Chapter 1

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## BACKGROUND AND SCOPE OF THE STUDY

Since 1881 when Pasteur in France and Sternberg in the United States independently isolated the pneumococcus, studies of this bacterium have been associated with pathbreaking discoveries in the sciences of bacteriology and immunology. In 1981, the pneumococcus was also associated with a pathbreaking event in health policy when pneumococcal vaccine became the first preventive technology to be covered by the Medicare Program. According to legislation creating the Program in 1965, Medicare, like most other health insurance, explicitly excluded preventive technologies (e.g., vaccines) from coverage. Although legislation has repeatedly been introduced to cover influenza vaccine, and bills now before Congress would extend coverage to hepatitis B vaccine, to date pneumococcal vaccine remains the only preventive technology covered.

At the time that polysaccharide pneumococcal vaccine[1] was marketed in 1978, the Office of Technology Assessment undertook a study entitled *A Review of Selected Federal Vaccine and Immunization Policies.* Published in 1979, that report used pneumococcal vaccine as a case study and included a cost-effectiveness analysis of the vaccine's use against pneumococcal pneumonia. In December 1983, as an outgrowth of their interest in preventive services for elderly people, the Subcommittee on Health and Long-Term Care of the House Select Committee on Aging requested OTA to update that work. The Subcommittee expressed particular interest in evaluation of the vaccine's efficacy and safety and in Federal activities regarding its use, including experience with Medicare coverage.

In the time allotted for this technical memorandum, it was not possible to totally recalculate OTA's previous cost-effectiveness analysis of pneumococcal vaccination against pneumococcal pneumonia (77). However, the memorandum contains current information about many of the variables in the analysis and an evaluation of the degree to which previous predictions remain valid in light of new evidence. Particular attention is given to the vaccine's efficacy, which has been the subject of some uncertainty in recent years. Familiarity with the earlier report would be helpful because this technical memorandum concentrates on the literature and other developments after 1979.

Although there is great policy interest in compensation for recipients who suffer severe adverse reactions from vaccines, this technical memorandum does not consider that subject. As a polysaccharide (as opposed to a whole killed or attenuated live) vaccine, pneumococcal vaccine has been associated with a low rate of adverse reactions and few severe ones (see ch. 2). In addition, pneumococcal vaccine, unlike many other vaccines, especially those intended for children, is not recommended for general use, and its use in the general population has not been supported with Federal grant funds.

pneumococcal bacteria may cause disease in different parts of the body: pneumonia in the lungs, otitis media in the middle ear, meningitis in the brain, and bacteremia as a blood-borne infection. Although pneumococcal pneumonia is the most common form of pneumococcal disease (58), such a diagnosis is difficult to differentiate from other forms of pneumonia because pneumococcal bacteria exist in the upper respiratory tract without causing disease.

At the time of the OTA report on vaccine policy, two pneumococcal polysaccharide vaccines *were* being marketed, each with capsular polysaccharides of 14 of the 83 pneumococcal types. Merck Sharpe & Dohme began marketing PNEUMOVAX in February 1978, and Lederle Laboratories in-

[1]The vaccine is composed of purified polysaccharides from the capsules of different types of pneumococci. When injected into humans, these capsular polysaccharides stimulate the formation of serum antibodies that provide immunity against those types of pneumococci (77).



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troduced PNU-IMUNE in August 1979 (77). The Food and Drug Administration (FDA) in 1977 had approved the vaccine for immunization against pneumonia and bacteremia caused by the types of pneumococci in the vaccine in certain high-risk people 2 years of age or older. These groups, who were at higher risk of developing complications or dying from pneumococcal pneumonia, were identified as people 50 years or older; people with diabetes mellitus or chronic heart, bronchopulmonary, renal, or metabolic disease; residents of chronic care facilities; or people recovering from severe diseases. FDA also stated that data suggested efficacy for people over age 2 with sickle cell anemia, splenectomy, or impaired splenic function.

In 1978, the Advisory Committee on Immunization Practices (ACIP) (now the Immunization Practices Advisory Committee), a body of nongovernmental experts who advise the Public Health Service, issued recommendations on the use of pneumococcal vaccine (59). The ACIP stated that limited information on efficacy prevented definitive recommendations, but did indicate certain high-risk groups that might benefit from the vaccine. Although the statement noted that incidence and mortality from pneumococcal disease, and presumably the benefits from vaccination, increase with age, it did not indicate a specific age.

The remainder of this chapter summarizes material presented in the body of this technical memorandum on developments that have occurred since 1979 in refinement of the vaccine, recommendations for its appropriate use, and Medicare coverage. Also summarized is the reexamination of the 1979 cost-effectiveness analysis. The chapter concludes with a section on implications for policy.

## SUMMARY

### Federal Activities

Since 1979, Federal activities regarding pneumococcal vaccine have concentrated on developing a new vaccine with broader coverage of pneumococcal disease and on refining information about appropriate use.

In June and July 1983, the FDA approved for marketing two additional pneumococcal vaccines, each with antigens (polysaccharides) of 23 pneumococcal types. The two vaccines were marketed in July 1983, PNEUMOVAX-23 by Merck Sharpe & Dohme and PNU-IMUNE 23 by Lederle Laboratories. FDA established the 23-valent formulation based on the latest epidemiology and collaborative studies with the two manufacturers. FDA coordinated its activities with the World Health Organization, which adopted the same formulation for international standardization. The 23-valent vaccine contains more stable antigens for some pneumococcal types and provides coverage against 90 percent of the types causing pneumococcal bacteremia. By contrast, the 14-valent vaccine contained types responsible for 75 percent of pneumococcal bacteremia (see ch. 2).

The National Institutes of Health (NIH) and particularly the Centers for Disease Control (CDC) have funded or gathered information on the immunogenicity and efficacy of the vaccine, especially for elderly and other high-risk groups (see ch. 3).[2] The ACIP has used this and other information to reformulate their recommendations. An ACIP statement in 1981 again noted the lack of definitive information on which to judge vaccine efficacy for many high-risk groups, including elderly people. But the 1981 recommendations stated that certain high-risk people "should be considered" for vaccinations or "should benefit" instead of the 1978 language that they "might benefit" (58). In both years, the ACIP noted that mortality from pneumococcal disease increases with age, but did not cite a particular age group as be-

[2] Immunogenicity refers to the production of an immune response, such as the production of antibodies **in response to the antigens in the vaccine. Efficacy is the probability that the vaccine will protect against disease under ideal conditions of use, such as clinical trials. Although a vaccine may also reduce the seventy of disease, the only data for pneumococcal vaccine relate to prevention of disease. Effectiveness refers to the probability of vaccine protection under average conditions of use, such as clinical practice.**

ing at high risk. The ACIP did identify people at high risk of developing pneumococcal disease or having more severe complications because of certain underlying conditions: sickle cell anemia, multiple myeloma, cirrhosis, renal failure, splenic dysfunction, splenectomy, and organ transplant. In addition, people with other chronic conditions may be at higher risk: alcoholism, diabetes milletus, congestive heart failure, chronic pulmonary disease, or conditions associated with immunosuppression. People with cerebrospinal fluid leakage may be at higher risk of pneumococcal meningitis (59).

In light of additional data on the efficacy of the vaccine, the ACIP in February 1984 expressed a much more positive attitude regarding the use of the vaccine (see ch. 2) and stated the intention of reevaluating its recommendations. After a subcommittee report at the April 1984 meeting, the ACIP began to draft a revised statement.

As a result of legislation passed in December 1980, the Medicare Program began covering pneumococcal vaccination as a Part B service on July 1, 1981. Unlike most other Part B services, which are subject to a deductible and copayment by the beneficiary, Medicare pays 100 percent of the reasonable charge for the vaccine and its administration.

No data are available on the use of pneumococcal vaccine by Medicare beneficiaries or expenditures by the Medicare Program for pneumococcal vaccination (see ch. 4). On the basis of sales reported by vaccine manufacturers and different definitions of the target group, 20 to 25 percent of the people over age 65 or as many as 6.6 million Medicare beneficiaries may have received pneumococcal vaccine.

## Reconsideration of the Cost Effectiveness of Vaccination Against pneumococcal Pneumonia

OTA's cost-effectiveness analysis calculated the expected changes in health effects and medical care costs produced by vaccination against pneumococcal pneumonia as compared with continuation of the situation before the vaccine was available, in which the disease was treated if it occurred. The analysis first took a societal perspective and included all medical care expenditures, whether paid by patients or third parties. The subsequent analysis included only expenditures that would be paid by the Medicare Program. The base case used estimates of variables that were considered most likely in 1978, and a sensitivity analysis tested the effect on the results of varying the values of certain factors *over* reasonable ranges.

No data were available for this technical memorandum on the current incidence of pneumonia, which has declined substantially over recent decades in all age groups. It is therefore not known whether the use of pneumococcal vaccine has prevented pneumococcal pneumonia to such a degree that the secular decline in pneumonia has been accelerated.

Reconsideration of OTA's analysis confirmed the base case estimates for all the variables except the incidence of pneumococcal pneumonia and the duration of immunity for elderly people. Although most of the information concerned the 14-valent vaccine, available data on the 23-valent vaccine were incorporated as well.

OTA's base case estimated that 15 percent of all pneumonia is pneumococcal, which corresponds to about 2.2 cases per 1,000 U.S. population per year. The low estimate was 10 percent of all pneumonia. Because of the difficulty of distinguishing pneumococcal from other pneumonias, estimates of incidence have been extrapolated from data on the incidence of pneumococcal bacteremia. Data on bacteremia that have been accumulated since 1979 suggest that the rate of pneumococcal pneumonia is closer to the low estimate of 10 percent of all pneumonia or 1.4 cases per 1,000 population per year (see ch. 2). By calculating incidence as a percentage of all pneumonia, OTA's analysis had incorporated the fact that incidence and complications are higher for elderly people.

Although OTA's base case estimate of 8 years duration of immunity from the vaccine continues to apply for healthy adults, it may be somewhat shorter for elderly and chronically ill people. No data relate directly to the duration of immunity that has been observed for these groups; instead, the new information comes from declines in an-

tibody levels over time. For pneumococcal vaccine as for immune responses in general, people with disease causing immune suppression are likely to have much shorter durations of immunity. For most groups, the duration of immunity is likely to be well above OTA's low estimate of 3 years.

With the introduction of the 23-valent vaccine, OTA's base case estimate that pneumococcal vaccine has an efficacy rate of 80 percent continues to appear reasonable (see ch. 2). This conclusion is based on information regarding efficacy that has been reported by the CDC and other investigators. The 14-valent vaccine has been about 65 percent effective in preventing pneumococcal bacteremia in people over age 2, including those who are elderly. On the basis of the increased coverage against pneumococcal types in the 23-valent vaccine, it is estimated that the new vaccine will have an efficacy rate of about 80 percent against pneumococcal pneumonia.

In 1978, OTA estimated that each vaccination cost $11.37, including the vaccine and its administration.[3] The current estimate of $14.65 incorporates a lower vaccine price and higher administration fee. The Medicare Program, which reimburses only for reasonable charges, may pay less than this amount. In one State, for example, Medicare is currently reimbursing $9.60 for a pneumococcal vaccination. The current estimated cost of vaccination under a public immunization program is $3.80, compared with the 1978 estimate of $3.45 (see ch. 2).

**If the medical costs of survivors are excluded, OTA's** 1978 analysis indicated that pneumococcal vaccination against pneumonia would be cost saving to society for people 65 years or older. **With survivors' medical care costs included,** vaccination was estimated to gain a year of healthy life for an elderly person for $1,000.

With the 1978 base case estimates, but **excluding survivors' medical costs,** vaccination for an elderly person would be even more cost saving in 1983 because treatment costs have risen more than vaccination costs. **Excluding survivors' medical costs** but incorporating the updated assumptions, a lower incidence of pneumococcal pneumonia (10 percent of all pneumonia) and a shorter duration of immunity (3 years), raises the net cost of gaining a year of healthy life. For a person 65 years or older, the net cost would then range from about $300 to $6,200 **per** year of healthy life gained by vaccination against pneumococcal pneumonia (see ch. 2). Continuing research and surveillance will be able to clarify the duration of immunity for elderly people, which has the most effect on these estimates.

The 1978 analysis estimated that the Medicare Program would incur a net cost per elderly beneficiary vaccinated of about $5 for a gain in 1.59 healthy days of life. The results for the Medicare Program parallel those for society except that Program costs **include survivors' medical costs** and do not include all savings in treatment costs (see ch. 2). With the 1978 base case estimates and 1983 costs, including $9.60 as the vaccination cost, Medicare would realize net savings of about $2.40 per elderly beneficiary vaccinated. With $9.60 as the reasonable charge paid by Medicare, a lower incidence of pneumococcal pneumonia (10 percent of all pneumonia), and a shorter duration of immunity (3 years), Medicare would incur net costs of about $5.50 per elderly beneficiary vaccinated or about $4,400 per year of healthy life gained. If 25 percent of elderly beneficiaries were vaccinated (about 6.6 million), the net cost to the Medicare Program over time in 1983 dollars would total about $37 million to gain about 8,400 years of healthy life.

[3] Ideally, a cost-effectiveness analysis measures the actual cost of resources used. **In practice, charges for services, especially for physician services, are often used as a proxy for costs.**

## POLICY IMPLICATIONS

As the adoption and use of a medical technology proceed, the evolution and refinement of indications for its use are a common and worthwhile phenomenon. This process is continuing for pneumococcal vaccine with the involvement of NIH, which is funding research to assess vaccine immunogenicity and efficacy; the Veterans Administration (VA), which is supporting a clinical trial; the CDC, which is conducting surveillance activities; and the ACIP, which is reconsidering its recommendations in light of new information.

Uncertainty concerning the duration of immunity and the immunogenicity and efficacy of the vaccine for high-risk groups remains (see ch. 2). It has been estimated that clinical trials to establish vaccine efficacy more definitively would require more than 100,000 people and large research expenditures (69). Alternative, less expensive methods are available and being used, such as retrospective case control studies. Although immunogenicity is only a proxy for efficacy, it would be less costly to reexamine the antibody levels of people in earlier clinical trials. These alternatives would be appropriate for NIH to consider in the context of its grant solicitations. The results of the VA clinical trial of high-risk veterans will bear on both the duration of high antibody levels and efficacy over at least a 3-year period (73). In light of these uncertainties, it is disturbing that the new 23-valent vaccine was not tested on elderly or other high-risk groups before FDA licensed it in 1983.

Approximately 25 percent of the target group has received pneumococcal vaccine since 1978, with a range from 20 to 35 percent, depending on the definition of high-risk groups and the size of inventories. This level of use may appear low considering the health benefits to be gained from greater use and the cost-effectiveness results.

From another vantage point, however, it is surprising that use has reached even this level considering the impediments faced by preventive technologies in general and pneumococcal vaccine in particular. The use of preventive technologies for adults has characteristically been low. Both influenza and pneumococcal vaccines have had low levels of use, even among the patients of physicians who support them (55). Neither adults nor the clinicians who care for them have been attuned to prevention in the way that parents and pediatricians have been for children. The strategies appropriate for preventive technologies for adults may also differ by being targeted to specific high-risk groups instead of to the general population. For childhood immunization, entry to elementary school has served as a review point for vaccination, and the promotion of vaccines for adolescents and young adults has increasingly involved other institutions, such as colleges and the military. It is more difficult to conceive of institutional strategies for older adults.

pneumococcal vaccination has faced additional barriers. Uncertainty has surrounded the efficacy of the vaccine since it was first marketed in 1978, as indicated by the ACIP statements on its use. This situation may well have discouraged clinicians from vaccinating their patients. There is also a low level of public awareness of pneumococcal disease. Elderly people are therefore unlikely to feel at great risk of such disease and to seek the vaccine from their physicians. It is also not clear that clinicians perceive the greater risk of complications for elderly or other high-risk groups.

Because of these general and specific constraints, wider use of pneumococcal vaccine would require that further steps be taken. One is a clearer statement by the ACIP on whether or not the vaccine is recommended for certain high-risk groups, including elderly people. Primarily because of the uncertainty regarding efficacy and the tone of the ACIP recommendations, the CDC has not moved to implement the objective of the Department of Health and Human Services to have 50 to 60 percent of the target population vaccinated by 1990. The ACIP is working on a revised statement, which should be published this year.

If the Government wishes to promote the use of pneumococcal vaccine, efforts beyond Medicare coverage will be needed to reach elderly adults. The hospital may represent an institution through which pneumococcal vaccination could

be provided. On the basis of the percentage of patients with pneumococcal pneumonia or bacteremia who were hospitalized within the previous 3 years for any cause, it has been estimated that vaccinating certain patients on discharge from their previous hospitalization could avoid 10 percent of hospital admissions for all pneumonia (22). Since revaccination poses some hazard (see ch. 2), such an approach would require some precaution so that patients who have already received the vaccine are not mistakenly revaccinated. Since pneumococcal vaccination, unlike almost all other services, is excluded from the new system of payment by diagnosis related groups, Medicare will reimburse hospitals for the cost of vaccinating inpatients (see ch. 4).

Another possible mechanism is providing Federal grant funds for pneumococcal vaccine like those for childhood vaccines. This mechanism has been used for influenza vaccine, another vaccine targeted to specific segments of the population, although only for 1978-79 and 1979-80. The CDC would then administer these grants to States. In contrast to Medicare coverage, which takes a passive stance, this approach sets up at the Federal level a cadre of people interested in promoting vaccine use by working at State and local levels. The cost of vaccination under such public programs is also much lower than under private provision and hence Medicare, an estimated **$3.80** compared with $9.60 or $14.65 (see ch. 2).

Certain measures regarding preventive technologies for adults relate to pneumococcal vaccine. Segments of the medical profession are taking steps to promote the use of preventive technologies by physicians who care for adults. The ACIP has developed detailed guidelines for adult immunization and expects to publish them in CDC's *Morbidity and Mortality Weekly Report* in 1984. The Committee on Immunization of the American College of Physicians is developing guidelines for internists regarding adult immunizations and has coordinated its activities with the ACIP (74). The Committee intends to publish its statement in a medical journal and may channel information into medical schools through the Society for Research and Education in Primary Care and Internal Medicine. Both of these guidelines will include statements on pneumococcal vaccine.

Although special factors apply to pneumococcal vaccine, in many respects it typifies the problems of a preventive technology for adults. With increases in life expectancy, more adults have more years in which to benefit from prevention of disease and disability. As the percentage of the population that is elderly continues to grow, policy issues regarding such preventive technologies promise to take on added importance. More definitive findings about preventive technologies for adults and for the general population, however, would require a more exhaustive study of the literature and public policy than is possible in this technical memorandum.