regarding pneumococcal vaccine in February 1984.

The 1978 and 1981 statements reflected the Committee's sense that it had insufficient information about vaccine efficacy. The 1978 recommendations clearly stated that because of insufficient information on the efficacy of pneumococcal vaccine, " . . . definitive recommendations for its use cannot be formulated at the present time" (59). However, they also concluded that pneumococcal vaccine induces satisfactory antibody response in persons over 2 years of age, antibody titers are likely to remain high for several years, and the potential exists for reducing pneumococcal disease in the United States through use of the vaccine (59).

The 1981 statement also noted that available data were not yet sufficient for conclusive recommendations. Although it included a statement that the 14-valent vaccine had been shown in selected young healthy populations to reduce the incidence of pneumonia caused by types contained in the vaccine, the statement went on to say that the data upon which these findings were based came from adults who were at increased risk of disease but were not chronically ill **(58).**

Table 5 compares the two sets of recommendations for six groups. Neither list includes elderly people per se. This omission contrasts with the vaccine labeling, which includes people 50 years or older, whether or not they have underlying medical conditions.

The ACIP does issue unequivocal statements about the use of a vaccine when sufficient data supporting those recommendations are available. For example, in its 1982 recommendations on influenza vaccine, the ACIP "strongly" recommended the vaccine for all older persons, particularly those over age 65, and for five other high-risk groups **(37).** Thus, the tone of the 1978 and 1981 pneumococcal vaccine recommendations is a reflection of the ACIP's perception that definitive evidence on the efficacy of pneumococcal vaccine did not exist at that time.

NATIONAL OBJECTIVE FOR 1990

The 1979 Surgeon General's draft report on health promotion and disease prevention established reduction in the number of premature deaths from pneumonia and influenza as a primary goal (88). The goals established in 1979 were reaffirmed when a series of "1990 Immunization Objectives" were published in 1983. Among the objectives to implement that goal was one regarding pneumococcal vaccine:

> By 1990, at least 60 percent of high-risk populations., as defined by the ACIP. should have received vaccination against pneumococcal pneumonia; at least 50 percent of people in populations designated by the ACIP should be immunized within 5 years of licensure of new vaccines for routine clinical use.

This objective was given a *medium priority* for Federal activity and assigned to the CDC for implementation. The working groups that developed this and other national objectives foresaw their attainment through the active participation of or-

Table 5.–Recommendations of the Immunization Practices Advisory Committee (ACIP), 1978 and 1981

Target groups	1978	1981
Persons older than 2 with splenic dysfunction or anatomic asplenia (absence of spleen)	Should benefit from being immunized	Should benefit from immunization. Failures have been reported, perhaps due to impaired antibody responses, but vaccine is recommended because patients are known to be at high risk of developing fatal bacteremia
Persons older than 2 with certain chronic illnesses associated with a greater risk of pneumococcal disease	Might benefit from immunization. Because risk and case fatality increase with age, benefits of vaccination should increase with age	Should be considered candidates for vaccination. Vaccine may be increasingly beneficial as these patients grow older because of increased fatality rate from pneumococcal infections. Vaccine efficacy in these groups needs further evaluation
Healthy populations	Mass immunization is not currently recommended	Insufficient data to formulate a recommendation on routine use of the vaccine for the general population, including the elderly. This should not preclude health care providers from immunizing healthy persons whom they believe may benefit
Closed populations such as those in nursing homes or residential schools when there is an acute outbreak or high rate of endemic pneumococcal disease	Immunization of the entire closed population might be an effective control measure	Vaccination of the entire closed population should be considered
Populations living in areas where there are localized outbreaks of pneumococcal disease caused by types represented in the vaccine	Selective immunization of groups in the community epidemiologically believed to be at particular risk may be useful	Selective immunization of those at high risk should be considered
Patients at high risk of influenza complications (particularly pneumonia)	Consideration should be given to vaccinating such patients	pneumococcal and influenza vaccines can be given at different sites at same time without increased side effects
Pregnant women	Theoretically should not be harmful but in view of recommendations that unnecessary drugs and vaccines should not be given during pregnancy, pneumococcal vaccine should only be used when there is substantial risk of infection	Safety for pregnant women has not been evaluated. Should not be given during pregnancy unless risk of infection is substantially increased
Second or booster doses	There appears to be no booster effect with additional doses	Should not be given at this time because of marked increase in adverse reactions with reinfection of pneumococcal vaccine

SOURCES: "Recommendation of the Immunization practices Advisory Committee (ACIP): pneumococcal Polysaccharide Vaccine," *Morb. Mortal.* Weekly *Rep.* 30:410-419, 1981; and "Recommendation of the Public Health Service Advisory Committee on Immunization practices: pneumococcal Polysaccharide Vaccine," *Morb. Mortal* Weekly *Rep.* 27(4):25-31, Jan. 27, 1978.

ganizations and interested parties at all levels of Government and within the private sector (41).

At the time the objective was set, it was noted that baseline data for measuring progress toward the objective were not available. Periodic sample surveys were noted as the source of data for future assessment of whether or not the objective was being approached (86). The CDC has at least two potential sources of information: the Annual Immunization Survey and Biologics Surveillance. Through the Bureau of the Census, the CDC collects information on the use of vaccines in its annual U.S. Immunization Survey. Using a random sample of 35,000 housing units, the survey reports the percent of the population that have had rubella, measles, diphtheria-tetanus-pertussis, poliomyelitis, mumps, and influenza vaccinations. Although the U.S. Immunization Survey has not covered pneumococcal vaccination, the CDC plans to include it in the survey beginning this year **(21).** However, because of the small numbers of people who receive pneumococcal vaccine each year, the survey may not be able to provide statistically significant data about use in the target population.

The CDC also compiles "Biologics Surveillance" on a semi-annual basis. This document lists sales net of returns for the major vaccines marketed in the United States by three or more manufacturers. Although data on pneumococcal vaccine have not been included to date, they maybe added in the future. Since only two manufacturers market pneumococcal vaccine in the United States, this step would require special arrangements between the CDC and the manufacturers.

Despite the existence for several years of the objective of vaccinating **60** percent of the target group, the CDC has only recently begun to collect baseline data and has not actively promoted vaccine use. This passive posture has been consistent with uncertainty regarding efficacy (33), appropriate target groups, and the indefinite recommendations of the ACIP. However, at its recent meeting, the ACIP began to reconsider pneumococcal vaccine and expressed an intention to change substantially its previous statement. In light of data that suggested efficacy of about **60** to **70** percent for elderly people and some other high-risk groups (see ch. 2), the Committee stated a desire to develop more definite recommendations for specific target groups. It also charged a subcommittee to prepare draft recommendations for the April **1984** meeting.