
Chapter 2

**Reconsideration of the Cost
Effectiveness of Vaccination
Against Pneumococcal
Pneumonia**

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A 1979 OTA report on Federal vaccine policy included as a case study a cost-effectiveness analysis of vaccination against pneumococcal pneumonia (77). That 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 results, expressed as cost-effectiveness ratios, represented the net medical cost per year of healthy life that would be gained by a person who was vaccinated.

The analysis first took a societal perspective and included all medical care expenditures, whether paid by patients or third parties. The subsequent analysis from the perspective of the Medicare Program included only expenditures that would be paid by that program. Children under age 2 were excluded because the vaccine has not been shown to be uniformly efficacious for them. A sensitivity analysis tested the effect on the results of varying the values of several uncertain factors over reasonable ranges.

This technical memorandum draws on information accumulated since 1979 to reevaluate several assumptions in that analysis. Also incorporated is information on the 23-valent pneumococcal vaccine which, has been marketed since July 1983. Specifically examined are assumptions regarding the following variables outlined in table 1:

- incidence of pneumococcal pneumonia,
- proportion of pneumococcal pneumonia caused by the types of pneumococci against which the vaccine is directed,
- efficacy rate,
- duration of immunity,
- safety,

- **cost of** vaccination, and
- medical costs in extended years of life.

This chapter first reexamines the estimates of those variables and then *uses* the revised estimates to reexamine the cost-effectiveness results and the costs to the Medicare Program of paying for pneumococcal vaccination. It was not possible within the confines of this technical memorandum to obtain current information on some of the assumptions made in the cost-effectiveness analysis. No new information was obtained on deaths from all pneumonia cases or on the rate at which mortality from all pneumonia cases is declining. Nor was there a reexamination of the way pneumonia cases are treated, including the extent to which people are treated as inpatients or on an ambulatory basis, the use of diagnostic procedures such as chest X-rays and laboratory tests, and the use of antibiotics. It was also not possible in this technical memorandum to recalculate the sensitivity analysis, with high and low ranges of uncertain variables.

Although discount rates and the weights used for the morbidity-mortality index (quality-adjusted life years or QALYs,) were not specifically reexamined, their values continue to appear reasonable. The discount rate takes into account the preference that people have for obtaining benefits now instead of in the future and the fact that funds can be invested in alternative ways (78). The discount rate, which concerns time, is distinct from inflation, which concerns the level of prices. OTA's cost-effectiveness analysis expressed all costs in terms of 1978 dollars. Although it was not possible to reexamine the use and price of treatment for *pneumonia*, the section on the cost of vaccination reviews changes that have occurred in the relative prices of hospital and physician services.

Table I.—Assumptions for OTA's Base Case and Sensitivity Analysis,^a1978

Variables	Base case	Sensitivity analysis ^a	
		High	Low
Proportion of pneumonia that is pneumococcal	15%	35%	10%
Deaths from pneumonia	Death certificates with pneumonia as the underlying cause	Death certificates with pneumonia mentioned	Base case estimate
Decline in mortality from pneumonia	Same decline as overall death rate	Fast decline ^b	No decline
Cases of inpatient pneumonia	First listed diagnoses of pneumonia from Hospital Discharge Survey	All listed diagnoses of pneumonia from Hospital Discharge Survey	Base case estimate
Cases of ambulatory pneumonia	Based on pneumonia visits from National Ambulatory Care Survey and adjusted data from Health Interview Survey	Based on data from Health Interview Survey	Base case estimate
Proportion of pneumococcal pneumonia caused by vaccine types	75%	100%	50/0
Efficacy rate	800/0	100%	40%
Duration of immunity	8 yrs.	72 yrs. (lifetime)	3 yrs.
Safety: General side effects	1 case of severe systemic reaction per 106,000 vaccines, 5 cases of fever per 100 vaccines	Base case estimate	Base case estimate
Guillian-Barré syndrome as side effect	No incidence	Incidence same as with 1976 swine-flu vaccination	Base case estimate
Cost of vaccination	\$11.37	Base case estimate	\$3.45
Medical costs in extended years of life	Included	Base case estimate	Base case estimate
QALY weights for disability days	Day in bed 0.4; day out of bed 0.6	Day in bed $\sqrt{0.4}$; day out of bed $\sqrt{0.6}$	Day in bed 0.4 ² ; day out of bed 0.6 ²
Discount rate	5%	10%	0%

^aFor some variables, the reasonable range of values was bounded by one alternative value, and for other variables, by two alternative values.

^bImplied elimination of 97 percent of pneumonia deaths within 40 Years.

SOURCE: J. S. Williams, C. R. Sanders, M. A. Riddiough, and J. C. Bell, "Cost Effectiveness of Vaccination Against pneumococcal Pneumonia," *N. Engl. J. Med.* 303(10):553-559, Sept. 4, 1980.

The QALY weights to calculate the morbidity-mortality index were used only to illustrate the effect on the results of different values (77). An implicit assumption is made that continued life is preferable to death, an assumption that seems reasonable for a fairly short acute illness, such as pneumonia.

In an evaluation of the efficacy of pneumococcal vaccination against pneumonia, several clinical points should be kept in mind. The pneumococcal bacteria may cause disease in different parts of the body: pneumonia in the lungs, otitis media in the middle ear, and meningitis in the brain. An infection may spread from one of the local sites

to a bacteremic or blood-borne infection. Pneumococcal vaccine contains the types of pneumococci most likely to cause pneumococcal bacteremia, a severe disease with a high incidence of death and disability. But the pneumococcal types frequently causing bacteremic disease maybe different from the types responsible for local infections. Thus, vaccination may not reduce the incidence of pneumococcal pneumonia by so high a percentage as pneumococcal bacteremia. The reduction in bacteremic disease, however, may disproportionately reduce morbidity and mortality and may reduce the severity of infections that would otherwise progress to bacteremia.

pneumococcal pneumonia is the most common form of pneumococcal disease. pneumococcal pneumonia can be a severe form of pneumonia frequently worse in terms of morbidity and mortality than other community-acquired pneumonias. The diagnosis of pneumococcal pneumonia is difficult since the pneumococcal organism may be carried in the upper airways without producing pneumonia. As a result, culture of the organism does not always indicate that the pneumococcus is the cause of a pneumonia case.

INCIDENCE OF pneumococcal PNEUMONIA

OTA's cost-effectiveness analysis assumed that 15 percent of all pneumonia was pneumococcal. This percentage was assumed to be constant for all age groups. OTA estimated that in 1978 there were 3.2 million cases per year of pneumonia in the United States (77). For the 1978 U.S. population of 222.6 million (80), OTA's assumption for the base case is tantamount to an annual incidence of approximately 2.2 cases per 1,000 population. The low estimate assumed that 10 percent of pneumonia was pneumococcal or about 1.4 cases per 1,000 population.

The actual incidence of pneumococcal pneumonia still remains uncertain. The vaccine recommendations of the Immunization Practices Advisory Committee (ACIP) provided a broad range of estimates from 0.68 to 2.6 cases per 1,000 population per annum (58). Three different methods for estimating incidence of pneumococcal dis-

Three different concepts relate to protection against disease and, specifically, the protection that pneumococcal vaccine confers against pneumococcal pneumonia. The efficacy of a vaccine is considered to be the probability that it will protect against disease under ideal conditions of use, such as those in clinical trials. Although a vaccine may also reduce the severity of disease, the only data for pneumococcal vaccine relate to disease prevention. Immunogenicity refers to the production of an immune response, in this case the production of antibodies in response to the antigens in the vaccine. Antibody levels may be an indicator of protection against pneumococcal disease, but are not conclusive evidence. Despite certain antibody levels, a person may not be protected against disease if other components of the immune system are not operating normally. Conversely, a person maybe protected in spite of low rises in antibody levels. Effectiveness, the third concept, refers to the probability of protection against disease, but under average conditions of use, such as that of clinical practice.

ease have been used. Estimates at the low end of this range are based on recent studies of pneumococcal isolates of blood and cerebrospinal fluid from studies of entire communities. Estimates at the upper end of the range were obtained from selected populations using respiratory secretions of patients with and without pneumonia.

Mufson, et al. (54), conducted a prospective study of blood and cerebrospinal fluid from individuals admitted to hospitals providing 80 percent of the beds for a population base of 300,000 in Huntington, W. Va., and surrounding counties. They found an overall bacteremia rate of 7.5 cases per 100,000. This overall rate was similar to rates obtained by Filice, et al. (24), of 8.5 cases per 100,000 population in a retrospective study in Charleston County, S.C.

The studies of bacteremia do not provide a direct incidence of pneumococcal disease unless one

knows the percentage of pneumococcal disease that becomes bacteremic. In addition, these studies may underestimate the incidence of pneumococcal disease because not all patients with pneumococcal disease receive blood cultures, and prior antibiotic therapy rapidly renders blood cultures negative. In addition, studies of bacteremia do not provide an adequate assessment of the effects of meningitis due to pneumococci.

Conversion of bacteremic data to pneumococcal incidence data requires an assumption about the percentage of pneumococcal disease that becomes bacteremic. Older estimates assumed that 20 to 30 percent of cases of pneumococcal pneumonia developed bacteremia. Recent studies (5,8,50) have found rates of bacteremia below 20 percent. The newer estimates of bacteremia may reflect a lower rate of bacteremia among those who seek or are provided care early in the course of their disease.

In applying these lower estimates of the percentage of individuals who develop bacteremia, one obtains rates of pneumococcal disease consistent with the low end of the ACIP incidence estimates.

Incidence rates at the high end of the range are based on studies at selected sites. Estimates from health maintenance organizations (HMOs) provide data on populations not necessarily at high risk or high incidence of pneumococcal pneumonia. According to Austrian's data from the Kaiser-Permanente Medical Care Program, San Francisco area enrollees over age 45 had an annual rate of about 1.5 cases of pneumococcal bacteria per 1,000 population (5). Patrick and Woolley (56) found a rate 2.3 cases per 1,000 population among about 10,000 patients 18 years and older at the Salt Lake City Family Health Program, a staff model HMO. Despite efforts to carefully define pneumococcal pneumonia, these studies may overestimate the frequency of pneumococcal

pneumonia since, as mentioned earlier, pneumococci are frequently carried in the upper airways without being the cause of pneumonia.

A third method of estimating the incidence of pneumococcal pneumonia relies on isolates of pneumococci from the throats of those with pneumonia v. control individuals. These studies develop measures of attributable risk. Fey, et al. (25), used this method to estimate a rate of 1.3 cases per 1,000 population among patients at Group Health Cooperative, a 'prepaid group in Seattle. But as David Fraser formerly of the Centers for Disease Control (CDC) noted, the "delicate balance" of the bacterial flora of the throat "can be tipped by the use of antibiotics or the occurrence of various infections" (77). This situation renders questionable the meaning of the presence or absence of pneumococcus in the upper respiratory systems of people with and without pneumonia.

The American College of Physicians in their Clinical Efficacy Assessment Project concluded that overall incidence probably lies between the higher and lower estimates, in the range of 1 to 2 annual cases per 1,000 population per year (67).

In an evaluation of incidence data, it is important to remember that all available studies indicate a considerably increased incidence of pneumococcal pneumonia and bacteremia among elderly people. The population-based bacteremia data of Mufson, et al. (54), and Filice, et al. (24), suggest that the rate for those older than age 60 is more than two times the overall rate (with no control for confounding medical conditions) and that elderly people are more likely to die if they experience pneumococcal bacteremia.

In summary, the overall incidence rate of pneumococcal pneumonia probably approximates the rate of 1.4 cases per 1,000 population used as the low estimate in OTA's cost-effectiveness study.

PROPORTION OF pneumococcal PNEUMONIA CAUSED BY THE pneumococcal TYPES IN THE VACCINE

OTA's base estimate relied on data from Austrian, Fey, and Valenti suggesting that the 14-valent vaccine would be directed against the pneumococcal types causing 75 percent of the cases of pneumococcal pneumonia. This estimate in turn depended on additional assumptions, which are evaluated below:

1. The distribution of types of pneumococci occurring in bacteremia and meningitis would resemble that occurring in pneumonia.
2. The use of the vaccine would not result in a significant shift of pneumococcal types causing infections.
3. For those pneumococcal types with two or more subtypes, use of the most frequent subtypes would provide good cross protection against the other subtypes.

Assumption 1: The distribution of types of pneumococci occurring in bacteremia and meningitis would resemble that occurring in pneumonia.

Because of the difficulty of acquiring reliable data on the frequency of pneumococcal types and subtypes that cause pneumococcal pneumonia, selection of vaccine antigens and evaluation of the frequency of disease have been based on bacteremia and meningitis data. This situation may represent a significant limitation in formulating the vaccine and evaluating its efficacy and effectiveness against pneumococcal pneumonia.

Bentley, et al.'s, study (8) of institutionalized elderly patients found that the majority of the pneumococcal disease among those not vaccinated (as well as those vaccinated) was due to types not included in the 14-valent vaccine. This observation may have been attributable to the high percentage of vaccinated patients or may have reflected a preexisting tendency for nonvaccine types to cause pneumonia. The data from surveillance at Dorothea Dix Hospital (67) before introduction of the vaccine showed that 80 percent of the bacteremic cases but only 43 percent of all pneumococcal isolates from patients with pneumonia were included in the 14-valent vaccine.

Thus, it seems that the pneumococcal types included in the vaccine on the basis of frequency data from bacteremia and meningitis may not accurately reflect the frequency of types causing pneumonia.

Relying on data from blood and cerebrospinal fluid isolates, one cannot expect to include in the vaccine so high a percentage of the types of pneumococci causing pneumonia as was assumed in OTA's cost-effectiveness analysis. Because people with bacteremic disease have much higher mortality (4), it is still worthwhile to direct the vaccine against the types that most frequently cause bacteremia.

Knowledge of the frequency of isolates, the cross-reactivity of subtypes, and the stability of constituents have allowed the formulation of the 23-valent vaccine, whose components should be directed against almost 90 percent of the worldwide isolates from the blood and cerebrospinal fluid. With the same criteria, the 14-valent vaccine covered between 70 and 80 percent of the isolates. Again, only blood and cerebrospinal fluid specimens were used to assess the frequency of pneumococcal disease. The increased number of types included in the 23-valent vaccine are expected to provide increased protection against pneumococcal pneumonia as well, but at present no data confirm or refute this expectation.

Assumption 2: The use of the vaccine would not result in a significant shift of pneumococcal types causing infections.

The CDC has acquired evidence regarding stability of the distribution of types of pneumococci causing bacteremia despite the use of the vaccine (12). Since 1978, the CDC has collected approximately 2,500 pneumococcal blood and cerebrospinal fluid isolates from 37 hospitals in 22 States. These isolates show *no* evidence of a shift of pneumococcal types among vaccinated and unvaccinated patients at the current level of utilization of the vaccine.

Assumption 3: For those pneumococcal types with two or more subtypes, use of the most frequent subtypes would provide good cross protection against the other subtypes.

Data on the degree to which one subtype provides cross coverage against another have been acquired as a result of a worldwide surveillance system and studies conducted in preparation for the 23-valent vaccine (62). Most of the work on cross-reactivity has been directed at selection of new subtypes for inclusion in the 23-valent vaccine. These data, however, suggest that the subtypes included in the 14-valent vaccine have not always provided adequate cross-over protection against the other subtypes.

EFFICACY RATE

OTA's base case estimated that the 14-valent vaccine would be 80 percent effective in clinical practice against the types contained in the vaccine. Since 1979, additional information has been accumulated on the responses to the vaccine of high-risk people with chronic diseases, the responses of people with impaired immune systems, the responses of elderly people, and simultaneous use with influenza vaccine.

Most of the data on antibody response to the vaccine are based on levels of total antibody assessed by radioimmunoassay. Absolute levels required for protection have not been definitively determined, but levels below 300 ng antibody nitrogen/ml are not generally considered protective (45). Many studies report successful vaccination based on a doubling of the antibody levels. For individuals who double their antibody levels from low preexisting levels but fall under 300 ng antibody nitrogen/ml, questions of efficacy remain.

Antibody Responses of High-Risk Groups With Chronic Disease

The short-term antibody response of patients with sickle cell disease, renal disease, diabetes, and chronic obstructive pulmonary disease have been investigated. These diseases are believed to pre-

In summary, the 14-valent vaccine could be expected to cover almost 75 percent of the types of pneumococci causing bacteremia but may not cover 75 percent of the types causing pneumococcal pneumonia. OTA's low estimate of 50 percent would appear to more accurately reflect the coverage against pneumococcal pneumonia provided by the 14-valent vaccine. This may underestimate the health benefits, however, since a vaccine directed against bacteremia and meningitis should disproportionately reduce death and disability. Since the 23-valent vaccine covers types that cause 90 percent of bacteremic cases, the new vaccine may also cover a higher percentage of the types responsible for pneumococcal pneumonia as well. However, there are no studies that bear directly on pneumococcal pneumonia.

dispose people to pneumococcal disease or to cause increased mortality if it develops (58).

Sickle cell patients over 2 years of age have been shown to have a generally adequate antibody response (1). Unfortunately, responses, especially to certain pneumococcal types, have not been uniform for those under 2 years of age in whom a large proportion of the pneumococcal disease among sickle cell patients occurs. Sickle cell patients appear to respond suboptimally to type 6 pneumococcal antigen (7), and clinically, cases of type 6 bacteremia have been observed despite vaccination.¹ For most pneumococcal types tested, sickle cell patients over age 2 produce a twofold or greater increase in their antibody levels and are probably protected (7).

The situation for renal disease patients must be separated into the response of those in renal failure, those on dialysis, and those who have undergone transplantation with immune suppression. Cosio, et al. (18), have shown that renal failure patients respond poorly and dialysis patients re-

¹This situation is not specific to children with sickle cell disease; many children do not make antibodies to certain pneumococcal types until age 6 to 10. Conjugated vaccines (see ch. 3) are being developed to address such problems (4).

spend quite well. Renal transplant patients respond less than dialysis patients, but the majority reached adequate short-term levels of protection. Thus, assuming that most patients with renal disease can be vaccinated while on dialysis or before renal failure develops, one can assume that protection in renal disease is quite good. Linnemann, et al. 's, study (49) agrees with these findings.

Davis, et al. (19), have demonstrated good short-term antibody responses in chronic obstructive pulmonary disease and Lederman, et al. (47), have demonstrated similar data for diabetes. Thus, there is reason to believe that those with chronic diseases not associated with immunosuppression will be able to obtain effective protection from the vaccine, at least in the short-term.

Antibody Responses of Immunocompromised People

In contrast, patients with diseases causing immunological suppression have been shown to have a poor response to the vaccine. Hosea, et al. (34), demonstrated poor antibody responses among splenectomized patients, but found that the pattern of antibody response paralleled that of normal volunteers in terms of height and rate of increase. Schmid, et al. (64), found a similar pattern of poor response among those with multiple myeloma. The ability of myeloma patients to increase their low preexisting levels of antibodies caused them to recommend pneumococcal vaccine for myeloma patients despite their suboptimal responses.

Patients with Hodgkin's disease have been shown by Siber, et al. (72), and Ammann, et al. (2), to have a good response to vaccine before treatment. Antibody levels, however, decrease during subsequent therapy proportionally to the intensity of the therapy. Higher levels of antibodies are present in immunized v. nonimmunized Hodgkin's disease patients, and vaccine is recommended 2 weeks *or more* prior to beginning therapy.

Thus, it appears that individuals with a disease or undergoing therapy that impairs their immunological response have lower levels of antibodies and may well have substantially reduced protection from the vaccine.

Antibody Responses of Elderly People

Antibody responses for elderly people who are currently free of chronic disease have been assessed. For antigen types 3 and 8, Ammann and his colleagues found that elderly individuals had lower baseline levels of antigens, but usually responded with a greater than twofold increase in their antibody titers (3). Hilleman, et al. (31), cite similar data for five pneumococcal types. Immediate post-immunization antibody titers were generally above the 300 ng antibody nitrogen/ml levels considered protective.

Bentley, et al. (9), studied the antibody response of elderly individuals to 11 pneumococcal antigens contained in the 14-valent vaccine. For most types, the post-immunization levels were above the 300 ng antibody nitrogen/ml level even among those over age 80. Low prevaccine antibody levels, reduced response to vaccine, and decline in titer over the subsequent year left many elderly, especially those over 80, with levels below those considered protective at 1 year.

Use With Influenza Vaccine

Use of pneumococcal vaccine simultaneously with influenza vaccine has been studied in terms of antibody levels and side effects (31,51). The levels of antibody after simultaneous use were nearly as high as when each vaccine was used alone. There was only a minimally greater frequency of side effects compared to the use of pneumococcal vaccine alone.

Comparison of Antibody Levels

Comparisons of relative antibody levels among groups are complicated by different methods of detecting, reporting, and combining the antibody levels from individual pneumococcal types. A standard method of comparison has recently evolved. This method uses the geometric mean antibody levels and combines these levels from individual types to obtain an overall Grand Mean antibody level. This method permits comparisons among groups, but does not allow a direct estimate of the efficacy rate. It can be presumed, however, that when the Grand Mean is less than 300 ng antibody nitrogen/ml, a majority of antibody

levels will be below those adequate for protection. The short-term efficacy rate should increase as the Grand Mean increases.

Reported geometric mean or Grand Mean levels for selected groups are as follows:

- **Healthy adults:** 834 ng antibody nitrogen/ml (47) to 2,344 ng antibody nitrogen/ml (3).
- **Elderly:** 537 to 912 ng antibody nitrogen/ml (3).
- **Diabetics:** 1,009 ng antibody nitrogen/ml (47).
- **Chronic obstructive lung disease:** 662 ng antibody nitrogen/ml (19).
- **Hemodialysis:** 592 ng antibody nitrogen/ml (49).
- **Multiple myeloma:** 91 ng antibody nitrogen/ml (45).

Thus, the data from individual groups suggest only a slight reduction in immunogenicity among most groups at increased risk of pneumococcal disease or those at risk of increased mortality if the disease develops. Individuals with immunosuppression, however, are an exception, with evidence suggestive of poor antibody response even in the short term.

Assessing Vaccine Efficacy

In assessing the clinical use of pneumococcal vaccine, one must distinguish between measures of antibody levels and clinical protection against disease. Clinical effectiveness against pneumococcal disease is the end point that one wishes to measure.

Clinical studies to assess the overall efficacy of the vaccine are hampered by the lack of reliable data on the incidence of pneumococcal pneumonia and the extremely large numbers of people that would be required for a controlled clinical trial, except in high-risk groups. Because of relatively low incidence rates, studies in healthy elderly people would require large numbers.

A controlled clinical trial utilizing the 14-valent vaccine is currently underway as a cooperative study among five Veterans Administration Medical Centers. The study, which began in 1981 and will continue through 1985, has enrolled almost

2,300 patients considered at high risk because of at least one of the following characteristics: age 55 years or older; chronic renal, liver, cardiac, or pulmonary disease; alcoholism; or diabetes mellitus. This trial is the only current randomized prospective study designed to assess the efficacy of the 14-valent vaccine. Although the study is expected to provide information on efficacy in these high-risk people as a whole, the number of people in the trial is probably not sufficient to indicate efficacy for elderly people or other high-risk groups separately. (The study will also develop information on adverse reactions to the vaccine and distribution of pneumococcal types) (73).

The CDC (12,13,15) has developed a retrospective method of assessing efficacy that does not require data on the incidence of pneumococcal disease. This method compares the frequency of type-specific isolates from blood and cerebrospinal fluid among vaccinated and unvaccinated patients. It thereby assumes that without the vaccine, different populations would have the same distribution of pneumococcal types and that the vaccine itself leads neither to a shift in types in the unvaccinated group nor a change in the incidence of disease caused by nonvaccine types in the vaccinated group. Since the method utilizes isolates from blood and cerebrospinal fluid, it does not directly assess efficacy against pneumococcal pneumonia.

The CDC has collected almost 200 pneumococcal blood isolates from individuals who have received the vaccine and over 1,000 pneumococcal blood isolates from individuals who have not received the vaccine. The data suggest that the efficacy of the vaccine for type-specific bacteremia for those over 2 years of age is in the range of 60 to 70 percent. Those older than age 60 had a clinical effectiveness rate similar to the rate for those under 60 (12). Because of the relatively small number, confidence intervals are still large (10).

The CDC has also assessed efficacy for people with conditions that predispose them to complications, including death, from pneumococcal infection. Included are sickle cell disease, splenectomy, nephrotic syndrome, renal failure including those on dialysis, multiple myeloma, and cirrhosis of the liver. Based on comparatively small numbers

that result in wide confidence intervals, the CDC estimate of efficacy for these groups overall is about 35 percent (10,12).

Shapiro and Clemens (69) have applied retrospective case-control study methods to the assessment of vaccine efficacy and obtained efficacy rates very close to the CDC's estimates. Shapiro and Clemens matched 90 cases of systemic pneumococcal disease with individuals of similar age and indications for pneumococcal vaccine. Their overall estimate of efficacy was 67 percent with a similar rate for those over 55 years of age.

The new 23-valent vaccine contains antigens that attempt to protect against all types in which multiple antibiotic resistance has been reported. Increased knowledge about stability of individual antigens has been used to select a subtype antigen (type 6B) to replace a previously unstable antigen (type 6A) for one of the common pneumococcal types. It is hoped that this change will increase the clinical effectiveness of the vaccine against type 6 pneumococcal infections.

Despite the increased number of antigens, the total dose of antigen in the 23-valent vaccine is actually less than in the 14-valent since 25 µg of each antigen is used instead of 50 µg. The reduced dosage of each antigen has not been tested on the elderly, the chronically ill, or the immune suppressed. Despite its adequacy in immunogenicity studies for producing antibody levels among healthy adult volunteers, there is insufficient evidence to assure its adequacy in the groups most likely to need or benefit from the vaccine.

The studies of cross-reactivity regarding the 23-valent vaccine have demonstrated that for selected types the rabbit sera data do not correlate well with human data. Only limited human data were available to assess cross-reactivity. Thus, the estimates of potential efficacy may somewhat overestimate the clinical effectiveness.

In assessing the overall efficacy of the vaccine, one must recognize that pneumococcal vaccine is in fact composed of multiple vaccines (i.e., 14 for the 14 valent and 23 for the 23 valent). Even if each of the individual vaccines has 99 percent ef-

ficacy, the overall vaccine would have a substantially lower overall efficacy. For instance, if each of the 14 vaccines in the 14-valent vaccine had 99 percent efficacy, the overall rate would be less than 87 percent (4).

In summary, the overall efficacy of the 14-valent pneumococcal vaccine for the pneumococcal types included in the vaccine has been found to be lower than the 80 percent efficacy rate used in OTA's base case. The overall efficacy rate against bacteremic disease is probably between 60 and 70 percent. The rate for those older than age 60 is also consistent with this rate. Those with diseases associated with immune suppression that predispose them to pneumococcal pneumonia have substantially reduced efficacy rates. Since these efficacy rates are based on data from pneumococcus isolated from the blood, it is likely that the efficacy rate of the 14-valent vaccine against pneumococcal pneumonia is somewhat lower because of the probable disparity between types of pneumococcus causing pneumonia and the types which predispose to bacteremia.

There is reason to hope that with the 23-valent vaccine, the overall efficacy rate will increase to close to 80 percent of bacteremic disease among people older than age 2. This figure is derived by direct extrapolation with the following assumptions:

1. Elderly, chronically ill, and high-risk people will respond as well to the 23-valent vaccine as to the 14-valent vaccine.
2. The 14-valent vaccine provides coverage against 75 percent of the pneumococcal types causing pneumococcal bacteremia.
3. The 23-valent vaccine provides coverage against 90 percent of the pneumococcal types causing pneumococcal bacteremia.
4. The 14-valent vaccine has an effectiveness rate of 65 percent against pneumococcal bacteremia among those older than 2 years of age.

Under these assumptions, the expected efficacy rate with the 23-valent vaccine would approach the 80 percent rate used as OTA's base estimate in the cost-effectiveness analysis.

DURATION OF IMMUNITY

OTA's base case assumed an average 8-year immunity provided by the vaccine. This figure was based on data from previous vaccines tested by Heidelberger in the 1950's (77). There are no data to challenge this assumption among young healthy adults. Mufson's data (53) confirmed the persistence of adequate antibody levels for at least 5 years. Hilleman, et al. (31), presented data on 11 of the types in the 14-valent vaccine suggesting that beyond 2 years, levels of antibody remain relatively stable in normal adults.

Elderly individuals and those with chronic diseases not causing immune suppression tend to have a lower level of antibodies after vaccination. Bentley, et al. (9), have demonstrated that during the 12 months after vaccination, the rate of decline in antibody levels among the elderly tends to parallel those of young individuals. The lower post-immunization levels for the elderly, however, left many elderly with 1 year antibody levels below the 300 ng antibody nitrogen/ml level considered protective. This effect was most evident for those over 80. Preliminary data on dialysis patients (18) suggest that the level of antibody may decline at a rapid rate. It should be expected that the duration of protection for elderly and chronically ill people without immunosuppressive disease will be shorter than the estimate of 8 years for healthy young adults.

For patients at high risk of pneumococcal disease due to immune suppression, such as renal transplant patients, multiple myeloma patients, and patients undergoing immune suppressive ther-

apy for cancer, the response to the vaccine is poor and the duration of protection maybe very brief (45). Of course, such people have generally impaired immune responses that extend beyond pneumococcal infection or pneumococcal vaccine. In addition, children who have their spleens removed for hereditary spherocytosis (a disease affecting the shape and survival of the red blood cells) or after trauma have been shown to have a rapid rate of decline of their antibodies during the first year after vaccination (28). Thus, patients whose immune system is impaired by immune suppression or removal of the spleen may have a reduced duration of protection. Consideration of revaccination of these patients requires further evaluation. At the present time, it seems appropriate to conclude that the duration of protection afforded by the vaccine to these high-risk, low-protection patients is lower than for healthy, young vaccinees.

The effect of lower doses of the antigens in the 23-valent vaccine on the duration of antibody levels is unknown. If the duration of adequate antibody levels is reduced in elderly and immunosuppressed people using the 50 µg dose, there may be even shorter duration of effective immunity produced by the 25 µg doses of the 23-valent vaccine.

On the basis of very preliminary data, elderly and chronically ill people without immunosuppressive disease most likely have a duration of immunity between 3 years (OTA's low estimate) and 8 years (the base case estimate).

SAFETY: SIDE EFFECTS

Recent data based on experience from the first 4 million doses of pneumococcal vaccine distributed have helped clarify the side effects of the 14-valent pneumococcal vaccine:

- Local reactions are frequent with local redness developing in approximately 30 percent of vaccinees, local discomfort in 40 percent, and local swelling in up to 3 percent. Those reactions are self-limiting (67).
- Three to seven percent of vaccinees develop a mild fever of 1 to 2 days duration (67).
- Approximately 1/100,000 vaccinees develop high fever and generalized symptoms that are also self-limiting (58).
- Three cases of possible anaphylaxis have been reported among the first 4 million doses distributed (67).
- The American College of Physician's Clinical Efficacy Assessment Project found that

no cases of Guillain-Barré syndrome have been reported as of 1982 (67). The Food and Drug Administration does indicate that Guillain-Barré syndrome has rarely been reported in temporal association with pneumococcal vaccine, but that no cause and effect relationship has been established (82).

- The ACIP does not recommend the vaccine for use during pregnancy “unless the risk of infection is substantially increased” (58).
- Local and systemic reactions are more frequent when revaccination occurs within 5 years. The ACIP recommends against revaccination of adults (58). Vaccine manufacturers also recommend against revaccination.
- Adults of blood group O or B immunized with pneumococcal vaccine manufactured by Merck Sharpe & Dohme prior to 1980 responded with an elevation of their anti-A antibodies. This reaction had the potential for inducing hemolytic disease of the newborn. The substance causing this response was found to be an impurity and was removed from subsequent vaccines. This episode does illustrate the potential for unpredictable side effects of current and future vaccines (62).
- Two patients with thrombocytopenia have been reported to have relapses after receiving the vaccine (43).
- Theoretical concerns that existed about vaccinating individuals with autoimmune dis-

eases have not been substantiated in studies of Sjogren’s syndrome (42) or systemic lupus erythematosus (39). No evidence of reduced renal function resulting from deposition of antigen-antibody complexes has been observed (42).

OTA’s cost-effectiveness analysis assumed an incidence of fever of 5 cases per 100 vaccinees and an incidence of severe systemic reactions of 1 case per 100,000 vaccinees. The base case estimate of Guillain-Barré syndrome was zero. These estimates correspond closely to those subsequently observed in clinical practice.

Local reactions are related to total dose, and severe reactions on revaccination may be related to antibody levels. Since the total dose of 23-valent vaccine contains fewer micrograms than the 14-valent one (575 v. 700 µg), the potential for adverse reactions is expected to be the same or less than with the 14-valent vaccine.

Revaccination of patients who have received the 14-valent vaccine with the 23-valent vaccine is contraindicated due to the higher frequency of severe local and systemic reactions that has been observed with booster doses (82). If the 23-valent vaccine proves substantially more effective than the 14-valent one, a new preparation will be required to deal with this problem.

COST OF VACCINATION

For OTA’s base case with costs expressed in 1978 dollars, vaccination by a private physician was expected to cost \$11.37, \$4.90 for the vaccine and \$6.47 for the physician’s fee to administer the injection.

For this technical memorandum, costs were recalculated in 1983 dollars. Until December 1983, both manufacturers of pneumococcal vaccine continued to list the price of 5-dose vials at \$24.50 or \$4.90 per dose. The price was then raised 8 percent to \$26.50 or \$5.30 per dose. Since 1979, most sales (about 80 percent) have been at discounts averaging about 20 percent off the list price. With such a discount, the average price charged at the

end of 1983 was \$4.43, an actual decrease of 9 percent over the 1978 price.

From 1978 to 1983, the Consumer Price Index for physician services increased 57.9 percent (38). If the injection fee increased at that rate, it would have reached \$10.22 in 1983. The 1983 estimate for the total cost of vaccination is therefore \$14.65 per person, an increase of 28 percent over the 5-year period, entirely because of the increased injection fee.

The important cost consideration in reexamining the assumptions of the cost-effectiveness analysis is the relative cost of preventing pneumococ-

cal pneumonia through vaccination versus the cost of treating the disease if it occurs. The 1978 analysis, which expressed all costs in constant 1978 dollars, projected through 2050 the medical care costs that would be incurred with and without vaccination. Although the specific costs of treating pneumonia in 1983 have not been derived, the per capita costs of medical care and especially hospital care have risen much more rapidly than the cost of pneumococcal vaccination. From 1978 through 1983, the medical care component of the Consumer Price Index rose 62.9 percent and the index for hospital and other medical services rose 82.6 percent (38). As noted above, the price index for physician services rose more slowly than for hospitals.

It is possible that reductions in the extent to which pneumonia patients were hospitalized, in their lengths of stay, or in their inpatient or ambulatory use of diagnostic tests could have offset these price rises. From 1964 to 1971, for example, the number of laboratory tests and X-rays fell for an ambulatory pneumonia patient (68). But

during that period, use of these same services rose for a pneumonia patient treated in a hospital as an outpatient or an inpatient. More information is needed to determine whether or not changes in technology use offset all or part of the price increases from 1978 to 1983.

OTA's cost-effectiveness analysis included as a low estimate of vaccination cost an estimate of the cost under a public immunization program (\$2.45 for the vaccine and \$1.00 for its administration). In 1983 dollars, the estimated cost would be \$3.80 (\$2.22 for the vaccine and \$1.58 for its administration), a sum substantially lower than private provision.

As noted in chapter 4, each Medicare carrier establishes its own reasonable and customary charge that it will reimburse for a pneumococcal vaccination given to its beneficiaries. At least one State carrier in January 1984 was paying \$9.60 for the vaccine (\$7.50 for the vaccine and \$0.10 for the syringe) and its administration (\$2.00), a figure substantially below the \$14.65 estimated for private provision.

MEDICAL COSTS IN EXTENDED YEARS OF LIFE

The 1978 cost-effectiveness analysis included in all of its calculations the added costs of medical care during the extended years of life gained by vaccinated persons who avoided death from pneumococcal pneumonia. These costs of treating other illnesses during survivors' extra years of life varied by age and were adjusted for decreased expenditures for treating pneumococcal pneumonia. Before adjustment for decreased pneumococcal pneumonia, for example, annual medical expenditures for a person 65 years or older averaged \$1,689 in 1978 dollars.

There is no consensus on whether a cost-effectiveness analysis that takes a societal perspective should include medical costs of survivors as they live out their life expectancies (61). Medical costs of survivors' additional years provide information about the cost implications for the medical care sector of the program being analyzed, and another cost-effectiveness analysis included such costs (90). However, these costs are secondary ef-

fects of vaccination and reflect the fact that people who live will continue to incur expenses, for medical care as well as for other items. There is concern that it may be misleading if not inconsistent to include one secondary and costly financial effect of vaccination, but to exclude other similar effects, such as expenses for food and clothing or improvements in production (89).

Agreement does exist on two points. One is that the effects of the medical intervention being analyzed should be followed through time. That situation does not pertain to pneumococcal vaccination against pneumonia because the disease is acute and fairly short in duration. The other point of agreement is that the factors that are appropriate to include vary if the perspective is one of a program such as Medicare. In that case, it is clearly relevant to include the present and future costs that the Program will incur because of the medical intervention. In the case of pneumococcal vaccination, those costs include the costs of

vaccination, treating side effects, and of treating other illnesses throughout the vaccinated person's

life as well as savings in the costs of treating pneumococcal pneumonia.

RECONSIDERATION OF THE COST-EFFECTIVENESS RESULTS

OTA's cost-effectiveness analysis indicated that vaccination against pneumococcal pneumonia would improve health at the rate of \$4,800 per healthy year of life gained across all age groups. The net gains in health were positive but small: 0.43 day for a vaccinee age 45 to 64 and 1.59 days for a vaccinee age 65 or older, for example. The net cost in 1978 dollars, which included the cost of vaccination, the cost of treating side effects, the saving in reduced costs of treating pneumococcal pneumonia, and the cost of other medical expenses in survivors' extended years, was also small: \$6.80 for a vaccinee age 45 to 64 and \$4.40 for a vaccinee age 65 or older. Expressed in terms of years, vaccination was estimated to gain a year of healthy life for a person age 45 to 64 for \$5,700 and for a person age 65 or older for \$1,000.

If medical costs in survivors' extended years were excluded and the analysis limited to the direct effects of the vaccination, the net costs of vaccination in 1978 were estimated to be lower for a person age 45 to 64 (\$5.65 per vaccinee or \$4,780 per healthy year gained) and to be slightly cost saving for a person age 65 or older (a saving of about \$0.013 per vaccinee or \$3.25 per healthy year gained).

Evaluation of the assumptions of the 1978 analysis, including available information on and the potential of the new 23-valent vaccine, has concluded that the base case assumptions are reasonable for the proportion of pneumonia caused by the vaccine types, the efficacy rate, and side effects from the vaccine. On the contrary, the low estimate seemed more likely for the incidence of pneumococcal pneumonia and for the duration of immunity. With the low estimates for these variables, health benefits would be lower and net costs higher (see table 2). For a vaccinee 65 years or older, the lower incidence of pneumococcal pneumonia would raise the cost-effectiveness ratio to \$1,300 per healthy year gained, and the shorter duration of immunity would result in \$3,000 per healthy year gained. If the lower incidence of the disease and shorter duration of immunity applied at the same time, an elderly vaccinee would gain about 0.5 of a healthy day for a net cost of \$7.60 or about \$6,000 per healthy year gained.

These figures change if allowance is made for the rise in treatment costs relative to the cost of vaccination (table 2). With the relative costs of care that prevailed in 1983, treatment costs and the savings in them from preventing pneumococ-

Table 2.—Cost-Effectiveness Results With Lower Estimates for Incidence and Duration of Immunity and 1983 Relative Prices, for Pneumococcal Vaccinees > 65 Years^a

Variable	Results per elderly vaccinee				
	1978 dollars		1983 dollars ^c		
	Healthy days gained	Net medical costs	Net cost per healthy year gained	Net medical costs	Net cost per healthy year gained
1978 base case estimates	1.59	-\$0.01	^b	-\$6.05	^b
10 percent pneumonia as pneumococcal	1.05	3.78	\$1,300	0.84	\$ 291
3-year duration of immunity	0.69	5.75	3,000	4.33	2,286
3-year duration of immunity and 10 percent of pneumonia as pneumococcal . . .	0.46	7.60	6,000	7.81	6,154

^aAll net medical costs exclude medical expenditures in survivors' extended years of life.

^bCost saving.

^cFrom 1978 to 1983, the price of medical care rose 62.9 percent, of physicians' services 57.9 percent, and of hospital and other medical services 82.6 percent (38).

All estimated net medical costs and net cost per healthy year gained would have cost savings if vaccination was administered under a public program (with a cost of \$3.60 per vaccination) instead of private provision (with a cost of \$14.65 per vaccination).

SOURCE: Office of Technology Assessment,

cal pneumonia are relatively greater. In the case of the lower incidence of pneumococcal pneumonia, the savings in treatment costs almost offset the cost of vaccination so that the net cost per elderly person vaccinated would be less than \$1 for a healthy day or about \$300 per healthy year of life gained. With a shorter duration of immunity, the savings in treatment costs offset about two-thirds the vaccination cost for a net cost per

elderly person vaccinated of \$4.33 for 0.7 healthy day or about \$2,300 per year of healthy life gained. With both a lower incidence of pneumococcal pneumonia and a shorter duration of immunity than used in the 1978 analysis, but the different relative costs that prevailed in 1983, an elderly vaccinee would gain about 0.5 of a healthy day for a net cost of about \$8 or about \$6,000 per healthy year gained.

RECONSIDERATION OF COSTS TO THE MEDICARE PROGRAM

The 1978 analysis concluded that the Medicare Program would incur a net cost per elderly beneficiary vaccinated of about \$5 if the Program covered 100 percent of the vaccination cost. Based on the general results for elderly people, a vaccination was also expected to gain 1.59 healthy days of life.

Since the Medicare Program does not pay for the total medical expenditures of its beneficiaries, Medicare's expenditures per enrollee are a fraction of these totals. In 1978, Medicare paid 72.8 percent of hospital costs, 56.7 percent of physician charges, and 42.8 percent of the total medical expenses of their beneficiaries (27). OTA's 1978 estimate of Medicare expenditures was therefore \$760 per elderly beneficiary. Medicare subsequently reported that it had actually spent \$864 per elderly enrollee in 1978 (83). By 1981, the most recent year available, Medicare was paying 74 percent of hospital and other medical services,

57.9 percent of physician services, and 45.3 percent of the total personal health care of aged beneficiaries.

As described above, if pneumococcal pneumonia accounted for only 10 percent of all pneumonia cases and immunity from the vaccine lasted only 3 years for elderly people, each vaccinee would gain about 0.5 of a healthy day of life. The net result for the Medicare Program of the reduced effect on pneumonia cases and of changes in relative prices of treatment and vaccination costs would be an increase in net program cost to about \$5.50 to \$10.50 per elderly vaccinee (table 3). If about 25 percent of elderly Medicare beneficiaries received pneumococcal vaccination (about 6.6 million people), the net cost to the Medicare Program over time in 1983 dollars would be \$37 million to \$69 million to gain about 8,400 years of healthy life.

Table 3.—Estimated Net Medicare Expenditures for Pneumococcal Vaccinees > 65 Years, 1978 and 1983^a

Variable	Results per elderly vaccinee				
	1978 dollars		1983 dollars ^b		
	Healthy days gained	Net medical costs	Net cost per healthy year gained	Net medical costs	Net cost per healthy year gained
1978 base case estimates	1.59	\$5.02	\$1,153	-\$2.38 - \$ 2.67	-\$ 613
10 percent pneumonia as pneumococcal	1.05	7.14	2,477	1.60 - 6.65	555 - 2,307
3-year duration of immunity	0.69	8.14	4,298	3.51 - 8.56	1,853 - 4,520
3-year duration of immunity and 10 percent of pneumonia as pneumococcal	0.46	9.21	7,258	5.54 - 10.59	4,366 - 8,345

^aAll net medical costs include medical expenditures in survivors' extended years of life.

^bSame price increases assumed as in table 2. Lower cost estimates were based on cost per vaccination of \$9.60, and higher cost estimates on \$14.65.

^cCost saving.

SOURCE: Office of Technology Assessment.