Cost Effectiveness of Influenza Vaccination

December 1981

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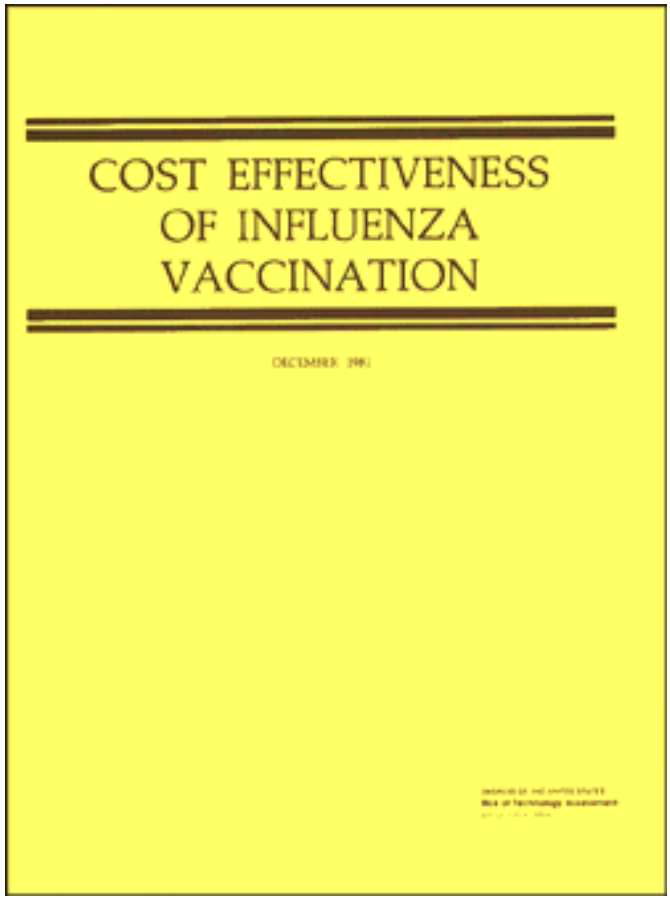

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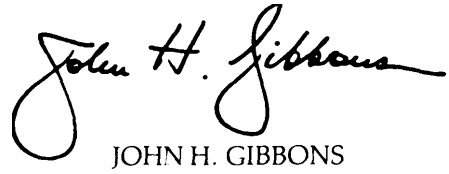
Foreword

In September 1979, the Office of Technology Assessment published a report *A Review of Selected Vaccine and Immunization Policies.* The report included a case study of pneumococcal vaccine, as part of which a cost-effectiveness analysis of the vaccine was carried out using a computer-based simulation model. The study found that, given the range of factors involved, vaccinations would entail positive net medical expenditures for every age group and would be most cost effective for those 65 years of age or older. Net health effects were expressed in quality-adjusted life years (QALYs). The cost-effectiveness ratio was about $4,800 per QALY gained for all ages and $1,000 per QALY for ages 65 years and older. These findings stimulated considerable interest and helped lead to passage of an amendment (1980) to the medicare law to cover pneumococcal vaccine.

The report noted that influenza vaccine was likely to be cost effective as well. Early in 1980, the House Interstate and Foreign Commerce Committee (now Energy and Commerce) asked OTA to conduct a cost-effectiveness analysis of influenza vaccine and influenza immunization programs similar to that developed for pneumococcal vaccine.

The study was conducted by OTA staff using a computer model similar to that of the pneumococcal vaccine study. A number of expert consultants assisted with the study. Drafts of the final report were reviewed by the Health Program Advisory Committee, chaired by Dr. Sidney Lee, and by approximately 25 other individuals with expertise in economics, vaccines, or health policy (see *Acknowledgments* in app. F). We are grateful for their assistance.



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1. Findings, Issues, and Options

Influenza is an infectious disease that affects the population of the United States to varying degrees almost every year. In some years, influenza occurs in epidemic proportions in all States. In 1957-58, for example, it contributed to approximately 70,000 excess deaths. In other years, such as 197&71, influenza occurs very infrequently and reportedly produces no excess deaths. During the 7-year period from 1971-72 through 1977-78, there were an estimated 127,000 influenza-related excess deaths reported in the United States, and Americans spent over $1 billion on influenza treatment.

The preferred method of controlling influenza is its prevention through vaccination. Inactivated influenza vaccines have been marketed in the United States since the 1940's. Because the chemical (antigenic) makeup of prevalent influenza virus(es) changes almost yearly, the composition of influenza vaccine is reevaluated annually and in most years reformulated.

The Federal Government is responsible for conducting influenza surveillance (monitoring influenza occurrence and mortality) and establishing standards for influenza vaccine composition, purity, safety, and efficacy. In one year, 1976-77, the Federal Government supported a nationwide effort to immunize virtually the entire U.S. population against the so-called swine influenza virus. In two subsequent years, the Federal Government gave assistance to State and local health departments to purchase and distribute influenza vaccine.

Influenza vaccine has never enjoyed widespread acceptance or demand by either the public or health professionals. In each of the years from 1971-72 through 1977-78, only about 10 percent of the Nation's population received influenza vaccine. Further, in any given year, only about 20 percent of the high-risk population (people at greater risk of dying from influenza if they contract the disease) received influenza vaccine. (In 1976-77, however, both of these percentages doubled.)

The effectiveness of influenza vaccination has been examined repeatedly. Its effectiveness can vary from year to year because of changes in the influenza virus. On the basis of data from clinical trials, OTA estimates that the clinical efficacy or effectiveness of influenza vaccine was about 60 percent from 1971-72 through 1977-78 (see app. B).

In 1976-77, swine flu vaccinations were associated with about 500 cases of a rare paralytic condition called Guillain-Barre Syndrome (GBS). As a result, the vaccine's safety was seriously questioned. However, since 1976-77, influenza vaccinations have proven to be quite safe. GBS may have been an adverse reaction (side effect) peculiar to swine flu vaccine (see app. D).

This OTA study evaluates influenza vaccination on the basis of another criterion-cost effectiveness. In this analysis, prevention of influenza by vaccination is compared to treatment of the disease if it occurs. Changes in health effects and medical care costs produced by influenza vaccination from 1971-72 through 1977-78 are estimated. Costs and health effects are viewed primarily from a societal perspective, although a medicare perspective is also included. Using data obtained from selected Government agencies and incorporating certain assumptions, OTA developed a computerized cost-effectiveness model to generate the following findings concerning influenza vaccinations. Details regarding the data and methods used in the cost-effectiveness analysis are described in chapter 2 and appendix E.

[1] Excess deaths occur when the observed number of deaths exceeds the expected number of deaths in a given time period.

FINDINGS

The findings below were generated by OTA's cost-effectiveness model and apply to influenza vaccinations administered from 1971-72 through 1977-78.

General and Productivity Effects

1. The medical care costs associated with influenza vaccination in the United States during this 7-year period totaled $808 million; for that cost, about 150 million doses of vaccine were given, and those vaccinations yielded approximately 13 million years of healthy life, for a per vaccination cost of $63 per year of healthy life gained.

2. Medically attended influenza-related illness during this 7-year period accounted for an average of 15 million days of self-reported work loss each year. Productivity loss associated with that work loss totaled $764 million each year.

3. Influenza vaccination prevented 5 million days of self-reported work loss and saved $253 million in productivity loss from medically attended influenza-related illness during this 7-year period.

4. Influenza vaccination prevented 3.6 million days of self-reported housekeeping loss with an imputed economic value of $136 million during this 7-year period.

Cost Effectiveness for the General Population

Vaccination of a population may result in added years of life for some members of the population. These members will, on average, incur typical medical care costs during the added years. Analysis of the costs of a vaccination program, therefore, could include these added medical care costs. Analysts disagree on whether such inclusion is appropriate for a cost-effectiveness analysis. Thus, OTA has calculated the cost effectiveness of vaccination both ways: by excluding such added costs, and by including them.

5. When vaccinations are administered to the general population and the *medical cure costs* incurred during additional years of life yielded by vaccination are *excluded,* the age-specific costs of generating a year of healthy life through influenza vaccination are these:

Age in 1971-72	*Per uaccination cost/year of healthy* life
<3 years	$258
3-14	196
15-24	181
25-44	64
45-64	23
≥65	(cost saving)
All ages	$63

The cost effectiveness of influenza vaccination improves with increasing age of the vaccinee at the time of vaccination.

6. When *medical care costs* incurred during additional years of life yielded by vaccination are *included,* the age-specific costs of generating a year of healthy life are these:

Age in 1971-72	*Per vaccinaiton cost/year of healthy life*
<3 years	$1,745
3-14	1,880
15-24	2,010
25-44	*2,027*
45-64	*2,084*
≥65	1,782
All ages	$1,956

Cost Effectiveness for Medically High-Risk Populations Only

7. When vaccinations are administered to the *medically high-risk* population (i. e., those most susceptible to influenza morbidity and mortality), and *medical care costs* during additional years of life yielded by vaccination are *excluded,* the age-specific costs of generating a year of healthy life through influenza vaccination are these:

Age in 1971-72	*Per uaccination cost/year of healthy* life
15-24 years	$44
25-44	23
45-64	15
≥65	(cost savings)
All ages	$10

With the assumptions about treatment costs and health effects that are used in this analysis, vaccination of high-risk persons within a given age appears more cost effective than vaccination of the general population (see app. E).

8 When estimated *medical care costs* in additional years of life are *included,* however, the costs of generating 1 year of healthy life among *high-risk persons* are these:

Age in 1971-72	*Per vaccination cost year of healthy life*
15-24 years	$3,050
25-44	3,620
45-64	4,150
≥65	4,040
All ages	$3,880

Factors That Affect Cost Effectiveness

9. Three factors substantially affect the cost effestiveness of influenza vaccination in both the general and high-risk populations: 1) vaccine efficacy, 2) cost of vaccination, and 3) ineluding medical care expenditures in extended years of life.

Substantial alterations in *vaccine* efficacy produce directly proportional, but smaller, changes in the cost-effectiveness ratio. For example, a 30-percent increase in vaccine efficacy produces about a 17-percent drop in the cost of gaining a year of healthy life for all ages combined.

For the period 1971-72 through 1977-78, the cost of *vaccination* (vaccine cost plus administration fee) substantially affects the cost effectiveness of annual influenza vaccination. For example, at a cost of $1.55, vaccination of a person 65 years old produces net savings in medical care costs, while at a cost of $9.39, that same vaccination yields a net cost of $34 for each year of healthy life gained.

Including *medical care expenditures* in extended years of life substantially increases the cost of gaining a year of healthy life through influenza vaccination. This variable completely overshadows the changes produced by all other variables combined in the sensitivity analysis.

ISSUES

- To what extent, if any, should the Federal Government promote the use of influenza vaccine?
- What mechanisms are available to the Federal Government to promote influenza vaccination?
- For whom should influenza vaccination be promoted?

Prior to 1976-77, the Federal Government had not extensively promoted the use of influenza vaccine. Thus, for example, it did not purchase influenza vaccine for distribution to Federal, State, and local public health clinics (as it did selected vaccines for childhood immunizations), Prior to 1976-77, Federal activities related to influenza vaccine included the following:

- establishing the formula for, and evaluating the safety and efficacy of, each year's vaccine (Food and Drug Administration (FDA));
- disseminating to health professionals and medical care institutions the recommendations of the Immunization Practices Advisory Committee (ACIP)—a governmentally financed outside advisory group that establishes nationally recognized standards for the use of all marketed vaccines in the United States (Centers for Disease Control (CDC));
- conducting annual surveillance of influenza virus activity and influenza-related mortality (CDC);
- occasionally mounting public educational programs to encourage the use of influenza vaccine by selected groups identified by ACIP (Public Health Service (PHS)); and
- attempting to develop more effective influenza vaccines (National Institutes of Health (NIH)).

In 1976-77, the Federal Government mounted the National Influenza Immunization Program, the so-called swine flu immunization program. For that initiative, the Federal Government took the following actions to help ensure that virtually every person in the United States received the swine flu vaccine:

- purchased almost the total 1976-77 influenza vaccine production from vaccine manufacturers;
- indemnified vaccine manufacturers from selected types of product liability (86,88);
- launched massive public education programs to encourage the use of influenza vaccine by most of the U.S. population; and
- strongly encouraged State and local public health departments to participate in the National Influenza Immunization Program.

The swine flu immunization program received much derogatory press coverage, primarily for the following reasons:

- the targeted influenza virus—A/New Jersey/76 (Hsw1N1)—never occurred in epidemic proportions; and
- vaccination was associated with GBS.

In spite of its problems, the swine flu program demonstrated a Federal capability to increase the rate of influenza vaccination throughout the United States. During the 1976-77 season, influenza vaccination rates for all age groups combined were twice the rates from previous years.

Since 1976-77, Federal activities related to the promotion and distribution of influenza vaccine have been sporadic. During the years 1977-80, the Department of Health, Education, and Welfare (HEW), now the Department of Health and Human Services (DHHS), sponsored a series of at least eight conferences in which the Nation's leading experts on several aspects of influenza (e.g., surveillance, diagnosis, prevention, and treatment) discussed how the Federal Government could best use its resources to detect and control influenza (97-104). In addition, in 1978-79 and 1979-80, the Federal Government either: 1) purchased influenza vaccine directly from manufacturers at a fixed nationwide price and distributed it to State and local public health departments, or 2) provided financial assistance to State and local health departments (for the purchase of influenza vaccine. There was no such Federal support in 1977-78 or 1980-81. In 1978, former HEW Secretary Joseph Califano unsuccessfully attempted to persuade Congress to finance a continuing federally sponsored influenza vaccination program.

At present, there is no federally financed program to influence the use of influenza vaccine. Existing Federal policy regarding influenza vaccination appears to be laissez-faire. In the absence of Federal support, the use of influenza vaccine is primarily determined by private sector physicians, State and local health departments, employers, and self-initiated public demand.

The results of this OTA study indicate that influenza vaccination is a low-cost preventive medicine intervention that yields health benefits among all age groups. Influenza vaccination appears to be most cost effective among high-risk populations.

In addition to generating the costs and savings included in the cost-effectiveness calculations, influenza vaccination improves productivity in the economy. Using historical rates of vaccination from 1971-72 **through** 1977-78, **OTA calculated the value of work loss prevented by influenza vaccination to be** $253 **million and the value of housekeeping loss prevented to be** $136 **million during that 7-year period.**

These results relate to decisions regarding which groups in the population should be targeted to receive the vaccine. If work loss and housekeeping loss are taken into account, the benefits to be gained from vaccinating adults age 17 to 64 increase. When the economic gains from reductions in work loss are included, and the medical care costs incurred during extended years of life are excluded, the cost of gaining a year of healthy life falls to $134 for ages 17 to 24, $32 for ages 25 to 44, and $11 for ages 45 to 64.

Present ACIP recommendations for recipients of influenza vaccination do not explicitly include healthy working-age adults in the general population. Some employers, including Federal

agencies, provide voluntary annual influenza vaccination, usually at low cost. Vaccination rates for working age groups are low, i.e., about 10 percent, as one would expect in light of current ACIP recommendations.

It appears that without strong Federal support, the use of influenza vaccine remains at a level too low for society to fully reap the potential benefits—in terms of health benefits and prevention of productivity losses—of the vaccine. For example, in the period from 1971-72 through 1977-78, approximately 70 percent of influenza-related work loss occurred in the 25- to 64-year-old age group; yet, on the average only 10 percent of that age group received influenza vaccine during the 1970's.

Likewise, only about 20 percent of the medically high-risk population in the United States receives influenza vaccine in any given year.

OPTIONS

The information contained in the findings and issues presented above has certain implications for the future of influenza vaccination and the Federal role related to it. Based on the findings and issues, the following discussions lay out some of the implications that may follow from various Federal actions.

If *the Federal Government decides to retain its laissez-faire approach to influenza vaccination,* then neither Congress nor DHHS would need to enact any new programs. If funding for the Bureau of Biologics (BOB) and CDC remains a t current levels, adjusted for inflation, then the following Federal influenza activities would likely remain intact. Influenza investigators within DHHS could continue to meet once or twice yearly to: 1) assess which strains of influenza virus(es)—if any—are likely to invade the United States and 2) formulate the subsequent year's vaccine makeup. BOB would continue to evaluate the safety and efficacy of each year's vaccine formulation, CDC could continue its surveillance of influenza occurrence and mortality. The availability of Federal funds to purchase, distribute, and promote the use of influenza vaccine would be quite limited unless Congress were to specifically appropriate funds for this use. Reductions in funding for these two agencies could easily jeopardize current Federal influenza-related activities.

If *the Federal Government instead decides to consistentl, promote the use of influenza vaccine for selected target populations,* it could take one or more of several actions. Three possible options and their implications follow (the three actions are not mutually exclusive; in fact, taking all three simultaneously would maximize the immunization status of the population).

1. **The Public Health Service (PHS), if funded to do so, could mount a continuing national campaign to increase the awareness of practicing health professionals, employers, labor unions, and the public about the benefits and costs associated with influenza vaccination among selected target populations.**

It has long been stated that health care consumers have insufficient knowledge to evaluate the use of medical technologies (4,39). Because of their greater expertise in health matters, physicians are considered to act as patients' agents. Studies in the area of medical technology during recent years have dramatically illustrated that physicians themselves sometimes lack knowledge about appropriate technology use. Moreover, once evaluations of technology have been performed, they are rarely disseminated in an effective way to physicians and other users (87).

This option would promote the dissemination of information concerning the economic and health benefits of influenza vaccination. Potential users of the information include physicians, consumers, employers, labor unions, and third-party payers. Each of these groups would have an interest in knowing the effects of vaccination on health benefits, medical care costs, and productivity losses.

The dissemination of information about medical technologies is a legislated function of the

National Center for Health Care Technology (NCHCT). NCHCT has arranged for certain information to be published in major medical journals. In addition, a subcommittee of its National Advisory Council is considering the generic issue of dissemination of medical technology information.

Other areas of PHS are also concerned with vaccination information. CDC and its ACIP, as well as the Office of Health Promotion and Disease prevention, could undertake special information dissemination efforts.

This option is consistent with the perceived need by providers, consumers, and others for better information about the appropriate use of preventive technologies. Information could be provided to groups within the private sector who could then take whatever action they considered appropriate. This approach does not involve Federal financing of influenza vaccination, although it would be compatible with doing so (see below). An assumption behind the strategy of disseminating information is that potential vaccine users in the private sector have incomplete information about influenza vaccination and will act themselves on better information.

If the private sector does not accept the responsibility of using information about influenza vaccination, then any Federal effort to disseminate information would not by itself be likely to alter existing influenza vaccination rates. A 1979 study commissioned by CDC, for example, illustrated that although most physicians are aware that certain groups of high-risk patients should receive influenza vaccine each year, they do not routinely administer it to such groups (90). In that study, 92 percent of 1,000 participating physicians believed that annual influenza vaccinations are necessary for persons with chronic diseases and the elderly. Yet, those same physicians reportedly administered influenza vaccine to only 54 percent of their elderly patients with chronic disease and to only one-third of their elderly patients without chronic illness. If validated by results from other studies, these data indicate that educational efforts may need to be combined with other incentives to promote influenza vaccinations.

The Federal Government could expand the scope of its traditional influenza vaccination strategies by encouraging vaccination of all persons in the work force, not just those with high-risk medical conditions. OTA estimates that influenza caused a productivity loss of approximately $764 million *each year* from 1971-72 through 1977-78. The Federal Government could encourage employers to help prevent such productivity losses by creating work site immunization programs, educating employees about the benefits of immunization, or reimbursing employers for incurred costs associated with immunization.

2. **Congress could authorize and appropriate Federal support for a continuing (annual) publicly assisted nationwide influenza immunization program analogous to federally supported childhood immunization efforts.**

There are four potentially beneficial implications of such an influenza immunization program. First, if the Federal Government negotiated a vaccine selling price with manufacturers that applied to public sector sales nationwide (as it did in 1979-80), then vaccination costs would likely be lower than private sector costs. Second, by using participating State and local public health clinics, the Federal Government would have a readily accessible and experienced network for distributing vaccine and information to health professionals. In general, when the Federal Government finances the purchasing and distribution of a vaccine, the rate of use for that vaccine is higher than when its use is determined solely by the private sector. Third, by controlling the public sector distribution of influenza vaccine, the Federal Government could conceivably improve its capability to monitor the occurrence of vaccine side effects. Fourth, supplying the vaccine would probably encourage physicians to provide it to their patients.

There are two possible disadvantages of such a program. First, if public clinics were relied on too heavily for influenza vaccine distribution, such a program could provide disincentives for

private sector physicians to administer influenza vaccine. Private sector physicians could send their patients to public health clinics for their "flu shots" and interrupt their patients' normal pattern of receiving medical care. Second, the adoption of this program would raise the issue of Federal liability for adverse vaccine reactions under certain conditions.

As to the first disadvantage, CDC believes, as a result of its experiences with childhood immunization programs, that public immunization programs do not significantly disrupt patients' patterns of health care (26). About 50 percent of all children still receive their immunizations from private physicians.

The second potential disadvantage may be more serious. At present, when the Federal Government purchases and distributes a vaccine, it assumes from the vaccine manufacturers the responsibility of warning potential vaccinees about the inherent risks of vaccination, i.e., rare, unpreventable, adverse reactions. The Federal Government in turn passes this responsibility on to State and local government agencies that accept and administer federally purchased vaccines. The legality of such contractual transfers of responsibility has not been tested in court; as a result, the Federal Government's liability for adverse reactions that occur in public immunization programs is unclear. This issue has been discussed at length in two prior OTA reports (86,88).

3. Congress could **amend the Social Security Act of** 1965 to authorize medicare to pay for influenza vaccination.

Until recently, Title XVIII of the Social Security Act explicitly prohibited medicare reimbursement for all preventive vaccinations (42 USC 1395(y)). On December 28, 1980, President Carter signed Public Law 96-611, which authorized medicare payment for vaccinations to prevent pneumococcal pneumonia. At present, medicare pays for the treatment of influenza, but not for its prevention through vaccination.

Adoption of this option by itself would affect only about 45 percent of the population *over* 20 years old that is at high risk of being seriously afflicted by influenza. Approximately 55 percent of this high-risk population is between 20 and 65 years old.

The impact of reimbursement on medicare beneficiaries' demand for influenza vaccination is difficult to project. The effect of third-party coverage on the use of preventive services is not clear. To date, results of such analyses have been conflicting (41,108). Consumers' demand for vaccines can also be influenced by their attitudes regarding personal susceptibility to disease, likelihood of disease occurring locally, and vaccine safety and efficacy (86).

It is possible that medicare payment for vaccination would not increase the total number of vaccine recipients among persons over age 65. Payment could simply transfer the cost of vaccination to medicare from those who currently pay for influenza vaccinations among the elderly (e.g., State and local health departments, employers, individual consumers, and in some years, CDC).

In a 1979 study commissioned by CDC, 43 percent of 1,000 participating physicians believed that more patients would receive influenza vaccination if it were covered by medicare or medicaid (90).

Congress could amend the medicare law to permit reimbursement for influenza vaccination by using the same provision regarding pneumococcal vaccination in Public Law 96-611. Alternatively, Congress could approach the reimbursement of influenza vaccination with a broader perspective and could establish criteria for preventive health services to be included in the medicare benefit package. Examples of such criteria include:

- services/technologies that help prevent disease that particularly affect the elderly; and
- services/technologies that have proven safe and efficacious, and possibly cost effective, when used by individuals 65 years and older.

Special payment mechanisms, for example, waiver of copayment (deductibles and coinsurance) requirements, could be used to encourage beneficiaries' use of selected preventive health services, especially low-cost items such as vaccinations.

In this analysis, the economics of medicare reimbursement for influenza vaccination would be as follows:

- When the *medical care costs* in extended years of life are *included,* each influenza vaccination administered to a person 65 years or older (in the general population) yields an additional month of healthy life for about $60.
- When the *medical care costs* in extended years of life are *excluded,* each influenza vaccination administered to a person 65 years or older (in the general population) yields an additional month of healthy life for about $2.

In either case, influenza vaccination generates a notable health benefit at a reasonably low cost to the medicare program.

2.
The Cost-Effectiveness Analysis: Data, Methods, and Results

2. The Cost= Effectiveness Analysis; Data, Methods, and Results

INFLUENZA

Clinical Description

Influenza is an acute infectious disease caused by influenza viruses. A case of influenza usually begins abruptly with fever and usually includes frequently recurring short chills; headache; malaise; pain behind the eye; a hacking, irritating cough; and severe muscle aches and pains (75). The manifestations of influenza can vary widely. In up to 25 percent of influenza infections, there is no clinical evidence of illness. However, in some cases, the disease can rapidly progress to overwhelming pneumonia and may cause death within hours to days.

Other potential complications of influenza include middle ear infections (94), acute encephalopathy (inflammation of the brain) (22), Reye's Syndrome (a rare, potentially life-threatening syndrome occurring in children) (61), renal failure (32), and rejection of kidney transplants (58). Further, influenza can lead to a deterioration of an existing disease (e. g., heart disease) that can be fatal.

The extent to which influenza leads to such complications is not known. In general, however, those individuals with certain types of chronic illnesses (e. g., lung, heart, or kidney disorders) and those with selected major illnesses (e.g., certain cancers) appear to be at greatest risk of incurring severe medical complications including death as a result of influenza.

Diagnosis and Treatment

A case of influenza is often diagnosed on the basis of clinical and epidemiologic information and the laboratory-confirmed absence of bacterial infections. When presented with a case of upper respiratory tract infection (URI), physicians may order laboratory tests (e. g., a throat culture) to help rule out bacterial causes. When bacterial causes are ruled out, on the basis of a patient's medical history, physical examination, or laboratory findings, viruses are generally assumed to be the cause of infection. During an influenza epidemic, validated by surveillance data reported by the Centers for Disease Control (CDC) or local public health laboratories, a case of viral URI is likely to be diagnosed as influenza. Outside of an epidemic period, e.g., during summer months, a viral URI is usually not attributable to influenza, although such infections are often referred to as "the flu. "

Influenza is treated largely through supportive measures. Clinical relief is obtained by resting in bed, drinking lots of liquids, and taking drugs that relieve symptoms of the disease (e.g., pain relievers, fever reducers, and decongestants). Unless a case of influenza leads to a secondary bacterial infection, antibiotics have no role in treatment of influenza. However, evidence demonstrates that the drug amantadine can help prevent certain types of influenza, help reduce the severity of a case of influenza, as well as serve as effective treatment for influenza in some cases (82).

Influenza Morbidity and Mortality

CDC has recently estimated that influenza contributed to approximately 127,000 excess deaths during the period from 1970-71 through 1977-78 (see app. E).

INFLUENZA VACCINE

The preferred method of reducing the incidence, morbidity, and mortality of influenza is by preventing the disease through vaccination. Various forms of inactivated (killed) influenza virus vaccines have been used for this purpose in the United States since the 1940's. Many factors affect the impact of such vaccines on influenza, including:

- vaccinees' prior exposures to influenza viruses and their antibody response to such exposures;
- the efficacy and duration of immunity acquired from vaccination;
- the percentage of individuals (especially those at high risk) vaccinated (see table 1, table 2); and
- the degree to which the virus(es) in the vaccine matches the virus(es) causing disease.

The influenza viruses present a peculiar problem for those who formulate, develop, produce, and distribute influenza vaccine. The extent to which these viruses circulate varies from year to year, and the composition of antigens (chemicals) on the virus surface changes with irregular frequency to unpredictable new forms (27).

Within the 6 to 9 months needed to manufacture influenza vaccine, influenza viruses can change their surface chemicals faster than vaccine manufacturers can change their product's formulations. As a result, in some years, the producers and promoters of influenza vaccinations have distributed vaccines that contained viruses that did not exactly match the circulating influenza viruses (see app. C). However, small changes in the circulating viruses do not appear to have substantially altered the efficacy of the vaccine (see app. B).

The safety of influenza vaccine became a major issue during the 1976-77 swine flu vaccination program (see app. D). Approximately 500 recipients of swine flu vaccine developed a disorder characterized by paralysis called Guillain-Barre Syndrome (GBS) (112). Although there is a strong correlation between GBS and the swine flu vaccine, such a relationship has not been documented between the use of other influenza vaccines and GBS in subsequent years, notwithstanding relatively intense surveillance of GBS cases by CDC (66). GBS might have been an adverse reaction peculiar to swine flu vaccine. Aside from GBS, influenza vaccines produce mild to moderate local reactions (e. g., pain, swelling, and redness at the injection site) as well as systemic reactions (e. g., fever and malaise) and rare allergic reactions (see app. B).

Table I.–Size of the General and High-Risk Populations Vaccinated With influenza Vaccine, 1970-71 Through 1977-78 (by age group)

	Size of general population (in thousands)				Size of high-risk population
Year	1-19 years	20-64 years	≥ 65 years	Total	≥ 20 years
1970-71	5,319	10,374	3,399	19,092	NA
1971 -72....	4,951	9,320	3,300	17,571	NA
1972.73	4,050	8,608	3,210	15,868	3,316
7973-74	4,511	8,975	3,628	17,114	3,964
1974 -75....	3,469	10,616	4,601	18,686	5,003
1975-76	3,426	9,055	4,621	17,102	4,764
1976.77	4,678	30,120	8,436	43,234	10,151
1977 -78....	3,872	11,170	5,381	20,423	5,975
Total	34,276	98,238	36,576	169,090	33,173
Average (excluding 1976-77). .,	4,228	9,731	4,020	17,979	4,604

NA = not available.

SOURCE: US. /*mmunization* Survey, 1970-78 (124).

Table 2.—Percentage of the General and High.Risk Populations Vaccinated With influenza Vaccine, 1970.71 Through 1977-78 (by age group)

	Percent of general population				Percent of high-risk population
Year	1-19 years	20-64 years	≥ 65 years	Total	≥ 20 years
1970-71	6.6%	9.80/0	17.5%	9.60/0	NA
1971-72	6.8	8.6	16.5	8.7	NA
1972-73	5.6	7.8	15.8	7.8	16.40/,
1973-74	6.3	8.0	17.4	8.4	17.7
1974-75	4.9	9.3	21.5		21.0
1975-76	4.9	7.8	21.1	3.2	19.6
1976-77	6.8	25.5	37.7	20.9	36.4
1977-78	5.7	9.3	23.5	9.7	20.8
Average/year (weighted)	6.0%	10.9°/0	21.6%	10.3%	22.50/o
Average/year (excluding 1976-77)	6.09%	9.00/0	19.1 0/0	9.0 "/0	19.3%

NA = not available.

SOURCE: U.S. *Immunization* Survey, 1970-78 (124)

INFLUENZA VACCINATION STRATEGIES

There are three basic strategies used to prevent influenza through vaccination. Each strategy—medical risk, socioeconomic risk, school children—is distinguished by the target population intended to be vaccinated.

Medical Risk Strategy

People with certain demographic characteristics and medical conditions are at the greatest risk of being seriously affected (either dying or becoming severely ill) by influenza during an epidemic. People over 45 years of age, for example, tend to be at greater risk of dying from influenza than do those under 45. Other so-called risk factors include selected chronic diseases (e.g., selected ailments of the heart, lungs, and kidney) and possibly certain types of cancer (l).

The premise of the medical risk strategy is that those persons most vulnerable to influenza mortality and severe morbidity should be protected through vaccination. This strategy is employed in the United States **(56,57)** and has been used in the United Kingdom (116).

Socioeconomic Risk Strategy

This strategy is designed to prevent influenza among those persons who are deemed to be essential to either the social or economic life of a country or community. This strategy targets in general the working population, and in particular, persons in selected occupations such as health professionals, armed forces personnel, and certain public servants (e. g., police, firemen, and postal workers). In the United States, this strategy has been combined to a minor extent with the medical risk strategy.

School Children Strategy

This strategy is designed to vaccinate school children as the primary method of preventing influenza epidemics. It is based on the premise that school-age children comprise a large, susceptible segment of the population and regularly have a high influenza-attack rate (52,74). School children also appear to be responsible for bringing influenza into the home, and therefore are important disseminators of influenza viruses (6,20,73).

The Government of Japan has sponsored a national program for immunizing school children as a public health measure for more than 15 years **(28)**.

COST-EFFECTIVENESS ANALYSIS

In this cost-effectiveness analysis, influenza vaccination is compared to treatment of the disease if it occurred. Changes in health effects and medical care costs produced by influenza vaccination during 1971-72 through 1977-78 were estimated. The analysis is limited to events within the medical care sector. Quantification of health effects and costs was based on data relating to the morbidity, mortality, and medical care costs associated with influenza and on data relating to the safety, effectiveness, use, and cost of influenza vaccine. Costs incorporate both medical care expenditures and savings. Effects consist of changes in years of healthy life.

Costs and health effects are viewed primarily from a societal perspective, which includes all medical care costs and health effects, regardless of who paid for them. They are viewed in a later section from the perspective of the medicare program.

In addition, the effects of vaccination on influenza-related work, school, and housekeeping losses were calculated separately.

MEASUREMENT OF HEALTH EFFECTS AND MEDICAL CARE COSTS ASSOCIATED WITH INFLUENZA VACCINATION

Simulating the Effects of Influenza Vaccinations for Years 1971-72 Through 1977=78

OTA constructed a computerized simulation model that quantified the health effects and medical care costs associated with influenza for years 1971-72 through 1977-78. The health effects of influenza measured were:

. restricted activity:
  —bed disability days,
  —nonbed disability days; and
• premature deaths.

The primary factors calculated to determine the health effects associated with influenza vaccine were:

- mortality from influenza;
- morbidity from influenza;
- vaccine effectiveness rate; and
- incidence of vaccine side effects.

The medical care costs measured were:

- hospitalization expenditures;
- expenditures for ambulatory cases (including physician visits, ancillary services, and drugs);
- vaccination costs (including treatment of vaccine side effects); and
- costs of treating GBS associated with vaccination.

In determining the effects and costs associated with influenza, it was assumed that excess morbidity and mortality occurred only in the unprotected (i.e., unvaccinated plus the not effectively vaccinated) portion of the population. Higher than average morbidity and mortality rates were estimated for the unprotected population, but the overall average values for the entire general population were not altered from those observed each year.

The changes in health effects and medical care costs were then calculated between two closed populations: one vaccinated and the other unvaccinated. Cost-effectiveness ratios based on these changes were developed for each epidemiologic year (July l-June 30), for an average year, and for all 7 years combined.

Quantifying Morbidity and Mortality Related to Influenza

Quantifying the degree of morbidity and mortality caused by influenza is a difficult task, primarily because influenza is seldom diagnosed definitively in routine medical practice. Over 100 types of viruses have been associated with URI. At least for the last 4 years, in a given geographical location, there have been either none, one (influenza A (H1N1 or H3N2) or influenza B), or a combination of these viruses causing influenza. Diagnostic technologies are either not available or not commonly used in general medical practice to differentiate which virus is causing a person's URI. It is common medical practice to differentiate between certain bacterial and viral infections, but not to differentiate among viral URIS. Techniques currently available to diagnose influenza (e.g., isolating influenza viruses from nasal secretions or measuring serum antibodies to influenza viruses) are usually reserved for research and" surveillance purposes, such as the reporting of influenza viruses by certain laboratories to CDC.

Because of the lack of definitive diagnostic criteria, influenza, as reported in surveys of physicians and the lay public, can become a "catch-all" term used to identify several types of viral URIS. In the absence of clinical diagnostic criteria, physicians often base their diagnosis of influenza on indirect evidence. For example, a person's URI may be diagnosed as influenza when the following situations exist:

- URI occurs during an influenza epidemic validated by CDC's influenza surveillance system;
- the patient exhibits influenza-like symptoms, e.g., fever and generalized muscle aches; and

. . bacteria] infection has definitely been ruled out by laboratory findings or clinical diagnosis.

To attribute morbidity to influenza, OTA used a technique developed by Kavet (55). OTA selected 1970-71 to serve as a nonepidemic influenza year—i.e., a year in which there was no influenza epidemic, were few reports of either influenza A or B viruses in circulation, and was no excess mortality attributed to influenza. During that year, however, influenza was reported as a cause of morbidity in surveys conducted by the National Center for Health Statistics (NCHS). OTA subtracted all influenza and pneumonia morbidity (measured in terms of hospitalization, physician visits, days of disability, work loss, and school loss) reported in 1970-71 from each of the following years, i.e., 1971-72 through 1977-78 (see app. E). The amount of excess morbidity remaining was attributed to influenza.

OTA selected influenza (ICDA codes[1] 470-474) and pneumonia (ICDA codes 480-486) combined as the primary diagnostic category by which to measure morbidity. Most illness attributed to influenza during an epidemic would be reported in these two diagnostic categories by physicians, hospitals, and patients. Because influenza leads to increases in pneumonia rates, data concerning the two illnesses are difficult to separate.

Mortality was measured in "excess deaths" due to all causes as calculated by CDC. Excess deaths are calculated by subtracting "estimated" or "expected" mortality from observed mortality during an influenza epidemic period (see app. E).

Health Effects

Changes in health effects from influenza vaccination are expressed in years of healthy life,[2] an index that incorporates days of illness and days of death related to influenza and to side effects of influenza vaccine. Different disability states are assigned rankings in terms of their relationship to the extremes of full functioning, on the one hand, and death, on the other. For example, on a scale where a year of full functioning is 1 and a year of death is O, a year with a minor health problem might rank as 0.9, and a year with a major health problem might rank as only 0.2. Rankings of different degrees of health can be thought of as representing preferences between more years of unhealthy life and fewer years of healthy life (86).

For purposes of this analysis, degrees of health were divided into four categories: death, disability days with confinement to bed, disability days without confinement to bed, and full functioning. Weighings for these different states were drawn from an analysis by Kaplan, Bush, and Berry: O for a year of death, 0.4 for a year of bed disability, 0.6 for a year of nonbed disability, and 1.0 for a year of full functioning (54).

This scale of weights was applied to years of life at whatever age changes in health status might be expected to occur. Thus, a year of health or life gained by a 5-year-old was weighted the same as a year gained by a 65-year-old. This simplifying assumption was made despite the fact that individuals and society may well value years of extra health or life differently depending on the age at which the additional years occur.

Medical Care Costs

In this analysis, costs, expressed in 1978 dollars, measure changes in medical care expenditures that likely resulted from influenza vaccination. Included as costs are increases or decreases in the medical expenditures incurred by all payers—patients, private third-party payers, and governments—for the treatment of influenza, the cost of influenza vaccine, the treatment of vaccine side effects, and (in the sensitivity analysis) total medical care expenditures in extended years of life yielded by influenza vaccination (see app. E).

[1] Eighth Revision, International Classification of Disease.

[2] The entity "years of healthy life" has been used for over a decade by several researchers, including Bush and associates (16,18, 19,54), Zeckhauser and Shephard (127), and Weinstein and Stason (126).

Health Effects and Medical Care Costs Over Time

Influenza vaccination not only affects illness and medical costs related to influenza, but also has implications for other health effects and medical costs over time. Some vaccinees, for example, avoid death from influenza and gain extended years of life. These added years, adjusted for disability, are included in this model, as described previously.

The health benefits gained—added years of life and reduced disability—have implications that reach beyond the medical care sector, but such implications are not included in this analysis. Added years of life, for example, may imply increased production and income as employed survivors continue their occupations, or increased social welfare as survivors continue their personal and family relationships. The cost-effectiveness ratios do not include such effects because they lie outside the medical care sector. Some productivity changes are calculated separately.

Another implication for a person who gains extended years of life is that the person will incur substantial medical expenses in each additional year. As secondary effects of vaccination, medical care costs in extended years of life do not appear in the base case because including one secondary and costly financial effect of vaccination, while excluding other secondary and beneficial financial effects, such as improvements in production, could be confusing. For example, in 1978, a person age 65 or older had average medical expenditures of about $2,000. If medical care costs in extended years of life were included in the cost-effectiveness analysis, the addition of an extra year to that person's life would worsen (increase) the cost-effectiveness ratio by increasing annual medical care costs by $2,000. The sensitivity analysis shows the effect of including these medical costs. Some previous cost-effectiveness studies have included medical costs in extended years of life (86,126).

All health effects and medical care costs were discounted in the base case using a S-percent rate (see app. E.)

Work, Housekeeping, and School Loss

Days lost from work, housekeeping, and school because of influenza were calculated. These three measures of influenza morbidity were not included in the cost-effectiveness analysis of influenza vaccination; however, the impacts of influenza vaccination on these measures were calculated separately. These lost days are already included as disability days in the cost-effectiveness model. A 1978 dollar value was assigned to work and housekeeping losses (see app. E).

COST-EFFECTIVENESS EQUATION AND MODEL

Cost-effectiveness ratios (C/E) for influenza vaccination, expressing the net medical expenditure per year of healthy life gained by vaccination, were computed with the following model:[3]

$$\frac{\text{net medical costs}}{\text{net health effects}} = \frac{c = (C_p - c_t + C_{se} + c_,)}{E \qquad (El_Y + E_m - E_{se} - E,)}$$

C_p = Expenditure for vaccination
C_t = Saving in costs of treating influenza
C_{se} = Cost of treating vaccine side effects
C, = Cost of treating future illnesses not prevented by vaccination among vaccinees whose lives are prolonged as a result of vaccination (in sensitivity analysis only)
@ = Increased years of life from vaccination
E_m = Increased health from preventing influenza morbidity
Ese = Reduced health from vaccine side effects
E, = Reduced health from future illness not prevented by vaccination among vaccinees whose lives are prolonged as a result of vaccination.

Separate cost-effectiveness ratios were calculated for vaccinating people in each of six different age groups: under 3, 3 to 14, 15 to 24, 25 to 44, 45 to 64, and 65 years and older. The model is applied to high-risk groups in a subsequent section of this chapter.

[3]The model used in this analysis is similar to that used by Weinstein and Stason in their analysis of a hypertension treatment program. One difference is that the term E, has been added to account for illnesses in extended years of life (see 126).

BASE CASE AND SENSITIVITY ANALYSIS

In the base case, values assigned to all variables were based on the best estimates available. A sensitivity analysis was used to test the importance of values assigned to selected variables and hence to identify those variables that significantly affect the cost-effectiveness ratio of influenza vaccination. The sensitivity analysis is particularly useful in determining the importance of those variables for which data are uncertain or missing. The sensitivity analysis is also helpful in identifying important topics for future biomedical research and policy analysis.

Assumptions used in both the base case and the sensitivity analysis are listed in table 3. Values altered for the following variables in the sensitivity analysis are displayed in table 4:

- **cost** of vaccination,
- vaccine efficacy rate,
- discount rate,
- excess deaths, and
- medical care costs for treatment of illnesses (other than influenza) in extended years of life.

Table 3.—Assumptions Employed in Both the Base Case and Sensitivity Analysis

1, Duration of immunity from vaccination was 1 year.

2. An ambulatory case of influenza-related illness consisted of 1.10 to 3.66 physician office visits (depending on patient's sex and age); during each visit, 0.16 clinical lab test, 0.17 X-ray, and 0.75 prescription were ordered. The total cost per ambulatory case ranged from $23.38 to $51.60 (depending on patient's sex and age). (See app. E.)

3. For persons 65 years and older, medicare paid for 55.6 percent of all physician charges, 74.6 percent of all hospital expenditures, and 44.1 percent of all medical care expenditures (37, 24).

4. A hospitalized case of influenza-related illness consisted of 3.92 to 12.5 days of hospitalization (depending on patient's sex and age and year of illness), one initial comprehensive physician visit, and subsequent daily routine followup brief hospital visits. The cost of a hospital case ranged from $657 to $2,031 (depending on patient's sex and age).(See app.E.)

5. The incidence of adverse reactions other than Guillain-Barre Syndrome (GBS) was as follows: (See app. D and E.)
   - Local or mild systemic reactions which resulted in a physician visit (at $10.36/visit):
     — 5 percent of vaccinees 18 years and over,
     — 13 percent of vaccinees under 18 years;
   - Severe systemic allergic reaction (anaphylaxis) (at $725/case):
     — 1 case per 4 million vaccinees.

6. Guillain-Barre Syndrome (GBS) occurred as a statistically significant side effect of influenza vaccination only in 1976-77. The effects of GBS were quantified according to data generated from 1976-77 and 1977-78. (See app. D and E.)

7. A day of nonbed disability was weighted at 0.6 and a day of bed disability was weighted at 0.4 (54).

8. The vast majority of treated influenza was reported to the National Center for Health Statistics as either influenza (ICDA codes 470-474) or pneumonia (ICDA codes 480-486) (unduplicated, all listed diagnoses).

SOURCE: Off Ice of Technology Assessment

Table 4.—Values Assigned to Uncertain Variables in the Base Case and Sensitivity Analysis[a]

Variable	Base case value	Sensitivity analysis	
		Low value	High value
Cost of vaccination:			
Vaccinees ≥ age 25	$6.00	$1.55	$9.39
Vaccinees < age 25	$11.09	$4.50	$19.60
Vaccine efficacy rate	600/0	30 "/0	90 "/0
Discount rate	5%	o	—
Excess deaths	Excess deaths calculated by CDC	Based on excess deaths calculated by NIH (Ailing, et al.)	—
Medical care costs for treatment of illnesses not prevented in extended years of life	Not included		Included

[a]For explanations of the data sources, calculations, and assumptions used to derive these values, see aPP. E

SOURCE: Office of Technology Assessment.

RESULTS

Most of the results are presented as "per vaccination. " Costs and effects per vaccination are not affected by the number of people vaccinated. This relationship reflects the following two assumptions made in the analysis.

- The price of vaccination is not changed by the number of vaccinees.
- Vaccination rates during the period 1971-72 through 1977-78 were below those necessary for unvaccinated people to derive herd immunity from vaccinees.

Base Case

Cost-effectiveness ratios for influenza Vaccination, derived using base case assumptions, are represented in table 5. With base case assumptions (see table 4), influenza vaccination would result in a net improvement in health for vacci-

Table 5.—Base Case Analysis: Per Vaccination Cost Effectiveness of Annual Influenza Vaccination,1971 -72 Through 1977-78[a] (by age group[b])

	Under 3 years	3-14 years	15-24 years	25-44 years	45-64 years	≥ 65 years	All ages
Per vaccination costs and health effects of vaccination							
Net cost	$ 10	$ 11	$ 8	$ 5	$ 3	—c	—d
Net health effect (days of healthy life gained)	15 days	20 days	17 days	30 days	49 days	28 days	—d
Cost-effectiveness ratio (cost per year of healthy life)	$258/ year of healthy life	$196/ year of healthy life	$181/ year of healthy life	$64/ year of healthy life	$231 year of healthy life	—c	$63/ year of healthy life

[a]Average cost-effectiveness ratios per vaccination are based on data from years 1970-71 through 1977-78; the impacts of annual vaccination from 1971-72 through 1977-78 were calculated over the lifetimes of vaccinees.
[b]Ages as of 1971-72. Vaccinated and unvaccinated populations were followed as a cohort over time.
[c]In these instances, vaccination resulted in negative costs — or savings. However, because they can be misleading, such savings are not displayed.
[d]Per Vaccination net costs and nethealth effects were not calculated for all ages combined.

SOURCE: Office of Technology Assessment.

nees of all ages, and would result in savings in medical expenditures (associated with influenza) for vaccinees 65 years and older.

In general, the cost-effectiveness of influenza vaccination, expressed in net medical costs (or savings) per year of healthy life gained, improves with increasing age of the vaccinee at the time of vaccination. Net medical cost per year of healthy life gained for a vaccinee under 3 years old is about $258. This ratio drops to $196 for ages 3 to 14, $181 for ages 15 to 24, $64 for ages 25 to 44, and $23 for ages 45 to 64. For vaccinees aged 65 years and older, vaccination produces a net savings. The net cost per vaccination ranges from a high of about $11 for vaccinees aged 3 to 14 years to an actual savings for vaccinees over 65 years. The gain in net health effects ranges from a low of 15 days of healthy life for vaccinees aged less than 3 to a high of 49 days of healthy life for vaccinees aged 45 to 64.

For all ages combined, the overall cost-effectiveness ratio per *vaccination* is about $63 per year of healthy life gained. This overall ratio illustrates by contrast the difference in the cost effectiveness of a vaccination program that can be achieved by targeting vaccination to specific subgroups of the population—namely, the lower cost-effectiveness ratio for vaccinating the elderly (a net savings per year of healthy life gained) and the higher cost-effectiveness ratio for vaccinating the very young ($258 per year of healthy life gained among vaccinees less than 3). It should be noted that even the highest ratio, i.e., $258, is a very low price to pay for a year of healthy life.

Even when a program is not actually cost saving, it may be deemed cost effective. The determination that a program or intervention is cost effective is a value judgment that can be made by either an individual or by society at large. A majority of people would be willing to pay something to gain a year of healthy life, and there exists a consensus that most people would willingly spend several thousand dollars for each healthy year gained (126). In terms of their economic efficiency, alternative programs or interventions with low cost-effectiveness ratios might be more easily justified than those with high ratios (e.g., those costing over $50,000 per year of healthy life gained) (126).

Net costs and effects of influenza vaccination for the *total population* are shown in table 6. Total population costs and effects depend on the number of people vaccinated. The results shown in table 6 are based on actual influenza vaccination rates from years 1971-72 through 1977-78 (124). Influenza vaccination generally is targeted to high-risk people (see app. E) and generally confers protection for a single year.

The numbers in table 6 demonstrate the degree to which per vaccination costs and health effects of an influenza vaccination program are magnified when considered for the population as a whole. Results in table 6 are based on the age-specific vaccination rates shown in tables 1 and 2.

For all ages combined, influenza vaccinations administered between 1971-72 and 1977-78 generated net medical costs (associated with influenza vaccination and medical treatment) totaling $808 million and yielded a net gain of 12.9 million years of healthy life.

Sensitivity Analysis

The importance of five variables in the cost-effectiveness model is shown by the results of the sensitivity analysis in table 7. Except for the "best case" and "worst case" analyses, the values of the five variables were altered one at a time; the variables that were not being tested were assigned their base case values. In the "best case" and "worst case" analyses, the values of four variables, (i. e., vaccine efficacy rate, vaccination costs, medical costs in extended years of life, and influenza mortality rates) were altered simultaneously. In both analyses, the discount rate remained at the base case value of 5 percent.

An influential variable for the cost-effectiveness ratio is the cost of *vaccination (see* table 7). The cost per dose used in the base case was $6.00 for vaccinees age 25 and older and $11.09 for vaccinees under age 25 (see app. E). These costs represent the estimates of vaccination costs when influenza vaccine was administered in the

Table 6.—Base Case Analysis: Cumulative Population Costs and Health Effects of Annual Influenza Vaccination, 1971.72 Through 1977-78[a] (by age group[b])

	Under 3 years	3-14 years	15-24 years	25-44 years	45-64 years	≥ 65 years	All ages
Population costs and health effects of vaccination							
Net costs	$41,800,000	$205,300,000	$229,400,000	$200,600,000	$112,600,000	–c	$807,800,000
Net health effects (years of healthy life gained)	160,000 years	1,000,000 years	1,300,000 years	3,100,000 years	4,800,000 years	2,000,000 years	12,900,000 years
Coat-effectiveness ratio (cost per year of healthy life)	$258/ year of healthy life	$196/ year of healthy life	$181/ year of healthy life	$64/ year of healthy life	$23/ year of healthy life	—c	$63/ year of healthy life

[a]The Population costs and effects of annual influenza vaccination were calculated based on the age-specific vaccination rates reported for years 1971-72 through 1977-78 in the U.S. *Immunization* Survey (see table 2, app. E) (124). It was assumed there would be no economies of scale in costs and no herd immunity
[b]Ages as of 1971-72. Vaccinated and unvaccinated populations were followed as a cohort Over time.
[c]In these instances, vaccination resulted in negative costs — or savings

SOURCE: Office of Technology Assessment.

private sector. Using lower vaccination costs —i. e., $1.55 for vaccinees age 25 and older and $4.50 for vaccinees under age 25 (low public sector estimates), improves the cost effectiveness of vaccination for every age group. Using higher private sector vaccination cost estimates—i.e., $9.39 for vaccinees age 25 and older and $19.60 for those under age 25—however, reduces the cost effectiveness of vaccination for every age group; and among vaccinees aged 65 and older, vaccination generates a small net cost.

The variable with the most profound impact on the cost effectiveness of influenza vaccination is the inclusion of medical *care costs in extended years of life (see* table 7, app. E). These medical care costs are incurred by people whose lives are saved as a result of influenza vaccination. Such costs were left out of the base case for conceptual reasons. When such costs are included, they completely overshadow the importance of changes in all other variables combined in the sensitivity analysis. Their inclusion elevates the cost of gaining a year of life to a minimum of $1,745 (age group less than 3 years) to a maximum of $2,084 (age group 45 to 64). For all ages combined, the cost of gaining a year of life becomes $1,956.

When no *discount rate* is used, the cost-effectiveness ratios improve for vaccinees of all ages.

Altering the *vaccine efficacy rate* had minimal effect on the cost-effectiveness ratios for any age group (see table 7). Among vaccinees over age 65, influenza vaccination generated medical care savings when the vaccine efficacy rate was varied between 30 percent and 60 percent.

The use of excess *influenza death estimates* generated by Ailing and associates at the National Institute of Allergy and Infectious Diseases (2), instead of those estimates calculated by Chow and Thacker at CDC had virtually no effect on the cost-effectiveness ratio for all ages combined (see table 7). Vaccination still yielded net savings in costs per year of healthy life (associated with influenza vaccination and medical treatment) for vaccinees aged 65 and over. The cost of gaining a year of healthy life was somewhat less among younger age groups, because of the allocation of excess influenza deaths to the lower age groups.

In the "best case" analysis—i.e., lowest vaccination cost, highest vaccine efficacy rate, exclusion of medical care costs in extended years of life, and NIH mortality rates—the overall cost of gaining a year of healthy life for all ages combined is $1.00. Under these conditions, influenza vaccination yields cost savings for age groups 45 and older,

In the "worst case" analysis—i.e., highest vaccination cost, lowest vaccine efficacy rate, inclusion of medical care costs in extended years of

life, and CDC mortality rates—the overall cost of gaining a year of healthy life for all ages combined is $2,018. Under these conditions, influenza vaccination does not yield cost savings for any age group.

table 7.—Sensitivity Analysis: Per Vaccination Cost Effectiveness of Annual Influenza Vaccination, 1971-72 Through 1977-78

Variable	Assigned values[b]	Per vaccination cost per year of healthy life by age group[a], [c]						
		Under 3 years	3-14 years	15-24 years	25-44 years	45-64 years	≥ 65 years	All ages
cost of vaccination	Public sector - Low /accinees ≥ age 25 - $4.50							
	Vaccinees < age 25-$1.55	$ 118	$ 90	$ 73	$ 18	–d	–d	$ 11
	• private sector - Low /accinees ≥ age 25 - $11.09							
	Vaccinees < age 25-$6,00	$ 258	$ 196	$ 181	$ 64	$ 23	–[d]	$ 63
	Private sector - High /accinees ≥ age 25 - $19.50							
	Vaccinees < age 25-$9.39	$ 439	$ 332	$ 306	$ 99	$ 45	$ 34	$ 112
Vaccine efficacy rate	30 percent.	$ 262	$ 198	$ 183	$ 66	$ 33	$ 74	$ 74
	● 60 percent.	$ 258	$ 196	$ 181	$ 64	$ 23		$ 63
	90 percent.	$ 253	$ 194	$ 178	$ 61	$ 14	–[d]	$ 52
Discount rate applied to costs and effects occurring after 1971-72	No discount rate	$ 9	$ 9	$ 13	$ 9	$ 7	–[d]	$ 8
	• 5 percent.	$ 258	$ 196	$ 181	$ 64	$ 23	–[d]	$ 63
Excess death rate	NIH (Ailing, et al,).	$ 187	$ 146	$ 146	$ 58	$ 26	–[d]	$ 61
	• CDC ... , ...	$ 258	$ 196	$ 181	$ 64	$ 23	–[d]	$ 63
Medical care **costs in extended years of life**	Included	$1,745	$1,880	$2,010	$2,027	$2,084	$1,782	$1,956
	• Not included. ., ...	$ 258	$ 196	$ 181	$ 64	$ 23	–[d]	$ 63
Best case situation (5 percent discount)	—Excess deaths - NIH (Alling, et al.) —Vaccine efficacy rate -90 percent —Medical care costs in extended years of life - not included —Vaccination costs - low public sector	$ 83	$ 66	$ 57	$ 14	–d	–d	$ 1
Worst case situation (5 percent discount)	—Excess deaths - CDC —Vaccine efficacy rate -30 percent —Medical care costs in extended years of life - included —Vaccination costs - high private sector	$1.937	$2,022	$2,143	$2,068	$2,118	$1,842	$2,018

" Base case values
[a] Ages are those in 1971.72 Vaccinated and unvaccinated populations were followed as a cohort over time
[b] For information regarding the data sources and calculation of the values used in this sensitivity analysis, see app E
[c] Actual calculated values were rounded off to the nearest $1.00
[d] In these instances, vaccination resulted in negative costs—or savings Such Savings are not displayed, however, because they can be misleading

SOURCE Off Ice of Technology Assessment.

EFFECT OF INFLUENZA VACCINATION ON PRODUCTIVITY

An implication of illness from influenza is the inability of those affected to carry on their usual major activities in the workplace, in housekeeping activities, or in school. Work days lost because of influenza reduce productivity in the economy. In fact, often raised in policy discussions is the question of whether or not influenza vaccination should be recommended for working people in the general population in order to reduce productivity losses (100).

Table 8 shows self-reported medically attended excess *work loss* from 1971-72 to 1977-78. During this period, such work loss averaged 15 million days per year—7 million days for females and 8 million for males, Almost

Table 8.—Self-Reported Excess Work Loss Related to Medically Attended Influenza, 1971-72 Through 1977.78[a]

	Work loss in days by age group				
Year	17-24 years	25-44 years	45-64 years	≥65 years	All ages
1971.72					
Male	566,560	2,527,748	2,513,321	1,145,913	6,753,542
Female	1,638,361	5,979,464	3,867,125	610,412	12,095,362
Total	2,204,921	8,507,212	6,380,446	1,756,325	18,848,904
1972.73					
Male	2,425,252	4,813,922	4,352,705	1,753,318	13,345,197
Female	3,503,367	2,608,446	1,097,946	325,628	7,535,387
Total	5,928,619	7,422,368	5,450,651	2,078,946	20,880,584
1973.74					
Male	1,914,235	3,105,884	530,791	1,038,803	6,589,713
Female	1,139,066	3,874,346	0	284,252	5,297,664
Total	3,053,301	6,980,230	530,791	1,323,055	11,887,377
1974-75					
Male	2,192,063	950,182	1,196,434	409,319	4,747,998
Female	3,440,273	4,195,904	0	0	7,636,177
Total	5,632,336	5,146,086	1,196,434	409,319	12,384,175
1975.76					
Male	552,808	6,693,126	1,689,008	204,613	9,139,555
Female	3,017,422	4,645,739	2,010,055	0	9,673,216
Total	3,570,230	11,338,865	3,699,063	204,613	18,812,771
1976-77					
Male	0	0	0	413,241	413,241
Female	1,942,255	4,336,791	298,460	0	6,577,506
Total	1,942,255	4,336,791	298,460	413,241	6,990,747
1977.78					
Male	4,898,327	6,806,237	3,966,569	0	15,671,133
Female	85,763	882,767	0	0	968,530
Total	4,984,090	7,689,004	3,966,569	0	16,639,663
Average number of excess days of work loss/year					
Male	1,792,749	**3,556,728**	**2,035,547**	**709,315**	**8,094,340**
Female	2,109,501	3,789,065	1,039,084	174,327	7,111,977
Total	3,902,250	7,345,793	3,074,631	883,642	15,206,317

[a]These data were based on unpublished work loss data related to influenza [8th Revision ICDA Codes 470-474) and pneumonia (8th Revision ICDA Codes 480-486) supplied by the Health Interview Survey at the National Center for Health Statistics (see app E). "Excess" work loss was derived by subtracting days of work loss (due to influenza and pneumonia) in 1970-71 from work loss (due to Influenza and pneumonia) for each subsequent year through 1977.78.

SOURCE: Office of Technology Assessment.

half of this work loss, an annual average of 7 million days, is reported by workers aged 25 to 44.

Table 9 reports *productivity lost* from these work days. Productivity loss was valued according to age- and sex-specific earnings (15). From 1971-72 to 1977-78, average *annual* Productivity lost was about $764 million. The age group from 25 to 44 years experienced the greatest productivity loss in each year, an annual average of almost $400 million.

Table 10 reports the effect that influenza vaccination had on reducing work loss related to influenza from 1971-72 through 1977-78. With vaccination rates that existed, about 5 million work days were gained for the overall work force, and these productivity gains were valued at about $250 million during that 7-year period.

Table 11 reports comparable figures for people who reported housekeeping as their major activity. The reduction in *housekeeping days* lost was also substantial. The gains rose with in-

Table 9.—Productivity Loss Related to Self-Reported Excess Work Loss From Medically Attended Influenza, 1971-72 Through 1977-78[a]

	Productivity loss by age group (thousands of dollars)				
Year	17-24 years	25-44 years	45-64 years	≥ 65 years	All ages
1971.72					
Male	22,100	174,400	183,500	68,800	448,800
Female	49,200	236,200	150,800	18,300	454,500
Total	$71,300	$410,600	$334,300	$87,100	$ 903,300
1972.73					
Male	94,600	329,800	317,700	105,200	847,300
Female	105,100	103,000	42,800	10,094	260,994
Total	$199,700	$432,800	$360,500	$115,294	$1,108,294
1973-74					
Male	74,700	212,800	38,700	62,300	388,500
Female	34,200	153,000	0	8,800	196,000
Total	$108,700	$365,800	$38,700	$71,100	$ 584,500
1974-75					
Male	85,500	65,100	87,300	24,600	262,500
Female	103,200	165,700	0	0	268,900
Total	$188,700	$230,800	$87,300	$24,600	$ 531,400
1975.76					
Male	21,600	458,500	123,300	12,300	615,700
Female	90,500	183,500	78,400	0	352,400
Total	$112,100	$642,000	$201,700	$ 12,300	$ 968,100
1976-77					
Male	0	0	0	24,800	24,800
Female	58,300	171,300	11,600	0	241,200
Total	$58,300	$171,300	$11,600	$24,800	$ 266,000
1977-78					
Male	191,000	466,200	289,600	0	946,800
Female	2,600	34,900	0	0	37,500
Total	$193,600	$501,100	$289,600	$ 0	$ 984,300
Average income loss/year					
Male	**69,900**	**243,800**	**148,600**	**42,600**	**504,900**
Female	63,300	149,700	40,500	5,300	258,800
Total	$133,200	$393,500	$189,100	$47,900	$ 763,700

[a]Productivity loss was calculated by multiplying excess days of self. reported work loss (see table 8) by age-specific daily earnings for full-time workers as reported by the Bureau of the Census (see app. E) (15)

SOURCE: Off Ice of Technology Assessment.

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Table 10.—Base Case Analysis: Effects of Vaccination on Reduction in Work Loss and Productivity Loss From Influenza, 1971-72 Through 1977-78° (by age group[b])

	3-14 years	15-24 years	25-44 years	45-64 years	≥ 65 years	Total
Per vaccination						
Work days gained	0.01	0.05	0.05	0.03	0.02	–
Productivity gained	$ .36	$2.10	$2.60	$1.60	$1.20	–
For work force						
Work days gained	198,100	1,452,000	1,922,000	945,000	576,200	5,093,300
Productivity gained	$6,965,000	$57,030,000	$101,000,000	$56,340,000	$31,520,000	$252,855,000

[a]Changes in work loss and productivity loss for the work force were based on influenza vaccination rates reported for 1971-72 through 1977-78 in the *U.S Immunization Survey* (124).
[b]Ages as of 1971-72. Vaccinated and unvaccinated populations were followed as a cohort over time.

SOURCE: Office of Technology Assessment.

Table 11.—Base Case Analysis: Effects of Vaccination on Reduction in Housekeeping Loss and Imputed Productivity Loss Related to Influenza, 1971-72 Through 1977=78 (by age group[a])

	3-14 years	15-24 years	25-44 years	45-64 years	≥ 65 years	Total
Per vaccination						
Housekeeping days gained	0.003	0.01	0.02	0,02	0.06	—
Imputed productivity gained	—[b]	—[b]	—[b]	—[b]	$1.86	—
For general population						
Housekeeping days gained	57,300	296,000	824,600	899,300	1,490,000	3,567,200
Imputed productivity gained	—[b]	—[b]	—[b]	—[b]	$46,190,000	$135,553,600

[a]Ages as of 1971-72. Vaccinated and unvaccinated populations were followed as cohorts over time. Productivity loss was imputed on basis of average female earnings.
[b]Not imputed.
[c]Based on influenza vaccination rates reported for 1971-72 through 1977-78 in the *U.S. Immunization Survey* (124).

SOURCE: Office of Technology Assessment.

creasing age at the time of vaccination. From 1971-72 through 1977-78, housekeeping days gained totaled about 3.5 million, with an imputed value of about $135.5 million based on average earnings for women.

Vaccination also reduced *school loss.* An estimate based on actual vaccination rates is that about 780 thousand school days were gained.

MODIFICATION OF THE MODEL FOR THE HIGH-RISK POPULATION

Influenza vaccination is most often recommended for those persons with certain medical conditions or demographic characteristics that render them at greater risk of complications if they contract the disease. Such persons are referred to as the influenza "high-risk" population. According to the Immunization Practices Advisory Committee, formerly the Advisory Committee on Immunization Practices, which advises the Federal Government on national vaccination policies, persons with the following conditions or characteristics are deemed to be at "high risk" and should receive influenza vaccinations annually (l):

- 65 years of age or older;
- selected types of acquired or congenital heart disease;
- any chronic disorder with compromised pulmonary function;
- chronic renal disease;

- diabetes mellitus or other metabolic diseases with increased susceptibility to infection;
- chronic, severe anemia, such as sickle cell disease; and
- other conditions which compromise the immune mechanism, including certain malignancies and immunosuppressive therapy.

The following analysis compares the cost effectiveness of influenza vaccination among high-risk persons to the cost effectiveness of vaccination among the general population.

Size of Vaccinated High-Risk Population

On the basis of data collected by the Bureau of the Census, CDC estimates the size of the high-risk populations. During each year from 1972-73 through 1977-78, there were an estimated 24.5 million persons over 20 years old in the influenza high-risk population (see app. E, table 12). Forty percent of all persons over 65 years old reportedly had one or more medical conditions that represent an influenza risk factor (124). Each year, an estimated 19 percent of the high-risk population (all ages combined) received influenza vaccine; during 1976-77, the year of the swine flu program, about 36 percent of the high-risk persons were vaccinated (see app. E, table 12 for age-specific rates).

Alteration of Selected Characteristics Describing the High-Risk Population

The values of the following variables were altered in the cost-effectiveness analysis for influenza vaccination among high-risk persons (see app. E):

- probability of a person's dying—from all causes as well as from influenza or pneumonia—within a given year,
- probability of a person's either being hospitalized or visiting a physician's office for influenza or pneumonia,
- the length-of-stay of a hospitalized influenza case and the number of physician visits per ambulatory influenza case,
- total medical care costs per person in any extended years of life,
- probability of a person's encountering bed or nonbed disability days from all causes and from influenza, and
- probability of a person's receiving influenza vaccine.

Results

With the assumptions in the base case, vaccination of high-risk groups is more cost effective at any given age than vaccination of individuals in the general population (see table 13). Vaccination of high-risk individuals 65 years and older is cost saving. Again, cost effectiveness improves with increasing age at the time of vaccination. Cost per year of healthy life gained drops from $44 for ages 15 to 24 to $15 for ages 45 to 64.

The inclusion of medical costs in extended years of life substantially changed the results for the high-risk population, as it did the results for the general population. The magnitude of the difference for the high-risk population, however, is relatively much greater. For example, when additional medical costs are included, the per vaccination cost per year of healthy life is $4,040 for a high-risk person 65 years or older. When additional medical care costs are excluded, vaccination of a high-risk person 65 years or older is cost saving. If medical care costs in extended years of life are included, the highest cost per year of healthy life gained occurs for a high-risk person aged 45 to 64, i.e., $4,150. Thus, cost per year of healthy life for a high-risk person 45 years or older is about twice the cost for the general population—about $4,000 compared to about $2,000, These differences stem from the greater probability that a high-risk person will become ill and from the higher medical costs in any extended years of life.

It is noteworthy that vaccination of high-risk people of a certain age may be more cost effective than vaccination of an older age group in the general population. For example, cost per year of healthy life gained for a high-risk person aged 15 to 24 is $44, a lower cost than the $64 for an average-risk person aged 25 to 44. Although these cost differences are small, they illustrate a point that has been made about the differences among members of a certain age group or

Table 12.—Size and Percent of High-Risk Population 20 Years and Older Vaccinated During Fiscal Years 1973-78[a] (by age group)

Fiscal year	20-29 years	30-39 years	40-49 years	50-64 years	≥ 65 years	All ages ≥ 20 years
1973						
Size of high-risk population (000's)	1,878	1,647	2,665	6,938	7,131	20,259
Percent of total relevant population	5.71%	6.970/o	11.60/0	22.60/o	35.1%	15.50/0
Percent of high-risk population vaccinated	10.1%	8.9 '/0	10.7%	16.1 '/0	22.2%	16.40/o
1974						
Size of high-risk population (000's)	1,995	1,928	2,848	7,601	7,964	22,336
Percent of total relevant population	5.93%	7.880/o	12.4%	24.40/o	38.20/o	16.8%
Percent of high-risk population vaccinated	10.5%	11.0 'J/o	12.70/o	17.1%	23.60/o	17.70!0
9 5						
Size of high-risk population (000's)	2,098	2,179	3,192	8,029	8,321	23,819
Percent of total relevant population	6.000/0	8.690/o	14.1%	25.50/o	38.90/o	17.60/o
Percent of high-risk population vaccinated	10.5%	12.1%	15.0'?!0	20.0%0	29.20/o	21.0%
1976						
Size of high-risk population (000's)	2,222	2,260	3,183	8,108	8,549	24,322
Percent of total relevant population	6.1 70/0	8.760/o	14.1%	25.50/o	39.0%	17.6%
Percent of high-risk population vaccinated	7.40%	10.8 '/0	11 .80/0	1 9.0%0	28.60/o	19.60/o
1977						
Size of high-risk population (000's)	2,313	2,636	3,676	9,171	10,089	27,885
Percent of total relevant population	6.360/o	9.650/o	16.40/o	28.70/o	45.1 %0	19.80/o
Percent of high-risk population vaccinated	24.2 '/0	26.0 '/0	29.90/o	36.70/o	44.00/0	36.40/o
1978						
Size of high-risk population (000's)	2,383	2,672	3,570	9,603	10,432	28,660
Percent of total relevant population	6.440/o	9.380/o	15.9%	29.80/o	45.60/o	20,00/0
Percent of high-risk population vaccinated	10.0%	10.4%	1 4.7%	19.40!0	29.50/o	20.80/o
Total high-risk population (000's), fiscal years, 1973-1978	12,889	15,200	19,137	49,450	52,486	147,281
Average high-risk population per year(000's)	2,148	2,533	3,189	8,242	8,748	24,547
Average percent of total population 20 years and older considered to be high-risk	6.11 '/0	9.820/o	14.1%	26.1 '/0	40.50/0	1 7.9%0
Average percent of high-risk population vaccinated per year	12.3 0/0	12.0%	16.30/o	23.80/o	30.20/o	22.50/o
Average percent of high-risk population vaccinated per year excluding 1976-77	9.65%	9.11%	13.1%	20.90/o	26.90/o	19.3%

aTh, high-risk populationcomprises persons with one or more of the following medical conditions: diabetes, selected types of lung disease, selected types of heart disease.

SOURCE: *U.S. Immunization Survey,* 1973-78 (124).

Table 13.—Per Vaccination Cost-Effectiveness Ratios for Annual Influenza Vaccination Among High-Risk Persons Compared to Ratios Among the General Population, 1971-72 Through 1977-78

	Cost per year of healthy life gained by age group[a]				
	15-24 years	25-44 years	45-64 years	≥ 65 years	All ages combined
High-risk population					
Base case	$ 44	$ 23	$ 15	–[b]	$ 10
Including medical care costs in extended years of life	$3,050	$3,620	$4,150	$4,040	$3,880
General population					
Base case	$ 181	$ 64	$ 23	—[b]	$ 63[c]
Including medical care costs in extended years of life	$2,010	$2,027	$2,084	$1,782	$1,956[c]

[a]Ages as of 1971-72 Vaccinated and unvaccinated populations were followed as a cohort over time.
[b]In these instances, vaccination resulted in savings, However, because they can be misleading, such savings are not displayed.
[c]All ages for the general population includes children < 15 years.

SOURCE: Office of Technology Assessment.

among members of the general population (114). High-risk people may experience greater benefits from vaccination than others, because the incidence and severity of the disease and the costs of treating it are higher for those at high risk. Therefore, the inclusion of high-risk people in the general population raises the average level of benefits to be obtained from vaccinating the general population. In fact, a non-high-risk member of the general population would realize a lower level of benefit and have a higher cost-effectiveness ratio than the average, which includes high-risk people.

As shown in table 13, the relationship is not so predictable when medical care costs in additional years of life are included. Medical care costs in extended years of life may be so much greater for high-risk people that their cost per year of healthy life gained may be greater than the same calculation for average-risk people.

These differences in results for high-risk people and for the general population indicate that efforts should be made to identify heterogeneity within a population. Analyses are most valuable that, to the extent that is feasible and manageable, take the differences in risk status into account.

MODIFICATION OF THE MODEL FOR MEDICARE

From a societal perspective, influenza vaccination for persons 65 years or older is cost saving in the base case. Even with worst case assumptions, notably the inclusion of medical costs in extended years of life, the net cost per year of healthy life gained was only about $1,800 for those 65 or older. These results for the elderly raise the issue of medicare coverage for influenza vaccination. The Social Security Act now prohibits medicare payment for influenza vaccination.

The societal model was modified to evaluate the effect on medicare expenditures of covering influenza vaccination. After copayments and deductibles, medicare insures about 75 percent of the hospital costs and about 56 percent of the physician costs for the treatment of influenza (37). In addition, it was estimated that medicare pays about 44 percent of medical costs in extended years of life (37). It was assumed that medicare would pay 100 percent of vaccination costs.

As shown in table 14, full coverage of influenza vaccination from 1971-72 through 1977-78 would have cost medicare $791 per year of healthy life gained by vaccinees 65 years and older. *Per vaccination* costs to medicare would have totaled $61: $6 for the original vaccination and treatment of any side effects; a negligible amount for treating GBS; $4 saving in reduced influenza treatment costs; and $60 for additional medical costs in extended years of life. **A** vaccination improved the health of an elderly person by 28 additional days of healthy life. In summary, every influenza vaccination among medicare beneficiaries would have generated about 1 month of healthy life at a cost of about $60 to the medicare program.

With the vaccination rates that existed from 1971-72 through 1977-78, coverage of influenza vaccination by medicare for that entire period would have cost the program about $1.6 billion for vaccinations that yielded about 2 million years of healthy life. Of this cost, $145 million would have been spent for vaccinations and treatment of their side effects, while savings from reduced influenza treatment costs would have been about $104 million. The additional medical costs due to survivors' living longer lives would total approximately $1.5 billion and thus represent the major costs.

Other effects of influenza vaccination on the Social Security program were not quantified in this analysis. Such effects would include:

Table 14.—Effect on Medicare Costs of Annual influenza Vaccination for Persons 65 Years and Older," 1971-72 Through 1977-78

Per vaccination	
costs	**Health benefits**
Cost of vaccination and and side effects	$ 6
Cost of treating Guillain-Barre Syndrome[b]	—[c]
Reduced influenza treatment costs	– 4
Medical costs in extended years of life	60
Total cost	$61[d]
	Days of healthy life gained 28
Cost/year of healthy life = $791	

For population	
costs	**Health benefits**
Cost of vaccination and side effects	$ 145,000,000
Cost of treating Guiliain-Barre Syndrome	296,000
Reduced influenza treatment costs	– 103,800,000
Medical costs in extended years of life	1,541,800,000
Total costs	$1,583,226,000
	Years of healthy life gained . .2,003,000
Cost/year of healthy life = $797	

[a] Those persons 65 years and older in 1971-72.
[b] Assumes medicare pays 44 percent of total medical costs (37).
[c] Cost is about $0.01.
[d] Column does not sum because of rounding.
[e] Based on vaccination rates reported for 1971-78 in the *U.S Immunization Survey* (124).

SOURCE: Office of Technology Assessment.

- increased payments to Social Security by vaccinees remaining in the work force longer as a result of reduced morbidity and mortality, and
- increased payments to beneficiaries resulting from people's living longer.

Appendixes

Appendix A.— Relationship of Serum Antibody Concentration to Incidence of Influenza Illnesses*

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June 5, 1980

The most instructive period for studying the relationship between immunity to influenza and levels of antibody produced by inactivated vaccines occurs on those rare occasions when vaccine produced from a major new antigenic subtype of influenza A is administered to individuals before their first infection with this new pandemic subtype, This opportunity has occurred only three times in over **40** years, i.e. in 1957 (H2N2 virus), in **1968 (H3N2** virus), and in 1978 (when H1N1 strains of influenza caused illnesses primarily among individuals born after 1957). Much useful information also may be obtained during interpandemic periods, but primed individuals respond better to vaccine than do unprimed subjects. The study of artificially induced infections of human volunteers may also yield useful information, but the virus challenge may not resemble that which occurs naturally, and thus interpretation of results is difficult.

The relationship between the concentration of influenza serum antibody and immunity to influenza infection or illness may be influenced by a number of variables. Serum antibody formed after a first infection with an antigenically new subtype of influenza A may be quantitatively and qualitatively different from antibody produced after several sequential infections with the same subtype of influenza A. The initial infection may produce a relatively low concentration of serum antibodies, but subsequent infections may boost antibody concentrations which may persist at measurable levels for a longer period of time. Repeated infections with familiar strains of influenza virus may stimulate some antibodies which are specific for the current infecting strain, and other antibodies which are more cross-reactive with earlier strains infecting the same individual. The method of measuring antibody in serum is also an important variable, since hemagglutination-inhibition (HI) and neutralization tests, and other tests such as single radial hemolysis of ELISA, may measure antibodies having somewhat different specific reactivities with influenza viral antigens. While both HI and neutralization tests primarily measure the biological function of hemagglutinin attachment to cell receptors, the single-radial hemolysis tests and enzyme immunoassay (EIA) measure antibodies against both hemagglutinin and neuraminidase, and *in* the **case** of EIA, common internal antigens as well. Although the HI test is the most universally accepted for measurement of serum antibodies in influenza, the actual dilution of serum which will cause complete inhibition of red blood cell (RBC) hemagglutination may vary somewhat depending on the avidity of the hemagglutinin-antibody interaction, as well as other variables such as the method used for removal of serum inhibitors and the type of RBC used.

When examining the relationship between serum antibody and immunity to influenza, it is important to specify whether antibody has been produced by parenteral administration of inactivated vaccine or by natural infection. While serum antibody induced by parenteral vaccination may reflect systemic immunity to virus infections of the lower respiratory tract (lung), resistance to the initiation of influenza virus infection at the mucosal surface of the upper respiratory tract may correlate better with the presence in secretations of virus-specific IgA, induced by replication of the virus at these sites during natural infection.

In 1957, one dose of 200 or 500 chick cell agglutination (CCA) units of inactivated A/Japan/305/57 vaccine was given to volunteers, and **2** to 4 weeks later an A/Japan/305/57-like live virus challenge (diluted nasal washings of infected boys) was given to both vaccinated and unvaccinated volunteers (1). of 33 unvaccinated individuals, 23 (78 percent) developed febrile influenza-like illness while 14 (44 percent) of those given vaccine developed similar illness, Attack rates varied inversely with HI antibody titers induced by vaccination, with rates of febrile illness of 60, 43, and 25 percent, respectively, in 10 individuals with titers <10, 14 individuals with titers of 10 or 20, and 8 individuals with titers ≥ 40. Conflicting data were obtained by Rose and Fukumi in 1957. Rose demonstrated that 200 or 750 CCA units

● NOTE: Reference citations for app. A refer to the **list** of references at the ***end*** of app A.

of monovalent A/Japan/305/57 vaccine provided some immunity to infection during an Asian influenza outbreak (60 to 78-percent efficacy), yet he was unable to demonstrate a serum HI response to the vaccine; a CF antibody rise did occur (2). Fukumi, on the other hand, reported that vaccines induced good HI antibody responses, and infections occurred rarely among individuals with HI titers of 32 or greater (although it is not entirely clear if he refers to antibody induced by vaccination or prior infection)(3).

In 1968, Dowdle, et al., demonstrated that 3,000 CCA, but not 300 CCA, units of inactivated influenza A/Hong Kong/68 vaccine conferred a protective effect against natural challenge with homologous virus (4). Although febrile influenza-like illness occurred among individuals with HI titers of **80** to **160,** illness severe enough to cause patients to remain in bed occurred in only approximately 11 percent of those with HI titers of 80 to 160, compared with an incidence of illness requiring bed rest of about 32 percent in those with titers ≤ 10. (Incidentally, when both HI and neuraminidase-inhibiting (NI) antibody were present at any titer, illness requiring bed rest was seen even less frequently.)

During an epidemic of A/Brazil /11/ 78(HlNl)-like virus infections among university students in Georgia during early 1979, Noble, et al., found that A/USSR/77 vaccine produced a protective effect. Two doses of inactivated vaccine containing 7 mcg of hemagglutinin were given to October and November 1978, and an epidemic occurred in January and February 1979. Among vaccinated individuals with HI antibody titers of ≤ 20 to the epidemic strain, the incidence of influenza-like illness (fever or feverishness and chills with respiratory symptoms and a significant rise of HI antibody to H1N1 virus) was **20** percent (19 of 97), whereas among individuals with titers ≥ 40 only 6 percent (4 of 72) had similar illnesses. The incidence of illness among placebo recipients, all of whom had HI titers ≤ 20, was 25 percent (45 of 179).

From the preceding review it is apparent that great variation is seen in different situations between the level of serum antibody and evidence of immunity. However, approximately a **60-** to 80-percent reduction in typical influenza-like illnesses is generally seen when serum HI antibody titers of 40 to 80 are achieved by vaccination during the first wave of a new major antigenic variant, when attack rates of a placebo group or individuals with titers of 20 or less after vaccination are used for comparison. Additional data have been generated by investigators who have examined serum antibody tiers and the resistance to an artificial challenge with intranasally administered live influenza virus. Hobson, et al., reviewed experience at the Common Cold Unit, Salisbury, England **(570** volunteers challenged with influenza "A2 viruses" and **462** volunteers challenged with influenza B viruses) and found that serological evidence of infection occurred rarely among individuals with prechallenge HI titers of 100 to 200 (5). At titers of 48, serological evidence of infection was reduced approximately 60 to 80 percent when compared with infection rates in those with prechallenge homologous HI serum antibody titers of 6 to 12.

During interpandemic periods, a similar correlation between serum HI antibody titers and protection has also been observed. Among vaccinated and unvaccinated individuals, the incidence of influenza-like illness was approximately 15 to 20 percent among those with titers ≤ 16, whereas attack rates were 3.5 percent or lower in those with titers of ≥ 32 (6). Likewise, Meiklejohn, et al., demonstrated a good correlation between serum HI antibody titer and the probability of clinical infection with A/FM/1/47-like viruses (7). The estimated incidence of infection among those with titers <8 was 18.3 percent, compared to a 1.6-percent infection rate among individuals with titers of 32; no influenza-like illnesses were reported among those with titers ≥ 64. Others have reported generally similar findings (8,9,10), although the method of expressing serum dilutions in early papers may result in titers higher than titers obtained with methods now in use, and thus a comparison of actual titers may be misleading (6).

It is clear from the review of existing data that no single titer of serum influenza HI antibody can be chosen to indicate any specific index of immunity to natural challenge. This is particularly true during the first appearance of a new major antigenic variant of influenza A, because the data available are limited, It is clear, however, that an increasing concentration of homologous serum HI antibody confers an increasing degree of protection against typical influenza illness. This appears to be true whether the antibody is induced by vaccination or by natural infection. Thus, HI antibody titers of **40** to 80 (or 32 to 64) have generally been found to provide a reduction in the incidence of typical influenza-like illness of 60 to 80 percent, when compared with the incidence of illness n those with tiers ≤ 20 or ≤ 16.

The question of what concentration of serum antibody is to be considered ideal following vaccination is, therefore, a matter of judgment, as stated by Salk 20 years ago (11):

> The incentive for achieving the highest levels that are practicably attainable is clear. In answer to the question as to how high the level should be, it might be said that the higher the better; the higher the level

attained, the greater the persistence at the more effective levels.

The limiting factors in attaining the highest level are clinical and economic. If one eliminates the economic considerations, the upper limit attainable, using a single dose of vaccine, is set by the frequency or severity of systemic reactions that accompany the use of concentrated virus preparations; in infants and young children the "severity" of the reaction is perhaps of greater consequence, and in the adult population the "frequency" of reactions is of first importance.

Appendix A References

1. J. A. Bell, T. G. Ward, A. Z. Kapikian, A. Shelokov, T. E. Rechelderfer, and R. J. Huebner, "Artifically Induced Asian Influenza in Vaccinated and Unvaccinated Volunteers, *J. Amer. Med. Assoc.* 165:1366-1373, 1975.
2. H. M. Rose, in "International Conference on Asian Influenza," Bethesda, Md., 2/17-19/60, *Amer. Rev. Resp. Dis.* 83(2):152-153, 1961.
3. H. Fukumi, in "International Conference on Asian Influenza," Bethesda, Md., 2/17-19/60, *Amer. Rev. Resp. Dis.* 83(2):156, *1961*.
4. W. R. Dowdle, S. R. Mostow, M. T. Coleman, H. S. Kaye, and S. C. Schoenbaum, "Inactivated Influenza Vaccines. 2. Laboratory Indices of Protection," *Postgrad. Med. J.* 49:159-163, 1973.
5. D. Hobson, R. L. Curry, A. S. Beare, and A. Ward-Gardner, "The Role of Serum Haemagglutination-Inhibiting Antibody in Protection Against Challenge Infection With Influenza A2 and B Viruses," *J. Hyg.* (Carob.) 70:767-777, 1972.
6. J. Salk and D. Salk, "Control of Influenza and Poliomyelitis With Killed Virus Vaccines," *Science* 195:837-847, 1977.
7. G. Meiklejohn, C. H. Kempe, W. G. Thalman, and E. H. Lennette, "Evaluation of Monovalent Influenza Vaccines. II. Observations During an Influenza A-Prime Epidemic, *Amer. J. Hyg.* 55:12-21, *1952*.
8. M. D. Eaton and G. Meiklejohn, "Vaccination Against Influenza. A Study in California During the Epidemic of 1943-44, *Amer. J. Hyg.* 42:28-44, *1945*.
9. E. R. Rickard, F. L. Horsfall, Jr., G. K. Hirst, and E. H. Lennette, "The Correlation Between Neutralizing Antibodies in Serum Against Influenza Viruses and Susceptibility to Influenza in Man, *Publ. Hlth Rep.* 56:1819-1834, 1941.
10. W. Henle, G. Henle, and J. Stokes, Jr., "Demonstration of the Efficacy of Vaccination Against Influenza Type A by Experimental Infection of Human Beings," *J. Immunol.* 46:163-175, *1946*.
11. J. Salk, in "International Conference on Asian Influenza," Bethesda, Md., 2/17-19/60, Amer. *Rev. Resp. Dis.* 83(2):153-156, 1961.

Appendix B.—Safety and Efficacy of Inactivated Influenza Vaccine

Description of Inactivated Influenza Virus Vaccine

Influenza vaccines can be categorized in two basic groups—live, which contain small amounts of live, attenuated (weakened) influenza viruses, and *inactivated,* which contain either whole influenza viruses or subunits of viruses. Only inactivated influenza viruses are licensed for general use in the United States; therefore, this discussion of vaccine safety and efficacy pertains exclusively to inactivated vaccines.

Inactivated influenza virus vaccines have been manufactured and used in the United States since the 1940's (64). Early development of influenza vaccines was spearheaded by the Armed Forces Epidemiological Board and its Commission on Influenza (12). The early vaccines have undergone several improvements.

Influenza virus vaccine production procedures have been described elsewhere (33,71).

Today, there are two types of inactivated influenza virus vaccine commercially available in the United States, whole virus and subunit. The antigenicity of whole virus vaccine has been demonstrated more extensively than that of subunit vaccines (91). On the basis of evidence generated from clinical trials conducted in 1976, however, subunit vaccines are now considered by some researchers to be equally antigenic with whole virus vaccines in adults with prior influenza virus antibody production and less antigenic in either children or adults with no prior influenza virus antibody production (51). In some studies, administration of a booster injection of subunit vaccine yielded antibody levels comparable to those produced by whole virus vaccines (21,44). In other studies, however, a second injection yielded no "booster" effect among those responding poorly to an initial injection (25). Subunit influenza vaccines tend to cause fewer adverse reactions than whole virus vaccines (30,51,65).

Vaccine Efficacy

There are two major types of investigations used to evaluate the efficacy of influenza vaccines. First, clinical trials—in which vaccinated subjects are exposed, either by design or by chance, to influenza organisms—can be used to determine a vaccine's protective efficacy. Second, antibody response studies—in which prevaccination and postvaccination serum antibody levels are measured in vaccinated subjects—are used to determine the capacity of a vaccine to induce antibody information. It can be difficult to conduct clinical trials involving influenza vaccine, because the occurrence of influenza epidemics caused by specific strains of viruses is often difficult to predict, and because intentional exposure of subjects raises ethical concerns. Antibody response studies by themselves are not usually relied on to assess a vaccine's efficacy; rather, they provide data from which efficacy or protection be inferred. Often, data from antibody studies are obtained from vaccinated subjects not subsequently exposed to influenza virus; therefore, achievement of a certain postvaccination serum antibody level, for example, a fourfold increase over prevaccination level, is sometimes used to help assess a vaccine's clinical efficacy. Antibody responses can also be described in terms of the percentage of a vaccinated population with postvaccination antibody levels $\geq 1{:}40$. Some clinical experiences document a correlation between a particular level of serum antibody rise and clinical efficacy. A few of these experiences are discussed briefly below. Others have been described previously (23,44,95).

Numerous factors affect a vaccinated person's antibody response to an inactivated influenza vaccine, and thus affect a vaccine's effectiveness. First, and obviously, the vaccine's potency (amount of antigen), purity (freedom from contaminating material), and other measures of quality are important. Second, the degree to which the antigenic components of the virus(es) in a vaccine match the antigenic components of the virus(es) circulating in the environment greatly affects the effectiveness of the vaccine (see app. C). Third, a vaccinated person's antibody response to a given vaccination is influenced by his or her prior exposures to influenza viruses either through vaccination or acquisition of disease (natural immunity) (21,29,36,49). Fourth, the duration of immunity conferred by influenza vaccination tends to be short (i.e., usually 1 year, possibly 3 years, and perhaps longer); further, the duration of immunity varies substantially with age and other host factors.

Usually, inactivated influenza vaccines contain either whole cells or antigenic subunits (neuraminidase and hemagglutinin) from two or more strains of influenza viruses. Ever since 1943, in the United States, vaccines have been marketed with at least one type of influenza A virus and one type of influenza B virus. In recent years, trivalent vaccines, containing

two types of influenza A viruses and one type of influenza B virus, have been marketed. Much more data are available concerning the safety and efficacy of influenza A virus vaccines than influenza B virus vaccines.

The type(s) of influenza virus(es) (e.g., type A or B) that circulate in the United States can easily change, sometimes from year to year (27), Furthermore, even in subtypes within a particular type of virus (e. g., H3N2 or H1N1 type A influenza viruses), the antigenic components can change in a fashion that alters the virus's susceptibility to a person's antibodies. Because the manufacturing and distribution processes for influenza vaccine take from 6 to 9 months, the type(s) of influenza virus selected to be represented in a vaccine for a given year may not be in circulation at the time the vaccine is actually used. As a result, in a given year, the vaccine being administered may not stimulate antibodies to—and therefore not help protect against—the type(s) of influenza virus(es) producing disease. Evidence of the protective efficacy of a current vaccine formulation is therefore often difficult or sometimes impossible to obtain before a vaccine is released by the Bureau of Biologics for general use. There can be, however, some degree of overlapping protection among different types of influenza viruses (70,118).

Clinical Studies

The clinical efficacy of inactivated influenza vaccines has been debated virtually since their development in the 1940's. Clinical studies have yielded clinical efficacy rates ranging from O to 90 percent (104). (Note: The clinical efficacy rate refers to the precentage decline in the incidence of clinical influenza among a group of vaccinated subjects as compared to the incidence of clinical influenza among a group of unvaccinated subjects.)

The following studies are used to illustrate clinical efficacy rates for inactivated influenza A virus vaccines:

1. Ferry, et al., in Australia conducted three clinical trials of a trivalent subunit influenza vaccine containing 250 international units (IU) of A/Victoria/3/75 virus, 250 IU of A/Scotland/840/74 virus, and 300 IU of B/Hong Kong/8/73 virus (36). The first trial involved 698 vaccinees and 2,034 unvaccinated controls; all subjects were members of a hospital staff. Although the difference in the incidence of respiratory tract infection (RTI) between the two groups was not significant, the incidence of influenza (diagnosed on the basis of clinical and serological determinations) was 81 percent lower among vaccinees.

   In the second trial, the same vaccine was administered to 480 laboratory workers; another 583 laboratory workers in the same institution served as controls. There were no statistically significant differences in either incidence of RTI (47 cases among vaccinees v. 51 cases among controls) or isolation of influenza viruses (24 isolates among vaccinees v. 24 controls) between the two groups. However, the vaccinated group lost only 493 days of work compared to 837 days for the unvaccinated. The differences in work loss between the two groups might be attributable to a less severe type of influenza among the vaccinated.

   In the third trial, involving patients in a geriatric home, 154 vaccinated volunteers were compared with 63 unvaccinated controls. There was no statistically significant difference in the incidence of influenza between the two groups, but the severity of influenza cases was deemed by the investigators to be less in the vaccinated group.

   The authors attributed the difference in vaccine efficacy in these three trials to possibly differences in prevaccination antibody levels; those with lower prevaccination antibody levels and those being vaccinated for the first time experienced less postvaccination influenza.

2. Hoskins, et al., in England studied the protective efficacy of inactivated influenza vaccines among 375 school boys who experienced three epidemics: 1972 (A/England/42/72), 1974 (A/Port Chalmers), and 1976 (A/Victoria) (49). During the three epidemics collectively, the cumulative case-rates were approximately the same (i. e., 40 to 50 percent) among all boys, regardless of their vaccination status. Those boys who were vaccinated before each epidemic experienced influenza at the same rate as those who received no vaccine at all when evaluated retrospectively over the three epidemics. Boys vaccinated for the first time were partially protected against the strain of influenza causing the next outbreak.

   In 1976, the year A/Port Chalmers virus caused the influenza outbreak, the attack rate among boys who received no relevant vaccination was similar to that among boys who received A/Port Chalmers vaccine that year and who in adddition had been vaccinated against other strains in earlier years. Boys vaccinated with A/Port Chalmers that year only (with no prior influenza history) experienced a substantially lower attack rate. Also in 1976, immunity derived from natural infection (A/Port Chalmers/1974 or A/England/1972) appeared

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to provide better protection than did any vaccination.

Hoskins concluded that "when a new antigen subtype, e.g., A/Port Chalmers, first appears and a population is completely susceptible, a vaccine will have its maximum effect and may be expected to protect 50 percent or more of those vaccinated . . . However, this benefit is short-lived. As a strain undergoes antigenic drift, subjects previously protected from natural infection by vaccination will be at risk and cannot be effectively protected by further vaccination with either the same or a later strain." On the basis of his findings, Hoskins questioned the effectiveness and wisdom of annual influenza vaccination within a population.

3. Sparks, in another English school, reported findings similar to those of Hoskins' (117). He claimed that influenza vaccination only postpones an attack and that transient protection provided by vaccination can prevent the development of the long-term immunity resulting from an attack of influenza.
4. During the 1977-78 influenza season, Couch and coworkers in Houston, Tex., compared the clinical protective efficacy of two successive annual influenza vaccinations among 129 elderly subjects (51 to 78 years old; median, 65 years) (21). In 1976, all subjects received bivalent influenza vaccine containing A/Victoria/75 (H3N2) and A/New Jersey/76 (Hsw1N1) antigens. In October 1977, 74 of those subjects received another bivalent vaccine containing A/Victoria/75 and B/Hong Kong/72 antigens. Vaccinees voluntarily submitted information about their history of respiratory illnesses, which were classified according to severity. Vaccinated subjects' sera samples were also analyzed for antibody content. Among the 74 subjects who received the second vaccination, there was no statistically significant reduction on the incidence of mild illness, but there was a 60-percent reduction in severe illness.
5. At the Surgeon General's Meeting on Influenza Immunization held on January 22, 1980, several vaccine efficacy studies were reviewed (104). In one of these studies, 169 college students in Atlanta, Ga., were given 2 doses of a vaccine containing an A/U.S.S.R.-like (H1N1) antigen and 181 students were given a placebo vaccine. An epidemic of A/Brazil/78-like (H1N1) influenza followed in Atlanta **7** to 10 weeks after the students were vaccinated. The use of this vaccine in this study reduced the incidence rate of laboratory-confirmed influenza illness by nearly **50** percent.

Reviews of influenza vaccine safety and efficacy are contained in the written summaries of conferences on influenza sponsored by the Department of Health and Human Services between 1977 and 1980 (97-104).

Vaccine Efficacy During Years of Inexact Antigenic Match Between Vaccine Virus(es) and Circulating Virus(es)

As described in appendix A, influenza viruses sometimes change their chemical makeup from season to season and even within a single season. Small changes—i.e., those within a given type of virus such as H3N2 influenza A virus—are collectively referred to as "antigenic drift." Larger changes—such as a replacement of an H3N2 influenza A virus by an H1N1 influenza A virus—are called "antigenic shifts."

During the 8-year period from 1970-71 through 1977-78, there were four episodes of antigenic drift in the predominate H3N2 influenza A virus circulating in the United States. These drifts occurred in **1972-73** (Hong Kong to England), **1973-74** (England to Port Chalmers), 1975-76 (Port Chalmers to Victoria), and 1977-78 (Victoria to Texas).

The degree to which antigenic drift affects the effectiveness of a given H3N2 influenza A virus vaccine creates yearly public debates (97-104). Because' antigenic drift can occur within the 6 to 9 months between vaccine formulation and vaccine distribution, in some years the influenza A virus contained in the distributed vaccine somewhat differed antigenically from the circulating viruses causing disease. In three clinical trials (70,85, 118) and one retrospective epidemiologic investigation (8), researchers have attempted to assess the clinical effectiveness of vaccines containing an H3N2 virus that differed from the predominant circulating H3N2 virus causing disease in a distinct geographical location.

Clinical Evidence.—In 1977, Meiklejohn and coworkers assessed the efficacy of a trivalent inactivated influenza vaccine (400 chick cell agglutinating (CCA) units of A/Victoria/3/75, 400 CCA units of A/New Jersey/76 and 500 CCA units of B/Hong Kong/72 viruses) against a variant of A/Victoria virus (A/Texas/1/77-like virus) among military personnel in Colorado **(70).** In November 1976, approximately 4,200 military students at Lowry Air Force Base (AFB) were given this vaccine; subsequently, this population was continually altered by the arrival of approximately 200 new students and the departure

of a similar number of students each week. The newly arrived students intermingled extensively with the remaining ones. An influenza outbreak (caused by an A/Texas/l/77-like virus) occurred at Lowry AFB in February 1977, causing 87 cases of influenza. During the first and second weeks of the outbreak, the attack rates among the unvaccinated students were 20.0 and 23.6 cases per 1,000 persons per week, and the attack rate among the vaccinated never exceeded 2.3 cases per 1,000 persons per week. For the remaining 3 weeks of the outbreak, attack rates were 1.4, 4.7, and 1.2 cases per 1,000 among the unvaccinated and 2.2, 2.3, and 1.2 among the vaccinated. The investigators, using three different methods of calculation, estimated the clinical efficacy rate of the vaccine to range from 69.0 to 83.1 percent,

During the winter of 1974-75, CDC conducted among university students an open field trial of vaccines containing either inactivated or live influenza A/England/42/72 (H3N2) virus (85). Influenza A/Port Chalmers/1/73 (H3N2) which differed antigenically from A/England/42/72, however, was the predominant H3N2 influenza virus causing disease among volunteer participants in this study. The influenza attack rate among placebo recipients (unvaccinated control group) was **69** cases per 1,000 persons, whereas the attack rate among inactivated vaccine recipients was 25 cases per 1,000 persons, and **36** cases per 1,000 persons among live vaccine recipients. Using the following formula, OTA calculated the clinical effectiveness rate of the inactivated influenza vaccine during this trial to be **64** percent (l):

$$\text{Vaccine effectiveness} = \frac{(\text{attack rate in unvaccinated group} - \text{attack rate in vaccinated group}) \times 100}{\text{attack rate in unvaccinated group}}\%$$

Retrospective Epidemiologic Investigation.—In 1972, Stiver and associates studied the clinical effectiveness of a vaccine containing Hong Kong influenza virus antigen (A2Aichi/2/68) during an outbreak of A2England/72 influenza among air force recruits in Colorado **(118).** Among 979 vaccinees, the influenza attack rate was 18.4 cases per 1,000 persons. Among 2,955 unvaccinated subjects, the influenza attack rate was 46.0 cases per 1,000 persons. The vaccine's clinical effectiveness rate was calculated to be 60 percent ($p < 0.01$ by chi-square test).

Barker and Mullooly attempted to assess the impact of the A/Hong Kong/68 (H3N2) influenza virus vaccine on the rates of pneumonia-influenza associated hospitalization and mortality among a defined population **65** years and older at Kaiser-Permanente Hospital in Portland, Oreg., during the 1972-73 epidemic caused by A/England/42/72 (H3N2) influenza virus (8). These researchers retrospectively reviewed the medical records of a 5-percent sample of Kaiser-Permanente patients **65** years and older. Prior to this epidemic, **20** to **30** percent of the chronically ill elderly Kaiser-Permanente patient population was vaccinated; vaccinees and nonvaccinees were comparable in age and distribution of chronic disease. Among those vaccinated, there was a **72** percent reduction in hospitalizations associated with pneumonia or influenza during the 1972-73 influenza epidemic. Further, no deaths were recorded among the vaccinated, while death rates among the unvaccinated were 6 out of 10,000 non-high-risk individuals and 35 out of 10,000 high-risk individuals.

These researchers conducted a similar analysis of the impact of the A/Taiwan/l/64 (H2N2) virus (8). There were no statistically significant differences in either hospitalization or mortality rates between the vaccinated and unvaccinated groups. The authors attributed the lack of vaccine impact during the 1968-69 epidemic to the major shift from an H2N2 to an H3N2 antigenic configuration in the circulating virus.

On the basis of the findings of these three clinical trials and one epidemiologic investigation, OTA assumed that the clinical effectiveness rate of the inactivated influenza virus vaccines used in three years involving antigenic drift of H3N2 virus (i. e., 1972-73, 1974-75, and **1977-78)** was at least 60 percent.

Antibody Response to Influenza Vaccine Among Specialized Populations

The following studies illustrate variations in antibody response to influenza vaccine among selected subpopulations who are likely to receive influenza vaccine. Several studies of influenza vaccines in special populations were published previously in the December **1977** (supplement) issue of the Journal of *Infectious Diseases.*

Neoplastic Diseases.—Shild and coworkers demonstrated an adequate antibody response to a trivalent influenza vaccine (A/New Jersey 1976 (Hsw1N1), B/Hong Kong/5/72, and A/Victoria/3/75 (H3N2)) among 36 patients with solid tumors and a less-than-favorable response in **46** patients with Iymphomas (110).

Ganz, et al., demonstrated a fourfold rise in antibody titers to a bivalent influenza vaccine (A/New Jersey /76(HswlNl) and A/Victoria/ 75(H3N2)) in 41 to 47 percent of 17 patients with various types of cancer and on various types of chemotherapy (40). Ortbals, et al., found that 71 percent of 42 cancer patients (21 with lymphoreticular neoplasms and 21 with solid tumors) demonstrated a fourfold or greater increase in serum antibody titers to A/New

Jersey/1976 influenza vaccine as compared to 91 percent of control subjects (92). Also, immunization at the time of chemotherapy administration lowered the incidence of seroconversion from 93 percent to 5O percent.

Silver and Weinerman administered a bivalent influenza vaccine (A/Port Chalmers/1/73 (H3N2) and B/Hong Kong/5/72) to 44 patients with cancer and **27** healthy controls (115). Against the A antigen, 16 of the cancer patients and 25 of the controls yielded a fourfold or greater increase in antibody titer. Against the B antigen, 14 of the cancer patients and 20 of the controls yielded a fourfold increase in serum antibodies. Nineteen of the cancer patients had lymphomas, and only four of these patients demonstrated a fourfold increase in antibody level.

Neoplasms in Children.—In **1978,** Douglas and associates gave one or more of the following antigens to 54 children with malignancies: A/U.S.S.R./77 (H1N1), A/Texas/77(H3N2), and B/Hong Kong/72 (25). By the end of the study, the percent of subjects who developed a serum influenza antibody titer ≥ 40 (indicative of a good antibody response) was as follows:

- 49 percent of those given A/U.S.S.R./77 vaccine,
- 59 percent of those given A/Texas/77 vaccine, and
- 24 percent of those given B/Hong Kong/72 vaccine

Systemic Lupus Erythematosus.—Ristow, et al., found a fourfold or greater antibody response to A/New Jersey/76 (Hsw1N1) vaccine in 14 of 29 patients with systemic lupus erythematosus, compared to 18 out of 29 control subjects (109).

Herron, et al., studied the safety and efficacy of an influenza vaccine (A/New Jersey/76 and A/Victoria/75) among 62 patients with rheumatic diseases, including systemic erythematosus, rheumatoid arthritis, and degenerative joint disease and among 32 healthy control subjects (46). Among the patients with rheumatic diseases, 62 to 87 percent seroconverted to A/New Jersey/76 and 62 percent seroconverted to A/Victoria/75. Thirteen of the rheumatic disease patients experienced a flare up of their disease.

Tecson and Bornstein have cautioned against repeated yearly influenza vaccination because of potential complications (121).

Pregnancy .—Sumaya and Gibbs administered A/New Jersey/76 influenza vaccine to 56 pregnant women and found no significant difference in the antibody responses between pregnant and nonpregnant adults (120). Further, no significant immediate maternal reactions or increased fetal complications were observed.

Murray and associates studied the antibody responses to A/New Jersey/8/76 (Hsw1N1), A/Japan/305 /57(H2N2), and A/Hong Kong/8/68 (H3N2) influenza vaccine in 59 pregnant and 27 nonpregnant women (77). There were no significant differences in antibody responses between pregnant and nonpregnant subjects.

Geriatric Population.—Serie and coworkers administered a trivalent influenza vaccine (A/Pasteur P 24.R (H3N2), A/Port Chalmers/73 (H3N2) and B/Hong Kong/73)) to 523 geriatric hospitalized patients with an average age of 83 years (113), Serologic and virologic investigations were performed in 110 patients. The incidence of clinical influenza caused by type A/Victoria was roughly twice as high among the unvaccinated as that among the vaccinated. The mortality rate among all vaccinees was 0.19 percent compared to 3.90 percent of those unvaccinated. When 80 percent of patients in a particular hospital section was immunized, the incidence of influenza was reduced by as much as three times.

Howells and associates have also assessed the value of this vaccine among the elderly (so).

Multiple Sclerosis.—Banford, et al., administered a bivalent influenza vaccine (A/New Jersey and A/Victoria) to 65 patients with multiple sclerosis and compared the incidence of adverse neurological conditions among vaccinees with that among 62 unvaccinated control multiple sclerosis patients (7). Sixty-one of the vaccinated patients tolerated the vaccine well, and four developed new necrologic complications. Among the 62 unvaccinated control patients, four also developed new necrologic symptoms. The authors concluded that influenza vaccine posed no excessive risk of necrologic symptoms among multiple sclerosis patients. Vaccine efficacy was not evaluated in this study.

Chronic Renal Failure, Renal Dialysis, and Transplant Populations.—McMillen and associates administered a bivalent influenza vaccine (A/New Jersey/76 and A/Victoria/75 by Wyeth Laboratories) to 23 chronic dialysis patients (age 30 to 72 years), 18 renal transplant patients (age 18 to 64 years), and 10 pediatric patients (6 on chronic dialysis and 4 with renal transplants) (68). Seroconversion was observed in 67 percent of all 29 dialysis patients and in 50 percent of all 22 renal transplant patients. Among the transplant group, patients 18 to 25 years old had a much lower seroconversion response (12.5 percent) than either those under 18 (75 percent) or over 25 (90 percent).

Osanloo and coworkers administered a bivalent

influenza vaccine (A/Victoria/75 and A/New Jersey/76) to 10 azotemic, undialyzed males, 19 hemodialyzed males, and **17** control subjects (93). Fifty-four percent of the control subjects, 53 percent of the hemodialysis patients, and 60 percent of the azotemic patients developed a fourfold greater increase in antibody levels to A/Victoria antigen. Against the A/New Jersey antigen, 92 percent of the controls, 89 percent of the dialyzed patients, and 90 percent of the azotemic patients developed a fourfold or greater rise in serum antibody levels. The authors noted that severe azotemia and/or immunosuppressive or corticosteroid therapy may depress certain antibody responses.

Vaccine Safety

The safety of influenza vaccine, like that of all vaccines, is evaluated on the basis of the incidence of adverse reactions to the vaccine that: 1) investigators in clinical trials report, or 2) practicing health professionals voluntarily report to CDC, FDA, or the vaccine manufacturer **(86).** Adverse reactions to vaccines can be classified as follows:

- Local Reactions: These reactions include pain, redness, and swelling at the vaccine injection site. Such reactions occur commonly, do not involve other areas of the body, and are usually minor and self-limiting.
- *Systemic Reactions:* These reactions include perturbations in one or more organ systems and can affect one or more areas of the body. Such reactions range from fevers to allergic reactions; their severity can be mild and short-lived, severe and long-lasting, or sometimes even fatal.

A recent study commissioned by the Department of Health and Human Services (DHHS) describes in detail the clinical and economic profiles of several selected types of adverse reactions to commonly used vaccines (4).

The safety of influenza vaccines became quite topical during the National Influenza Immunization Program of 1976, the so-called swine flu program. Unexpectedly, approximately 1 out of every 100,000 persons who received swine flu vaccine (A/New Jersey/76 Hsw1N1] virus) developed Guillain-Barre Syndrome (GBS), a neurological disorder that results in varying degrees of disability, ranging from temporary paralysis of extremities (arms and legs) to death (112). The relationship between influenza vaccines and GBS has received much publicity and the safety of influenza vaccines has been studied extensively during the past 4 years. The following descriptions of each type of adverse reaction associated with influenza vaccine are based largely on such studies.

During the 1976-77 influenza immunization program, CDC coordinated a nationwide surveillance program to detect adverse reactions following influenza vaccination. CDC received a total of 4,733 voluntarily submitted reports of such reations, including reports of 233 deaths, for the estimated 48 million persons vaccinated against influenza during the season (107). This surveillance program was the early warning system that led to the discovery of an association between GBS and influenza vaccination. Limitations to data collected in this system, however, are noted by CDC investigators (107):

> Reports of illness that depend on voluntary reporting during a time of varying publicity are inappropriate for retrospectively developing rates of illness in a target population. . . . The passively reported data gathered through this surveillance system are of such a nature that they cannot be compared with data gathered from monitored defined populations.

According to a 1979 survey conducted by Opinion Research Corp. for the Bureau of Health Education, CDC, approximately 13 percent of all children and 5 percent of all adults receiving influenza vaccine in 1978 had an adverse reaction that resulted in a visit to a doctor, hospital, or clinic (123).

Local Reactions

Noble and associates investigated among University of Georgia students the safety and efficacy of two trivalent inactivated influenza virus vaccines (both the vaccines contained 7 micrograms of hemagglutinin from A/Texas/l/77 (H3N2) and from A/Brazil/11/78 (H1N1) viruses. One vaccine (Vaccine No. 1) also contained 7 micrograms of B/Hong Kong/8/73 while the other (Vaccine No. 2) contained 50 micrograms of B/Hong Kong/8/73 (104). The vaccine with 7 micrograms of each virus (Vaccine No. 1) was administered to 394 volunteers. The vaccine with 50 micrograms of B/Hong Kong/8/73 virus (Vaccine No. 2) was given to another 386 subjects. A placebo vaccine was given to another 396 volunteers. About 20 percent of those subjects receiving Vaccine No. 1 and 36 percent of those receiving Vaccine No. 2 developed sore arms at the vaccination site.

Eastwood and associates studied the reactions of 49 children (aged 4 to 11 years) to a surface-antigen-absorbed influenza virus vaccine containing 8.4 micrograms HA (hemagglutinin) of A/Victoria/3/75 (H3N2) and 12.7 micrograms HA of B/Hong Kong/**8/73** per dose (30). Eighteen (37 percent) of the vaccinees experienced mild local reactions (slight soreness and aching at the inoculation site) during the **3**

days following immunization. Two children (4 percent) also had local swelling, two had redness, and one developed a bruise.

Systemic Reactions

Systemic reactions to influenza vaccine can be classified as follows (1):

- *minor* (fever, malaise, myalgia [muscle aches]) —all such reactions usually subside within **48** hours);
- *immediate—presumably* allergic—responses (breathing difficulties, certain skin eruptions, rarely severe allergic reactions [anaphylaxis]);
- *Guillain-Barre Syndrome (GBS)* **(a** paralytic disorder that usually starts in a person's extremities and moves up the body; approximately 50 percent of the cases recover completely within 1 year; 10 percent result in moderate to severe permanent disability; and 5 percent die); and
- *miscellaneous.*

1. *Minor:* In the study cited above, Noble and associates found a 2-percent incidence of fever (>100° F), a 5-percent incidence of malaise and myalgia, and a 6-percent incidence of headache among those subjects receiving Vaccine No. 2. Vomiting occurred in 6 recipients of Vaccine No. 2 (104).

Dr. William S. Jordan from the National Institute of Allergy and Infectious Diseases (NIAID) prepared an analysis of clinical trials involving the administration of inactivated influenza vaccine containing the A/U.S.S.R./77 (H1N1) antigen to approximately 2,000 subjects (100). Among nearly 1,000 subjects 13 years of age or older given two doses of either split or whole virus vaccine, only 18 developed fever (> 100° F). Twelve (36 percent) out of 33 subjects under 13 years old who received a placebo vaccine, however, also developed fevers.

In Eastwood's study cited above, one diabetic child experienced raised levels of urinary sugar and ketones which subsided in 2 days. No fevers were reported (30).

Dolin, et al., administered inactivated influenza A/New Jersey/76 virus vaccine in doses of 200, 400 or 800 CCA units to 199 adult health volunteers (23). All fevers subsided within 48 hours. Malaise—usually gone in 48 hours—occurred in **50** to **60** percent of vaccinees receiving 400 to 800 CCA units. Headache persisted beyond 48 hours in **9** to 19 percent of vaccinees.

Parkman, et al., summarized adverse reactions data from clinical trials involving 3,900 adults who in 1976 received various doses of A/New Jersey/76, A/Victoria/75, and B/Hong Kong/72 influenza virus vaccines (95). At doses below 800 CCA units, mild fever (<100° F) occurred in 0.6 to 12.8 percent of vaccinees. About 3.7 percent of recipients of a vaccine containing 800 CCA units developed fevers of 102° F.

2. *Immediate Reactions:* According to Dr. Kenneth McIntosh, University of Colorado, the incidence rate of severe allergic reactions (anaphylaxis) to influenza vaccine is 1 case per 4 million vaccinees (100).

Gross, et al., reported a case of meningoencephalitic syndrome following influenza vaccination in a 60-year-old woman allergic to chicken meat and eggs (45).

Horowitz reported a case of urticaria occurring in an n-year-old girl with asthma (48).

In the studies summarized by Parkman, et al., 2 of the 3,900 vaccinees experienced allergic reactions and both survived with no sequelae (95).

3. *Guillain-Barre_ Syndrome: (See* app. D.)

4. *Miscellaneous:* Perry and associates reported a case of reversible blindness from optic neuritis associated with influenza vaccination (96).

Appendix C.—Summary of Medical Literature Review of Effectiveness of Inactivated Influenza Virus Vaccines*

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For purposes of analysis, vaccines were characterized by populations used for testing, type of vaccine, dose, number of doses, whether the vaccine was proven to be immunogenic, the interval between vaccination and challenge, whether the naturally *occurring* challenge was with homologous or heterologous virus, the clinical attack rate of illness in the population, and the calculated efficacy.

Seventy-seven trials reporting effectiveness against naturally occurring influenza were identified, 60 for type A and 17 for type B influenza. Three trials were rejected; in two of these, no protection was seen but the attack rate was low and influenza virus was not shown to be a cause of illness, and in one, protection was 23 percent but vaccine was given during the outbreak. Two of these were type A trials and one was a type B trial. Two type A and four type B trials were with adjuvenated vaccine, a type of vaccine never distributed for general use in this country. These were also excluded from this analysis.

The range of reported effectiveness for each virus type was O to 96 percent. The effectiveness for aqueous inactivated vaccines varied according to virus type and relationship of challenge virus to vaccine virus. A designation of homologous challenge indicates that vaccine virus and epidemic virus were identical, whereas heterologous indicates the natural challenge was with a virus that exhibited minor (drift) or major (shift) antigenic differences from vaccine virus. The majority of trials reported effectiveness greater than 60 percent for homologous virus challenge, but protection against heterologous virus was more variable. Only six trials in the elderly were reported and these were for type A. No trials involving infants and small children were identified.

Effectiveness was also summarized by population group and vaccine dose among those experiencing challenge with homologous virus. Greater protection was reported for studies involving military personnel than civilian, and this was most notable for type B vaccines. This may be partly explained by the fact that early trials involved the military primarily and higher doses of vaccine were used than in later trials. Two of the civilian trials with type B vaccine were in remote populations (South Pacific natives and Alaskan Eskimos) who experienced very high attack rates of illness; the vaccines failed to exhibit any protective effect. No studies in remote populations were identified for type A virus.

Only eight trials used two doses of vaccine, although three others involved persons who had received either one or two doses. No difference in protection occurring in these trials compared to those using one dose was noted. Immunogenicity of the vaccine was proven in the majority of trials. In one trial, the vaccine was proven not to be immunogenic, and this resulted in 13-percent protection of an elderly population against a heterologous virus. Clinical attack rates of illness in the population appeared unrelated to degree of effectiveness. Only four reports involved very high attack rates (70 to 90 percent), the two noted above for type B with no protection and two with type A in the military with reported effectiveness of 57 and 77 percent. Protection against antigenically novel viruses (shift) with homologous vaccine virus was generally low in 1947 and 1968 but good in 1957.

Protection 14 to 16 months after vaccination was O, 35, 80, and 85 percent in four studies and 60 percent after 3 years in one study. All other studies involved challenge in 1 to 9 months after vaccination.

Thus, factors evaluated that might relate to degree of effectiveness of vaccine were remoteness of population studied, attack rates of illness and age and health status of given populations, dose of vaccine (particularly for type B), interval between vaccination and challenge, and antigenic novelty of the virus. Any one or more of these factors may be more important for one type of vaccine than for another, but the relative significance of each could not be discerned. Clearly, the most significant factor identified in this review that influences degree of effectiveness is the antigenic relationship between the vaccine and challenge (epidemic) virus.

● NOTE This report was presented at a Workshop on Influenza B Viruses and Reye's Syndrome, National Institute of Allergy and Infectious Diseases, **National Institutes of Health, Bethesda,** Md., July 30-31, 1979. It is based on a search of the English language literature, **Eighty-five percent of possible references identified were obtained. Sources** used were as follows: C G Loosli, International ***Bibliography of Influenza,*** 1930-1959; Medlars Service **of the National Library Medicine;** and *Cumulative Index Medicus.* The author's bibliography appears a t the end of this appendix.

Conclusion: Review of the medical literature on effectiveness of aqueous inactivated influenza virus vaccines provided support for the belief that these vaccines are generally effective for prevention of clinical influenza, particularly if the epidemic virus is antigenically similar to the vaccine virus and if vaccine is given in the immediate few months preceding exposure. The commonly quoted figure of 70-percent protection against illness in this circumstance seems reasonable. Deficiencies in present knowledge exist regarding effectiveness of aqueous vaccines in elderly and chronically ill persons, on duration of effectiveness, on the mechanism of protection, and on type B vaccines in general.

Appendix C Bibliography*

Bashe, W. J., Jr., Stegmiller, H., Leonida, D., and Greenwald, P., "Failure of Polyvalent Vaccine To Provide Clinical Protection Against Asian Influenza," *N. Eng. J. Med.* 270:870-874, *1964.*

Blake, F. G., "An Evaluation of Vaccination Against Epidemic Influenza in Man," Bull. N, Y. *Acad.* Med. 24:308-328, 1948.

Briscoe, J. H. D., "The Protective Effect of Influenza Vaccine in a Mixed Influenza A and B Epidemic in a Boys' Boarding School," *J. Royal Coll. Gen. Prac.* 27:28-31, 1977.

Brown, P., Felta, E. T., List-Young, B., Ritter, D. G., and Noble, G. R., "An Influenza B Epidemic Within a Remote Alaska Community: Serologic, Epidemiologic, and Clinical Observations," *). A.M.A.* 214:507-512, *1970.*

D'Allessio, D. J., Cox, P. M., and Dick, E. C., "Failure of Inactivated Influenza Vaccine To Protect an Aged Population," *J. A.M.A.* 210:485-489, *1969.*

Davenport, F. M., Hennessy, A. V., Houser, H. B., and Cryns, W. F., "An Evaluation of an Adjuvant Influenza Vaccine Tested Against Influenza B in 1954-1955," *Am, J. Hyg.* 64:304-313, 1956.

Fey, H. M., Cooney, M. K., and McMahan, R., "A/Hong Kong Influenza Immunity Three Years After Immunization," */. A.M.A.* 226:758-761, *1973.*

Fey, H. M., Cooney, M. K., McMahon, R., Bor, E., and Grayston, J. T., "Single-Dose Monovalent A2/Hong Kong Influenza Vaccine," *J. A.M.A.* 217:1067-1071, *1971.*

Francis, T., Jr., Salk, J. E., and Brace, W. M., "The Protective Effect of Vaccination Against Epidemic Influenza B," *J. A.M.A.* 131:146-156, *1946.*

Gundelfinger, B. F., Stille, W. T., and Bell, J. A., "Effectiveness of Influenza Vaccines During an Epidemic of Asian Influenza," N. *Eng. J. Med.* 259:1005-1009, *1958.*

Hammond, M. L. Ferris, A. A., Faine, S. and McAvan, T., "Effective Protection Against Influenza After Vaccination With Subunit Vaccine," *Med. J. Aust.* 1:301-303, *1978.*

Hennessy, A. V., Minuse, E., Davenport, F. M., and Francis, T., Jr., "An Experience With Vaccination Against Influenza B in 1952 by Use of Monovalent Vaccine, " *Am. J. Hyg.* 58:165-173, 1953.

● Prepared 9 months after search; four additional references could not be located.

Hirst, G. K., Vilches, A., Rogers, O., and Robbins, C. L., "The Effect of Vaccination on the Incidence of Influenza B," *Am. J. Hyg.* 45:96-101, *1947.*

Hoskins, T. W., Davies, J. R., Allchin, A., Miller, C. L., and Pollock, T. M., "Controlled Trial of Inactivated Influenza Vaccine Containing the A/Hong Kong Strain During an Outbreak of Influenza Due to the A/England/42/72 Strain, " *Lancet,* 116-122, 1973.

Knight, V., Couch, R. B., Douglas, R. G., and Tauraso, N. M., "Serological Responses and Results of Natural Infectious Challenges of Recipients of. Zonal Ultracentrifuged Influenza A2/Aichi/2/68 Vaccine, " *Bull. W.H. O.* 45:767-771,

Leibovitz, A., Coultrip, R. L., Kilbourne, E. D., Legters, L. J., Smith, D. C., Chin. J., and Schulman, J. L., "Correlated Studies of a Recombinant Influenza Virus Vaccine. IV. Protection Against Naturally Occurring Influenza in Military Trainees, " *J. Infect.* Dis. 124:481-487, 1971.

Mascoli, C. C., Leagus, M. B., and Hilleman, M. R., "Influenza B in the Spring of 1965," *Proc.* Soc. *Exp. Biol. Med.* 123:952-960, *1966.*

Maynard, J. E., Dull, H. B., Feltz, E. T., Berger, R., and Hammes, L., "Evaluation of Monovalent and Polyvalent Influenza Vaccines During an Epidemic of Type A2 and B Influenza," *Am. J. Epid. 148-157, 1967.*

McDonald, J. C., and Andrews, B. E., "Influenza in the United Kingdom, 1953-1956. Report to the Medical Research Council Committee on Clinical Trials of Influenza Vaccine by the Public Health Laboratory Service, " *Brit. Med. J.* 5035:8-10, 1957.

Medical Research Council Committee on Influenza and Other Respiratory Virus Vaccines, "Trials of an Asian Influenza Vaccine: Fourth Progress Report," *Brit. Med. J.* 1:415-418, *1958.*

Meiklejohn, G., "Effectiveness of Monovalent Influenza A-Prime Vaccine During 1957 Influenza A-Prime Epidemic," *Am. J. Hyg.* 67:237-249, *1958.*

Mogabgab, W. J., and Leiderman, E., "Immunogenicity of 1967 Polyvalent and 1968 Hong Kong Influenza Vaccines," *J. A.M.A.* 211:1672-1676, *1970.*

Nelson, A. J., "Evaluation of Asian Influenza Vaccine in an Industrial Population, " *Can, Med. Assn. J.* 79:888-891, *1958.*

Newnham, C. T., 'Evaluation of an Influenza Vaccine Program in Industry," *Brit. J. Clin. Prac.* 16:778-779, *1962.*

Norwood, W. D., and Sachs, R. R., "The Protective Effect

of Vaccination Against Epidemic Influenza B in an Industrial Plant," *Indus. Med.* 16:1-3, 1947.

Pavilanis, V., Frappier, A., Isomlo, F., Boudreault, A., and Claveau, P., "Evaluation of the Effectiveness of Anti-Influenza Vaccination," *Can.* Med. *Assn. J.* 79:527-532, ***1958.***

Philip, R. N., Bell, J. A., Davis, D. J., Beem, M. O., Beigleman, P. M., Engler, J. I., Mellin, G. W., Johnson, J. H., and Lerner, A. M., "Epidemiologic Studies on Influenza in Familial and General Population Groups, 1951 -1956," *Am. J. Epid.* 90:471-483, ***1969.***

Ruben, F. L., DeKalb, I., Akers, L. W., Stanley, E. D., and Jackson, G. G., "Protection With Split and Whole Virus Vaccines Against Influenza," *Arch. Intern.* Med. 132:568-571, 1973.

Salk, J. E., and Suriano, P. C., "Importance of Antigenic Composition of Influenza Virus Vaccine in Protecting Against the Natural Disease: Observations During the Winter of 1947-1948," *Am. J.* ***Pub. Health*** 39:345-355, ***1949.***

Salk, J. E., and Rapalski, A. J., "Evaluation of Influenza Vaccine in an Explosive Epidemic of Mixed Etiology," ***U.*** *S. A.* ***F. Med.*** *J.* 9:469-478, ***1958.***

Salk, J. E., and Suriano, P. C., "Importance of Antigenic Composition of Influenza Virus Vaccine in Protecting Against the Natural Disease: Observations During the Winter of ***1947-1948,"*** *Am. J. Pub. Health* 39:345-355, 1949.

Smith, J. W. G., and Pollard, R., "Vaccination Against Influenza: A Five-Year Study in the Post Off ice.," *J. Hyg. Carob.* 83:157-170, 1979.

Stiver, H. G., Graves, P., Eickoff, T. C., and Meiklejohn, G., "Efficacy of 'Hong Kong' Vaccine in Preventing 'England' Variant Influenza A in 1972," *N. Eng. J.* ***Med.*** 289:1267-1271, ***1973.***

Stuart, W. H., Dull, H. B., Newton, L. H., McQueen, J. L., and Schiff, E. R., "Evaluation of Monovalent Influenza Vaccine in a Retirement Community During the Epidemic of 1965-1966, *J. A.M.A.* 209:232-238, 1969.

Sugiura, A., Yanagawa, H., Enomoto, C., Ueda, M., Tobita, K., Matsuzaki, N., Suzuki, D., Nakaya, R., and Shigematsu, I, "A Field Trial for Evaluation of the Prophylactic Effect of Influenza Vaccine Containing Inactivated A2/Hong Kong and B Influenza Viruses," *J. Infect, Dis.* 122:472-478, *1970.*

Tyrrell, D. A. J., Buckland, R., and Rubenstein, D., "Vaccination Against Hong Kong Influenza in Britian, 1968-1969," *J. Hyg.* ***Carob.*** 68:359-368, ***1970.***

Van Ravenswaay, A. D., "Prophylactic Use of Virus Vaccine: Instance of Inadequate Protection Against Influenza, *J. A.M.A.* 136:435-437, 1948.

Waldman, R. H., and Coggins, W. J., "Influenza Immunization: Field Trial on a University Campus," *J. Infect. Dis.* 126:242-248, *1972.*

Waldman, R. H., Mann, J. J., and Small, P. A., Jr., "Immunization Against Influenza: Prevention of Illness in Man by Aerosolized Inactivated Vaccine," *J. A.M.A.* 207:520-524, 1969.

Warburton, M. F., Jacobs, D. S., Langsford, W. A., and White, G. E., "Herd Immunity Following Subunit Influenza Vaccine Administration," *Med. J. Aust.* 2:67-70, *1972.*

Appendix D.—A Description of Guillain=Barre Syndrome Due to Influenza Vaccine*

Reprinted from Arthur D. Little,
Estimated Economic Costs of Selected Medical Events Known or Suspected To Be Related to the Administration of Common Vaccine,
written for the Office of Health, Research, Statistics, and Technology,
National Center for Health Services Research,
DHEW contract No. 233=78-3013, appendix C, Dec. 31, 1979, pp. 157=161.

Clinical Profile

Etiology

The Guillain-Barre Syndrome (GBS) was first described by Landry in 1859 (l), then by Guillain, Barre, and Strohl in 1919 (2). It is also known as acute postinfectious neuritis, acute ascending paralysis and polyradiculoneuritis. The etiology has not been definitively established, although it has been associated with a variety of viral, bacterial, and other infections, as well as endocrine, hematologic, dermatologic, allergic and neuropsychiatric disorders, various toxins and drugs, and with vaccines for rabies, tetanus, typhoid, pertussis, diptheria, smallpox, polio, and influenza (3).

Clinical Manifestations

Although the clinical presentation is fairly uniform, numerous diagnostic criteria have been proposed without universal acceptance. In addition to the original descriptions, detailed criteria have been outlined by Osler and Sidell (4), Marshall (5), Wiedenholt, et al (6), McFarland and Heller **(7),** Ravn (8) and Masucci and Kurtzke (9). In 50 to 75 percent of nonvaccine-related cases, a history of mild respiratory or gastrointestinal infectious illness, within the preceding 4 weeks, can be elicited. In vaccine associated cases, there is no preceding acute infectious illness in 75 percent of cases (10). There is usually an asymptomatic afebrile period of 1 to 3 weeks, then vague pains or paresthesia of the hands and feet are reported in 75 to 90 percent of cases. The first symptom of prominence is muscle weakness, involving the proximal or distal muscles of the legs, then the arms, but this ascending progression is by no means constant. This involvement is usually bilateral (95 percent) but may be asymmetric. The progression of sensory and other symptoms is gradual and usually complete within 2 weeks, but occasionally can continue for months. Facial weakness and involvement of any or all cranial nerves occur in **50** to 80 percent of cases. Cranial nerves are more often involved in vaccine-associated cases (10). Urinary incontinence or retention may occur in 20 percent but is transient. From 10 to 25 percent of patients may have paralysis of breathing and require artificial respiratory support. Pulmonary complications, anoxia and seizures, and residual neurological deficits may occur, but complete recovery is gradually achieved in one year. Mortality, usually from respiratory involvement, is approximately 5 percent. Residual paralysis occurs in 10 to **30** percent of cases.

Physical examination is marked by bilateral motor weakness of the lower extremities, upper extremities, and trunk. Muscle atrophy and fasciculations may be noted. Sensory deficits may involve position, vibration pain, and light touch. Deep tendon reflexes are depressed or absent; superficial reflexes may be absent, but are usually intact. As noted, cranial nerves may be involved, and papilledema may be found. Some patients, especially children, may have neck stiffness as a sign of meningeal irritation (11). Autonomic dysfunction with hypertension, postural hypotension, facial flushing, and tachycardia may occur.

Laboratory abnormalities are few, but CSF findings are diagnostic. CSF protein should be elevated (above 60 mg/dl), but may be within normal limits early in the illness. The CSF cell count is usually less than **20** WBC/cmm. Peripheral white blood cell count, differential, and erythrocyte sedimentation rates are usually normal. Serum calcium may be elevated in patients immobilized for prolonged periods and electrolyte imbalances with inappropriate secretion of antidiuretic hormone have been reported. Electromyography is usually diagnostic (fasciculations), and motor nerve conduction is delayed.

Epidemiology

In February 1976, an influenza virus was isolated during an epidemic at Fort Dix, N. J., antigenically similar to the virus implicated in the 1918 influenza pandemic. The Federal Government then initiated a

● NOTE: Reference citations for app. D refer to the list of references at the end of app. D.

project to immunize much of the population of the United States. Between October 1, 1976, and December 16, 1976, nearly 43 million doses of killed influenza A/New Jersey/1976 vaccine were administered. The program was abruptly halted when an increasing number of reports of GBS (associated with vaccine inoculation) were reported. By January 10, **1977,** a total of **581** cases of GBS had been reported, of which **295** had received the vaccine. 11 percent of the patients who received vaccine were less than 3 years of age. Fifty-eight percent were between 30 and 59 years, and 31 percent were 60 years or older. Of 266 unvaccinated patients, 4 percent were less than 30 years, 39 percent between 30 and 59, and 17 percent were 60 or older. There was no differences between sexes. Cases were noted in 49 of 50 States (12).

The clinical states of vaccinated and non-vaccinated patients as reported by the Center for Disease Control were remarkably similar, significantly differing only in history of previous acute **(27 v. 62** percent) or chronic illness (44 v. 27 percent), involvement of cranial *nerves* (64 v. 47 percent), and sensory symptoms (87 v. 74 percent). Of the vaccinated patients, there were 41 percent with respiratory involvement, **23** percent placed on a respirator and 5 percent of 299 cases died. Within 8 to 28 days following vaccination, **75.2** percent had onset of paralysis, 3.3 percent within 7 days after vaccination, and 21.5 percent more than **28** days following vaccination (lo).

The relative risks of GBS in influenza vaccinated persons was approximately 12 times greater than in unvaccinated persons (10). The risk was similar for monovalent or bivalent vaccine. Age-specific attack rates per million population per month were *2.48* for vaccinated v. 0.34 for unvaccinated in ages O to 17 years, 3,45 and 0.70 for ages 18 to 24, 9.21 and 0.56 for ages 25 to 44, 6.49 and 0.81 for ages 45 to 64, 7.22 and 0.76 for over 65, and 6.99 and 0.58 for all ages. Thus, all ages were at risk.

Pathology

Pathological examination varies with the stage of disease progression. There are no significant pathologic changes in the cerebrum, brain stem, or spinal cord, except for severe changes in the anterior horn cells and motor nuclei of the brain stem. Acutely, there is marked edema of the spinal roots and cranial nerves. Later, demyelination and degeneration of the spinal and cranial nerve axons are *seen.* Lymphocytic inflammatory cells invade the myelin sheath and Schwann cell proliferation follows. Chromatolysis of dorsal root ganglia and anterior horn cells may be observed (13).

Diagnosis

Diagnostic criteria are those outlined under clinical manifestations and include:

1. acute *or* subacute onset of muscle weakness and/or sensory symptoms (i. e., paresthesia, numbness or pain);
2. usually ascending spread (may be descending, or variable) with progression over 1 to 2 weeks (up to 2 months);
3. bilateral (may be asymmetric) muscle involvement;
4. deep tendon reflexes absent or diminished;
5. cranial nerves may be involved; and
6. CSF protein elevated (>60 mg/dl), CSF WBC count < 20/cmm.

Differential Diagnosis

The differential diagnosis of influenza-vaccine-associated GBS includes:

1. *GBS secondary to other* causes, including viral infections (infectious mononucleosis, measles, hepatitis, upper respiratory and gastrointestinal infections, etc.), bacterial infections (strep tococcal, etc.), other vaccinations, (rabies, tetanus toxoid, etc.), autoimmune disorders (lupus erythematosis, polyarteritis nodosa, etc.) malignant diseases (Hodgkin's disease, etc.), endocrine disorders (diabetes mellitus, etc.), poisons and toxins and antibiotic therapy (penicillin, etc.). Only a complete history, appropriate viral cultures and serologies, toxic screens, and search for underlying disease can implicate these disease etiologies.
2. *Poliomyelitis,* which is differentiated by epidemic occurrence, meningeal symptoms, biphasic course (aseptic meningitis then paralysis), fever, asymmetric muscle involvement, CSF pleocytosis without cytoalbumin dissociation and positive viral cultures.
3. *Acute myelitis,* which is marked by sensorimotor paralysis below a specific spinal level.
4. *Diphtheric polyneuropathy* characterized by weakness or paralysis of limbs and muscles innervated by cranial nerves associated with loss of position and vibratory sensation. This can be easily diagnosed by the obvious symptoms of laryngeal, pharyngeal or nasal diptheria, i.e., fever, pseudomembrane, proteinuria and positive culture for Corynebacteria diptheriae.
5. *Porphyric polyneuropathy,* a rapidly advancing severe, symmetric polyneuropathy with or without psychosis or convulsions. Diagnosis of underlying porphyria is accomplished by usual serum and/or urine tests.

Outcomes

Few prognostic data are available regarding influenza vaccine associated cases of GBS. Prognosis of other **cases** is usually good. Death occurs in approximately 5 percent of cases (5,6,10,14).

In vaccine associated cases, 3 to 4 extremities are involved in 85 percent of cases, cranial nerves in 47 percent, respiratory impairment occurs in 41 percent, and ventilator assistance is required in 25 percent (10).

The duration of hospitalization ranges from weeks to years depending upon the eventual outcome. Of 97 patients from the Mayo Clinic (6), 50 made complete recovery with a year, 7 more in 2 years, and 4 more after 2 years. Twelve patients made incomplete recovery, five had moderate incapacity, four marked incapacity, and three respiratory insufficiency. Fifteen patients were improved when last seen, four unchanged 3 or more years after diagnosis, and five dead. From Columbia Presbyterian Medical Center, 49 of 81 patients were reexamined at least 2 years after onset of GBS. Of these, 8 had marked distal weakness, and 8 mild distal weakness (14).

Impairment may range from mild weakness of one or more extremities to marked paralysis and respiratory insufficiency requiring ventilator assistance, and constant nursing care. Relapses may occur weeks or years after resolution' of symptoms (14,15). Influenza vaccination of persons who have previously suffered from GBS may precipitate a second attack (16). From 50 to 60 perceni of patients should be able to return to their normal routine within 1 year of onset. Approximately 15 percent will be completely disabled (6,14).

Appendix D References

1. Landry, O., "Note sur las Paralysie Ascendance Aigue," *Gaz. Hebd. Med.* 6:472:474, *486-488, 1859,*
2. Guillain, G., Barré, J. A., and Stronhl, A., "Sur un Syndrome de Radiculo-Nevrite avec Hyperalbiminose du Liquide Cephalorachidien saris Reaction Cellulaire: Remarques sur las Caracteres Linques et Graphiques des Refexes Tendineux, " *Bull. Soc. Med. Hop. Paris* 40:1462-1470, *1916.*
3. Leneman, F., "The Guillain-Barré Syndrome, " *Arch. Int. Med. 118: 139-144, 1966.*
4. Osler, L. D., and Side] D. "The Guillain-Barré Syndrome," *N. Eng. J. Med.* 262:964-969, *1960.*
5. Marshall J., "The Landry-Guillain-Barré Syndrome," *Brain* 86:55-56, *1963.*
6. Wiederholt, C., Mulder W., and Lambert H., Mayo, *Clin. Proc.* 39:427-451, 1964.
7. McFarland, H., and Heller, L., "Guillain-Barré Disease Complex," *Arch, Neurol.* 14:196-201, 1966.
8. Ravn, H., "The Landry-Guillain-Barré Syndrome, " *ACTA Neurol. Scan. Suppl. 30,* 43:1-64, *1967.*
9. Masucci, E. F., and Kurtzke, J. F., "Diagnostic Criteria for the Guillain-Barré Syndrome, " *J. Neurol. Sci.* 13:483-501, *1971.*
10 Center for Disease Control, Handout #4, Jan. 7, 1977.
11 Paulson, G. W., "The Landry-Guillain-Barré-Strohl Syndrome in Childhood," *Devel. Med. Child. Neurol.* 12:604-607, *1970.*
12 Center for Disease Control, ***Morbidity & Mortality Weekly Report,*** 26:7, ***1977.***
13. Haymaker, W., and Kernohan, W., "The Landry-Guillain-Barr@ Syndrome, " Medicine 28:59-141, 1949.
14, Pleasure, E., Lovelace, E., and Duvoisin, R. C., "The Prognosis of Acute Polyradiculoneuritis," *Neurol.* 18:1143-1148, ***1968.***
15. Bolin, T. D., and DeCarle, D. J., "Recurrent Guillain-Barré Polyneuritis," *Med. J. Aust. 2: 263-264, 1972.*
16. Thomas, P. K., Lascelles, R. G., Hallpike, J. F., and Hewer, R. L., "Recurrent and Chronic Relapsing Guillain-Barre Polyneuritis, *Brain 92: 589-606, 1968.*
17. Seyal, M., Ziegler, K., and Couch, R., "Recurrent Guillain-Barré Syndrome Following Influenza Vaccine, " *Neurol.* 28:725-726, ***1978.***

Appendix E.—Values Assigned to Selected Variables

This appendix describes the sources of data, methods, and assumptions that OTA used to assign values to the following variables in its analysis of the cost effectiveness of influenza vaccination: 1) vaccination cost, 2) vaccine effectiveness rate, 3) duration of vaccine-induced immunity, 4) vaccine side effects and their treatment costs, s) hospitalization related to influenza, *6)* ambulatory care related to influenza, 7) excess mortality related to influenza, *8)* the cost of treating illnesses in extended years of life, 9) medicare expenditures, 10) work loss, 11) values assigned to selected characteristics of the influenza high-risk population, and 12) the discount rate.

Vaccination Cost

Base Case: Adult: $6.00 Child: $11.09
Sensitivity Analysis: Adult: $155 to $9.39
Child: $4.50 to $19.60

There are two components to vaccination cost—purchase price of the vaccine and the cost of administering the vaccine. Both components can vary substantially each year. The price of the vaccine is determined by such factors as these:

- manufacturers' production and distribution costs;
- manufacturers' desired profit margin;
- level of competition among manufacturers;
- number of doses being purchased (purchasers of large quantities usually pay a lower price per dose);
- type of vaccine (whole virus v. split product; monovalent v. polyvalent);
- type of purchases—public v. private;
- number of doses administered per person (children and young adults in some years require two doses per season; adults usually require one dose);
- type and size of product container purchased (e.g., prefilled syringes v. multiple-disc vial); and
- the "returned goods" policy of manufacturers (i.e., a manufacturer's willingness to purchase back unused portions of vaccine).

Factors that affect the cost (or the price) of administering the vaccine include these:

. number of doses administered per person;

- type of place or person administering the vaccine (e.g., private physician's office v. public health clinic);
- geographical location of vaccination; and
- type of vaccination procedure used (e. g., "jet" gun v. syringe and needle).

The estimates of influenza vaccination costs in OTA's study were based on the following data and observations. **First, data on vaccine selling prices were obtained from an OTA survey of selected vaccine manufacturers.** Overall, selling prices for the whole virus influenza vaccine—when purchased in lo-dose (5CC) vials—ranged from $0.45 to around $1.70/dose over the period from 1977 through 1980. The cost of split virus vaccine most often was higher than that of whole virus and ranged from about $1 to $2/dose. Whole virus vaccine sold in prefilled syringes from one company ranged from about $1.65/dose to approximately $2.00/dose in 1978-79.

Second, the vaccine purchase prices paid during the years 1977-78 through 1980-81 were obtained from selected public and private vaccine purchasers (see table E-1). The purchase price of influenza vaccine varied substantially from year to year (e.g., a private sector purchaser experienced a 50-percent increase in 2 years). Further, in all years, public sector purchasers commanded a lower price than private sector purchasers. In **1979-80,** the Federal Government through the Centers for Disease Control (CDC) negotiated with manufacturers a purchase price that applied to all State government vaccine consumption. In that year, public sector purchasers bought a dose of whole virus vaccine for *$0.29,* while some private sector purchasers paid $1.07. In 1980-81, CDC did not negotiate a uniform purchase price, but some State health departments are paying a price up to **20** percent lower than some private sector purchasers.

Third, the cost incurred or the price charged for administering influenza vaccine was solicited from selected private and public sector sources. The six public health clinics surveyed do not charge a fee for administering the vaccine. Some, however, are contemplating charging $1 to $2 per person. On the basis of data generated from the **1976** swine influenza program, Tolsma and Millar estimated that vaccine was administered in that program for about $1/dose, exclusive of the cost of vaccine **(122).** The use of "jet gun" vaccine administration undoubtedly contributed to low vaccine costs. Updated for inflation, that $1.00 cost would be $1.25 in 1978,

In the private sector, surveyed clinics charged $3.00 to $8.00 to administer the vaccine. In some

Table E-1.—Price per Dose of Influenza Vaccines Paid by Selected Purchasers, 1977-78 Through 1980.81

Purchaser and type of vaccine	1977-78	1978-79	1979-80[a]	1980-81
Public sector				
West **coast State** health department:				
Whole virus		$ .65	$ .29	$1.00
Split virus	$.65	$1.80	$.99	–
Southern State health department:				
Whole virus	—	—	$ .29	$1.18
Split virus	—	—	$ .99	$1.95
Center for Disease Control:				
Adult formula	—	$.34 to $ .49	–	–
Youth formula.	—	$.77 to $1.66		
Whole virus	—	—	$ .29	–
Split virus	—	—	$ .99	–
Private sector				
West coast university hospital:				
Whole virus		$ .82	$1.07	$1.12
Split virus	$.78			
Syringes	—	$1.15	$1.38	-
Northeast university hospital:				
Whole virus	—	$ .82	$1.07	$1.20

[a]In 1979-80 the Federal Government negotiated a set price with manufacturers for the price of influenza vaccine. State governments participating in federally sponsored influenza immunization programs received vaccines at those negotiated prices

SOURCE" Office of Technology Assessment.

cases, vaccine was supplied by State health departments free of charge to practicing physicians who can charge patients their normal vaccine administration fees, exclusive of the cost of vaccine. When persons require 2 doses of vaccine (e.g., those under 25 years), some physicians reportedly reduce their administration fees somewhat to yield a "package cost" per person.

Fourth, the vaccine administration fee charged by physicians was also calculated with data from three other sources. First, it was determined from the 1969 California Relative Value Scale that vaccine administration is valued at one-half the value of a brief examination followup visit for an established patient (17). Second, it was determined from an article by Muller and Otelsburg (76) that in 1977 the mean physician charge for such a visit for a medicare patient was **$9.56.** Third, one-half of this charge, i.e., $4.78, **was** then adjusted for inflation for years 1977-78 by multiplying it by the physician services component of the consumer price index (CPI). The vaccination charge thus calculated for 1978, for example, was $5.18.

For the past 3 to 4 years, the Immunization Practices Advisory Committee (ACIP), the official vaccination advisory body to the Federal Government, has recommended that children and young people receive two doses of split virus vaccine instead of one dose of whole virus vaccine. Therefore, OTA derived special vaccination costs for those vaccinees under 25 years of age.

For public and private sector provision of influenza vaccination in 1978, OTA derived the following costs:

	Vaccine price	+ Administration cost	= Total vaccination cost per person per year
Public Sector			
Low Estimate			
Adult ≥ 25 years	**$0.30/dose**	**+ $1 25/dose**	**= $1.55**
Child/young adult <25	**$2.00/2** doses	**+ $2,50/2 doses**	**= $4.50**
High Estimate			
Adult ≥ 25 years	$0.65/dose	+ $1 25/dose	= $190
Child/young adult <25	$3.60/2 doses	+ $2 50/2 doses	= $6.10
Private Sector			
Low Estimate			
Adult ≥ 25 years	**$0.82/dose**	**+** $5.18/dose	= $6.00
Child/young adult <25	$3.32/2 doses	+ $77712 doses	= $1109
High Estimate			
Adult ≥ 25 years	$1.39/dose	+ $8.00/dose	= $9.39
Child/young adult <25	$3.60/2 doses	+ $16.00/2 doses	= $1960

Vaccine Effectiveness Rate

As described in appendix B, the effectiveness of influenza vaccine is measured in terms of either: 1) its documented ability to reduce in clinical trials the incidence—and perhaps the morbidity and mortality—of influenza among vaccinated subjects; or 2) its ability to stimulate the production of antibodies which are presumed to provide protection against influenza among vaccinated subjects. In OTA's analysis, the effectiveness rate of inactivated influenza

virus vaccine was based only on data relating to the vaccine's ability to reduce clinical disease. Such data are difficult to find and, in some cases, quite difficult to interpret and extrapolate to populations beyond the clinical trial setting. Based on data outlined in appendix B, a vaccine effectiveness rate of 60 percent was used for all years in the base case analysis; that rate was varied from 30 to 90 percent in the sensitivity analysis.

Duration of Vaccine-Induced Immunity

As explained in appendix A (by Dr. Gary Noble, CDC), the duration of immunity provided by a particular influenza vaccine can vary substantially. Because there is no reliable indicator of the population's influenza antibody status—especially concerning antibodies to an upcoming variant of an influenza virus, ACIP recommends yearly influenza vaccinations for selected high-risk groups. On the basis of ACIP's recommendation, it was assumed in OTA's analysis that the effective duration of immunity of influenza vaccination would be 1 year. Undoubtedly, for some individuals, vaccine-induced immunity against some influenza viruses exceeds 1 year; however, on the basis of existing data, it is not possible to quantify differences in duration of immunity beyond 1 year among populations.

Vaccine Side Effects and Their Treatment Costs

The incidence, health effects, and costs of treating adverse reactions to influenza vaccines were quantified as described below.

Mild Local and Systemic Reactions (see app. B for description of reactions)

The following data were used to quantify mild local and systemic vaccine side effects in the base case and in the sensitivity analysis.

Adults (18 years and older)
- Incidence: 5 percent of all vaccinees (90)
- Treatment costs: 1 physician visit = $10.36 (in 1978) (76)
- Health effects: 1 day of nonbed disability

Children (under 18 years)
- Incidence: 13 percent of all vaccinees (90)
- Treatment costs: 1 physician visit = $10.36 (in 1978) (76)
- Health effects: 1 day of nonbed disability

Guillain-Barre Syndrome (GBS)

In the base case, it was assumed that, in all years except *1976-77,* no excess GBS was attributable to influenza vaccine. For 1976-77, the incidence and nature of GBS occurring during the swine flu immunization program were used, The types, incidence, and treatment costs of GBS during 1976-77 are displayed in table E-2 (4,112),

Table E.2.—Guillain Barre Syndrome Among 1976-77 A/New Jersey Influenza Vaccinees

Type of GBS case	Duration	Percent of GBS cases[a]	Death rate	Health effect (days of disability) Bed[b]	Nonbed[c]	Cost per case by age Under 3 years	3-14 years	15-64 years	≥ 65 years
Mild	≤ 1 year	25%	0%	21	161	$11,405	$ 9,347	$ 6,582	$ 9,087
Moderate	≤ 1 year	25%	0%	120	245	$24,500	$22,990	$23,071	$22,608
Moderate	≤ 1 year	35%	0%	21	344	$11,164	$ 9,106	$ 9,323	$ 8,838
						($663 for each added year of life)			
Severe (respiratory insufficiency)	≥ 1 year	5 %	00/0	365	–	$33,181	$30,241	$30,319	$29,865
						($1,832 for the 2nd year)			
						($1,552 for each added year of life)			
Severe (paralysis of extremeties)	≥ 1 year	5 %	0 %	365	–	$43,659	$37,779	$36,129	$37,040
						($5,140 for the 2nd year)			
						($3,661 for each added year of life)			
Death	—	5 %	1000/0	60	–	$23,685	$20,689	$20,839	$22,734

[a] To obtain age-specific incidences, these estimates were multiplied by the following attack rates (112):

Age	Attack rate (cases/million vaccinees)
0-17 years	1.1
18-24 years	3.3
25-44 years	9.1
45-64 years	7.5
≥ 65 years	7.3

[b] Bed days are equivalent to total number of days spent in a hospital or long-term care facility

[c] Nonbed days are equivalent to the difference between bed days and either 180 or 365, depending on type of GBS case.

SOURCE Based on data from *Estimated Economic Costs of Selected Medical Events Known or Suspected To Be Related to the Administration of Common Vaccines* (4)

Anaphylaxis

It was assumed in the base **case and** in the sensitivity analysis that the incidence of severe anaphylaxis (severe allergic reaction) associated with influenza vaccination for any year was 1 case per 4 million vaccinees (107). The assigned treatment costs (in 1978 dollars) and health effects of such a reaction were the following.

costs	
3 days of hospitalization	= $581.43
6 inpatient physician visits	= 132.72
1 outpatient physician visit	· 10.36
Total cost per case	$724.51
Health Effects	
3 days of bed disability	
2 days of nonbed disability	

Hospitalization Related to Influenza

The content and cost of a hospitalized case of influenza/pneumonia were constructed with data obtained from the Hospital Discharge Survey of the National Center for Health Statistics (NCHS), an article by Muller and Otelsberg **(76),** and the Blue Cross/Blue Shield option of the Federal Employee Health Benefits Program.

The construction of a hospitalized case is as described below.

Length of Stay

The length of stay for a hospitalized case of influenza/pneumonia was calculated from data provided by the Hospital Discharge Survey. The total number of days of hospitalization assigned to 8th Revision ICDA Codes 470-474 (all influenzas) and 480-486 (all pneumonias) as a first-listed diagnosis was divided by the total number of hospital discharges assigned to the same ICDA codes. The average length of stay (ALOS) ranged from *3.92* to 12.5 days per case, depending on patients' sex, age, and year of hospitalization.

Hospital Cost per Day

Hospital costs were obtained from the Blue Cross/Blue Shield option of the Federal Employees Health Benefit Program. In 1977, the average cost per day for a nonsurgical inpatient admission for influenza was $112.88. This figure includes charges for room and board, intensive care unit, treatment rooms, drugs and medication, oxygen, blood and ancillary services such as lab tests, X-rays, and other tests if billed by the hospital. It does not include physician-billed care.

The average cost per day for a nonsurgical inpatient admission for pneumonia in 1977, again based on data from Blue Cross/Blue Shield, was $140.12. According to data from the Hospital Discharge Survey of NCHS, approximately 80 percent of all hospital discharges with a diagnosis of either influenza or pneumonia (all listed-unduplicated) was attributed to pneumonia, in epidemic as well as nonepidemic years. In order to calculate the average cost per day for a nonsurgical inpatient admission for influenza-pneumonia (as a combined group), a weighted average cost was calculated as follows:

$$\$112.88\ (.20) + \$140.12\ (.80) = \$134.68$$

By using the CPI for hospital service charges, this $134.68 hospital cost per day was updated for inflation to yield a 1978 cost per day of $149.63 ($134.68 x 1.111).

Physician Hospital Visits and Costs

It was assumed that each hospitalized patient would receive one initial comprehensive physician visit *($39.62* in **1978)** and subsequently receive daily routine followup brief hospital visits **($10.51** per visit in *1978)* throughout the hospital stay.

Ambulatory Care Related to Influenza

The content and cost of an ambulatory case of influenza/pneumonia were constructed with data obtained from the National Ambulatory Medical Care Survey (NAMCS), an article by Muller and Otelsberg **(76),** and CPI data from the Department of Commerce.

The construction of a case is described below.

Number of Visits per Case

Calculated on the basis of data from NAMCS, the average number of physician office visits per case of influenza/pneumonia ranged from 1.10 to **3.65,** depending on patient's age and sex and the year of the case. To calculate this number, the total number of visits for influenza/pneumonia (listed as the first diagnosis) as reported in NAMCS was divided by the number of new visits for influenza/pneumonia (listed as the first diagnosis). The number of new visits served as a proxy for the number of ambulatory cases.

‘ These figures were based on data from references (4) and *(76).*

Procedures Ordered or Performed per Visit

Again based on NAMCS data, the following estimates were derived concerning the frequency with which selected procedures were either ordered or performed:

Procedure ordered or performed	*Percent of influenza 'pneumonia visits during which procedure was* ***ordered or*** *performed*
Limited physical examination	72
History/general examination	**15**
Clinical laboratory test	**16**
X-ray	**17**
Drug prescribed recommended.	**75**

A limited physical examination and a history / general examination were interpreted to be a limited office visit for a new condition in an established patient (17,76). NAMCS's categories for examinations changed during the early 1970's.

Cost per Case

Cost estimates for each of the visits and procedures included in an ambulatory case of influenza / pneumonia were based on 1977 medicare data (76), which were updated for inflation using the relevant medical care index from CPI data.

Physician cost of *an ambulatory visit.* —It was assumed that each case would include one initial limited office visit for an established patient at *$13.78* in **1978**[2] and 0.10 to **2.65** routine followup brief office visits (depending on sex and age of patient and year of case) at $10.36 per visit in 1978. Physician costs ranged from $14.82 to $41.23 in 1978.

Cost of *procedures ordered during an office visit in 1978.* —

	Number of procedures per visit	*Cost per procedure*	*cost per visit*
Clinical ***lab test (e.g.,*** complete blood count)	**0.16**	**x $ 7.68**	**"$1.23**
X-ray (e.g., chest)	0.17	**x $15.86**	**"$2.70**
Drug ordered (e.g., antibiotic, decongestant)	0.75	x $4.92[3]	= *$3.69*
Total cost of procedures per visit			*$7.62*

[2]The cost of an initial limited visit for an established patient was calculated in the following manner:

- Calculating the average charge for a routine followup brief office visit as billed by general practitioners and specialists (weighted evenly) to medicare in **1977 (76) and updating that charge to 1978 prices using CPI data; i.e.:**

  $8.63 + $10.48 = $9.56

  $9.56 X[2]*$10.84 "$10.36*

- Multiplying $10.36 by 16/12 (the ratio of values between a limited examination and a brief examination in the 1969 California **Relative** *Value Studies* **(17), i.e., $1036 x 16/12 = $13.78**

[3]**This estimated** cost per drug order was based on data from *Out-of-Pocket* ***Cost*** *and* ***Acquisition of Prescribed*** Medicines United States 1973 **(79). In 1973, the average price of a prescribed medicine** for conditions of the respiratory system (including influenza) **was $3 80; that figure was inflated to 1978 prices by using the CPI** for drugs and prescriptions.

Total cost per ambulatory case. —The total costs per ambulatory case (age-, sex-, and year-specific) were derived by combining the cost of an initial visit with the cost of followup visits (0.10 to **2.65** followup visits per case).

	Cost of ***initial visit***	***Cost of each followup*** visit
Physician fees.	$13.78	$10.36
Procedures	7.62	7.62
Total	$21.40	$17.98

Total costs per case ranged from $23.20 to $56.71, depending on patient's sex, age, and year of illness.

Excess Mortality Related to Influenza

The number of excess deaths used in the base case analysis were recently derived by CDC for this report (see tables E-3 and E-4). Excess mortality includes deaths from all causes during CDC-defined influenza epidemics. CDC estimates are calculated from NCHS mortality data.

In the sensitivity analysis, the number of total excess deaths due to all causes among all age groups combined for each year from 1970-71 through 1975 was derived by Dr. David Ailing and his associates at the National Institute of Allergy and Infectious Dis-

Table E-3.—Excess Mortality From All Causes Reported During Influenza Epidemics, 1970-71 Through 1977.78: Used in Base Case Analysis[a] (by age group)

Year	Under 1 year	1-44 years	45-64 years	≥ 65 years	All ages
1970-71	—	—	—		
1971 -72	359	1,640	7,580	22,100	31,679
1972-73	844	606	3,250	24,542	29,242
1973 -74	—	—	—		
1974 -75	173	676	1,270	5,371	7,489
1975-76 ...., ...	508	903	4,850	22,471	28,732
1976-77	—	—	—		
1977 -78., ...	578	1,173	5,200	22,851	29,803
Total deaths by age group	2,462	4,997	22,150	97,335	126,945
Average excess deaths/year	308	625	2,769	12,167	15,868
Average excess deaths/year with excess mortality	492	999	4,430	19,467	25,389
Average percent of total deaths by age groups . . .	2.0 "/0	4.0 "/0	17.0%	77.00/o	100 "/0

a Estimates for each age group for years 1970-71 through 1975-76 were derived by the Center for Disease Control (CDC). The estimates for all ages in 1976-77 and 1977-78 were calculated by CDC in a different fashion (100); the age-specific estimates for those 2 years were calculated by the Office of Technology Assessment.

Table E-4.—Estimated (Expected) Mortality From All Causes Reported During Influenza Epidemics, 1970-71 Through 1977-78: Used in Base Case Analysis[a] (by age group)

Year	Under 1 year	1-44 years	45-64 years	≥ 65 years	All ages
1970-71	—	—	—	—	
1971-72	10,140	28,573	80,234	210,960	329,907
1972-73	18,783	59,800	165,614	428,628	672,825
1973-74	—	—	—	—	—
1974-75	12,801	41,989	117,881	332,386	505,057
1975-76	11,540	40,610	111,466	326,382	489,998
1976-77	—	—	—	—	—
1977-78	17,244	55,353	153,846	420,347	646,791

[a]Estimated deaths for 1970-71, 1973-74, and 1976-77 were not used since there was no excess mortality calculated for those years. Estimates for each age group for years 1970-71 through 1975-76 were calculated by the Center for Disease Control. Estimates for 1977-78 were calculated by the Office of Technology Assessment,

ease. CDC's estimates of excess mortality were used for 1976-77 and 1977-78 (see tables E-5 and E-6).

From these data, "excess mortality rates" for deaths from all causes within four age groups—under 1 year, 1 to 44, 45 to 64, and over 65—were derived. A baseline "force of mortality" was calculated for each year, and an additional force of mortality—varied in accordance with the degree of excess mortality—was programmed for the influenza season in each epidemiologic year from **1970-71** through 1977-78.

Table E-5.—Excess Mortality From All Causes Reported During Influenza Epidemics, 1970.71 Through 1977.78: Used in Sensitivity Analysis[a] (by age group)

Year	Under 1 year	1-44 years	45-64 years	≥ 65 years	All ages
1970-71	—	—	—	—	—
1971 -72	42	188	870	6,800	7,900
1972 -73	1,508	1,083	5,809	19,000	27,400
1973-74	49	191	360	800	1,400
1974 -75					
1975-76	849	1,500	8,056	8,600	19,000
1976-77	—	—	—	—	—
1977 -78	1,307	1,585	8,077	18,834	29,803
Total deaths by age group	3,755	4,547	23,172	54,034	85,503
Average excess deathly ear	469	568	2,897	6,754	10,688
Average excess deaths/year with excess mortality	751	909	4,634	10,807	17,101
Average percent of total deaths by age groups	4.0 "/0	5.0 "/0	270/o	630/0	1000/0

[a]Estimates for th "65" age group and for "all ages" for all years 1970-71 through 1975-76 were derived by Dr. David Ailing and associates at the National Institute of Allergy and Infectious Diseases (2). The estimates for all ages for years 1976-77 and 1977-78 were derived by the Center for Disease Control (100). Age-specific estimates for age groups < 1, 1-44, and 45-64 were calculated by the Office of Technology Assessment

Table E-6.—Estimated (Expected) Mortality From All Causes Reported During Influenza Epidemics, 1970-71 Through 1977-78: Used in Sensitivity y Analysis[a] (by age group)

Year	Under 1 year	1-44 years	45-64 years	≥ 65 years	All ages
1970-71	–	–	–	–	–
1971-72	9,986	28,140	79,017	207,760	324,902
1972-73	18,140	57,754	159,947	413,962	649,804
1973-74	8,186	26,851	75,383	212,554	322,974
1974-75	—	—	—	—	—
1975-76	11,069	38,953	106,917	313,062	470,001
1976-77	—	—	—	—	—
1977-78	17,244	55,353	153,846	420,348	646,791

[a]Alling and associates calculated no excess mortality in 1970-71 and 1974-75 (2), and the Center for Disease Control calculated no excess mortality for 1976-77; therefore, no estimated deaths were used for those years. Estimated deaths for the "all ages" category for years 1970-71 through 1975-76 were calculated by Ailing and associates (2). The Office of Technology Assessment calculated estimated mortality for the age-specific groups ir all years.

Cost of Treating Illnesses in Extended Years of Life

To calculate the cost of treating other illnesses (those not prevented by influenza vaccination) in extended years of life gained by individuals who avoid death from influenza, per capita annual total medical care costs were multipled by the number of years of life generated by vaccination.

Data used to calculate total medical care costs per person were those published by the Health Care Financing Administration (HCFA) **(37,42).** According to HCFA, in **1978,** the average age-specific per capita total medical care expenditures were the following.

Age	*Total per capita expenditure*
Under 19.	$ 286
19-64.	764
65 and over,	2,026
All ages.	753

These averages were weighted for persons 19 years and over to assign higher costs to more specific age groups. Thus, for example, individuals aged 64 were assigned higher costs than individuals aged 20.

Medicare Expenditures

Medicare's portion of expenditures for the treatment of influenza, as well as for all other illnesses, was based on data from (37). In 1977, for persons 65 and older, after copayments, medicare paid for 74.6 percent of all hospital expenditures, 55.6 percent of all physician expenses, and overall 44.1 percent of all medical care expenditures.

Work Loss

"Excess" days of work loss caused by medically attended influenza (8th Revision ICDA codes **470-474)**

and pneumonia (8th Revision ICDA codes 480-486) were calculated by subtracting work loss reported in 1970-71 from work loss reported in each subequent year through 1977-78. Age- and sex-specific work loss data were obtained from the Health Interview Survey at the NCHS. Age- and sex-specific individual mean earnings data were obtained for years 1975, 1976 and 1977 from the Bureau of the Census (15). Earnings for 1978 were derived by multiplying 1977 earnings data by the ratio of the 1978 GNP deflator/1977 GNP deflator, i.e., 152.05/141.70 = 1.0730 (see table E-7). Daily earnings were derived by dividing annual earnings for full-time year-round workers by 260 working days per year. Days of work loss were multiplied by 1978 daily earnings to obtain age- and sex-specific productivity losses.

Values Assigned to Selected Characteristics of the Influenza High-Risk Population

Increased Probability of Dying Within a Given Year

Age-specific probabilities of a high risk person's dying from any cause within a given year were calculated with the following equation:

$$_{P}I = 1 - \exp [\ln(1 - me.) \times 2.2]$$

where

m_{pi} is the mortality for poor-risk patients at age 1 and
m_{GI} is the mortality for good-risk patients at age I.

This is a modified version of an equation developed by Fitzpatrick and associates based on increased probabilities of dying among persons with chronic bronchitis (38).

These probabilities were multiplied by the age-specific estimated death rates (for all causes) for the general population.

Probability of Dying From Influenza or Pneumonia Within a Given Year

Age-specific probabilities of a high-risk person's dying from influenza or pneumonia within a given year were derived from data displayed in table E-8. From these data, age-specific death rates for pneumonia in persons with medically attended heart disease were calculated (see table E-9). Heart disease was used as a proxy for all influenza high-risk conditions. Age-specific probabilities and relative risks of dying from influenza or pneumonia are displayed in table E-10. To derive high-risk mortality rates, these relative risk values were multiplied by the excess mortality rates for influenza and pneumonia calculated for the general population.

Although the mortality rates for both pneumonia and heart disease have changed since the 1950's, it was assumed that the ratio between the pneumonia mortality rate in the general population and the pneumonia mortality rate for those persons with heart disease has remained fairly constant over the past 25 years.

Table E-7.—Annual Individual Mean Earnings for Full-Time, Year-Round Workers, by Age and Sex, 1977-78

	18-24 years	25-34 years	35-44 years	45-54 years	55-64 years	≥ 65 years	All ages
Annual earnings							
1977[a]							
Both sexes	$ 8,564	$13,092	$15,739	$15,729	$14,506	$12,661	$13,856
Male	9,497	14,775	18,436	18,517	16,968	14,649	16,171
Female	7,338	9,555	9,587	9,597	9,241	6,604	9,133
1978[b]							
Both sexes	$ 9,189	$14,048	$16,888	$16,877	$15,565	$13,585	$14,867
Males	10,190	15,854	19,782	19,869	18,207	15,718	17,351
Female	7,874	10,254	10,287	10,298	9,916	8,159	9,800
Daily earnings							
1978							
Both sexes	$ 35	$ 54	$ 65	$ 65	$ 60	$ 52	$ 57
Male	39	61	76	76	70	60	67
Female	30	39	40	40	38	31	38

[a]Data for 1977 were obtained from the Bureau of the Census, *Current Population Reports*, Series P-60 (15).
[b]Earnings for 1978 were derived by multiplying 1977 data by the ratio of 1978 GNP deflator/1977 GNP deflator, i.e., 152.05/141.70 = 1.0730.

Table E.8.—Data Relating to Pneumonia Deaths in the 1950's, by Age Group

	≤ 44 years	45-64 years	≥ 65 years	All ages
Number of pneumonia deaths (underlying cause) in the general population	13,166	6,590	22,417	42,173
Estimated population of U.S.	116,865,000	33,359,000	14,079,000	164,303,000
Number of pneumonia deaths (underlying cause) among persons with medically attended heart disease	580	1,651	6,602	8,833
Estimated population with medically attended heart disease	579,000	1,341,000	1,677,000	3,598,000
Number of pneumonia deaths (underlying cause) in persons without medically attended heart disease	12,586	4,939	15,815	33,340
Estimated population without medically attended heart disease	116,286,000	32,018,000	12,402,000	160,705,000

SOURCES: (1) Vital *Statistics of the United States 1955*. National Office of Vital Statistics, Washington, D.C.: U.S. Department of Health, Education, and Welfare. Volume 1, p.LIX, table L., 1957 (82).
(2) Ibid. *Supplement*, p. 110, table 8, 1965 (83).
(3) *Heart Conditions* and High *Blood Pressure United States, July 1957-June 1958*. U.S. National Health Survey, Series B-No.13. Washington, D.C.: U.S. Department of Health, Education, and Welfare, Table 5, p. 17, February 1980 (78),

Table E-9.—Age-Specific Death Rates (Deaths/100,000) From Pneumonia in the 1950's, by Age Group

	≤ 44 years	45-64 years	≥ 65 years	All ages
Death rate from pneumonia (as underlying cause) among the general population	11.27	19.75	159.22	25.67
Death rate from pneumonia (as underlying cause) among persons with medically attended heart disease	100.2	123.1	393.7	245.5
Death rate from pneumonia (as underlying cause) among persons without medically attended heart disease	10.82	15.43	127.52	20.75

SOURCES: (1) *Vita/ Statistics of the United States 1955*. National Office of Vital Statistics, Washington, D. C.: U.S. Department of Health, Education, and Welfare. Volume 1p.LIX, tableL., 1957 (82).
(2) Ibid. *Supplement*, p. 110, table 6, 1965 (83).
(3) Heart Conditions *and High Blood Pressure: United States, July 1957-June 1958*. U.S. National Health Survey, Series B-No.13. Washington, D. C.: U.S Department of Health, Education, and Welfare. Table 5, p. 17. February 1960 (78),

Increased Probability of Either Being Hospitalized or Visiting a Physician's Office for Influenza/Pneumonia

Barker and Mullooly calculated age-specific hospitalization rates among the general population and among high-risk populations during two epidemic and one nonepidemic periods in a large health maintenance organization in Portland, Ore. (9). Using these data, OTA compared age-specific excess hospitalization rates among high-risk persons to rates among the general population during an epidemic (see table E-II).

It was assumed in OTA's analysis that the excess probability of a high-risk person's visiting a physician's office for influenza or pneumonia was the same as the excess probability of a high-risk person's being hospitalized for influenza or pneumonia. To derive

Table E-10.—Probabilities of Dying From Pneumonia in the 1950's, by Age Group

	≤ 44 years	45-64 years	≥ 65 years	All ages
Probability of dying from pneumonia among persons with medically attended heart disease	0.00100	0.00123	0.00394	0.00245
Probability of dying from pneumonia among the general population	0.00011	0.00020	0.00159	0.00026
Probability of dying from pneumonia among persons without medically attended heart disease	0.00011	0.00015	0.00128	0.00021
Increased probability of dying from pneumonia for persons with medically attended heart disease over the general population	0.00089	0.00103	0.00235	0.00219
Increased probability of dying from pneumonia for persons with medically attended heart disease over those without medically attended heart disease	0.00089	0.00108	0.00266	0.00224
Relative risk of dying from pneumonia in persons with medically attended heart disease over the general population	9.09	6.15	2.48	9.42
Relative risk of dying from pneumonia in persons with medically attended heart disease over persons without medically attended heart disease	9.09	8.20	3.08	11.67

SOURCES: (1) *Vital Statistics of the United States* 1955 National Office of Vital Statistics Washington, D.C. U.S. Department of Health, Education, and Welfare Volume 1, p LIX, table L., 1957 (82).
(2) Ibid Supplement, p 110, table 6, 1965 (83)
(3) *Heart Conditions and High Blood Pressure United States, July 1957-June 1958* U.S. National Health Survey, Series B-No. 13. Washington, D.C U S. Department of Health, Education, and Welfare Table 5, p. 17 February 1960 *(78).*

Table E-n .—Increased Probability of a High-Risk Person's Being Hospitalized for Pneumonia or Influenza During an Influenza Epidemic

Age group	Excess hospitalization rates[a] (persons hospitalized/100,000) Within the high-risk population	Within the hospitalized eve-r a general person in the general population	Increased probability of a high-risk person's being
15-44 years	83	26	83)26 = 3.19
45-64 years	514	95	514195 = 5.41
≥ 65 years	556	481	556/481 = 1.16

[a] Excess hospitalization rates are derived by subtracting hospitalization rates during a nonepidemic Influenza year (1970-71) from average rates during two epidemic Influenza years (1968-69 and 1972-73)

SOURCE. The Office of Technology Assessment's Interpretation of data from Barker and Mullooly (9).

rates of hospitalization and ambulatory cases among high-risk populations, these probabilities were multiplied by the hospital discharge rate and the ambulatory case rate (for influenza or pneumonia) in the general population.

Average Length of Hospital Stays and Number of Physician Office Visits/Ambulatory Case

The Hospital Discharge Survey of NCHS supplied length-of-stay data for persons hospitalized with pneumonia (any listed) who also had one or more of the following types of medical problems: cardiovascular, bronchopulmonary, renal, diabetes, or sickle cell disease. For high-risk populations, age-specific ALOS were calculated and compared to ALOS for a hospital case of pneumonia among the general population (see table E-12).

Likewise, the age-specific numbers of physician office visits per ambulatory case of influenza/pneumonia in the general population were multiplied by the age-specific ratios of:

$$\frac{\text{ALOS for high risk persons}}{\text{ALOS for the general population}}$$

Total Medical Care Costs

It was assumed that the total medical care costs in any extended year of life for a high-risk person were

Table E-12.—Average Length of Stay (ALOS) for a Hospital Case of Pneumonia Among Persons With One or More High-Rlsk Conditions,' 1976

Age group	Number of discharges	Total number of hospital days	ALOS (in days)	ALOS for high-risk persons/ ALOS for general population
0-1 years . . .	8,663	62,527	7.2	1.22
2-24 years . .	11,143	69,424	6.2	1.15
25-44 years .	16,615	130,886	7.9	1.00
45-64 years .	44,528	489,264	11.0	1.12
≥ 65 years . .	119,324	1,564,430	13.1	1.08
All ages	202,293	2,316,553	11.5	1.30

[a] High.risk conditions include the following types of medical problems: cardiovascular, bronchopulmonary, renal, and diabetes.

[b] ALOS for a hospital case of pneumonia (first-listed diagnosis) for the general population:

Age	ALOS
0-1 years, ...	5.9
2-24 years.	5.4
25-44 years	7.9
45-84 years ., . .	9.8
>=65 years.	1 2,1
All ages ., ...	8.9

SOURCE: Unpublished data, Hospital Discharge Survey, t976, National Center for Health Statistics, Hyattsville, Md.

twice those for a person in the general population. No known data exist regarding the extent to which total expenditures for medical care of a high-risk person exceed those of an average person.

The sensitivity analysis tested the effect of including total medical costs in extended years of life.

Treatment Costs for a Case of Influenza/Pneumonia

The cost of a day of hospitalization for influenza / pneumonia was not increased for high-risk persons. Total hospitalization costs related to influenza / pneumonia in the high-risk population increased, however, because of the steps described above, which increased the probability of being hospitalized and the average length of stay.

Likewise, the cost of a physician office visit for influenza / pneumonia was not increased for high-risk persons. Total ambulatory care costs related to influenza / pneumonia in the high-risk population, increased, however, because of the steps described above.

Disability Days

Bed and nonbed days of disability among high-risk persons were calculated in the following manner.

First, restricted activity days and bed disability days related to selected high-risk conditions were obtained from publications of NCHS (see table E-13). Nonbed disability days were calculated by subtracting bed disability days from restricted activity days. Weighted averages for all selected types of conditions combined were calculated.

Second, total days of bed and nonbed disability among high-risk persons were calculated by using the following equation:

[population' X percent with high-risk conditions x disability days for high-risk person'] +
[low-risk population' x disability days forlow-riskperson] =
[population' x disability days for average-risk person]

Discount Rate

It is generally accepted that streams of costs occurring over time should be discounted (86,89). The process of discounting involves the application of a rate—i. e., the discount rate—to outcomes to be realized over time. The magnitude of future outcomes is thereby changed to a present value.

Discounting has two theoretical bases. One is the fact that funds can be invested in alternative ways.

'Any age- or sex-specific population.
'Disability days are those calculated in table E-13.

Table E-13.—Disability Days Caused by Selected High-Risk Conditions

Type of high-risk condition	Prevalence	Restricted activity days per condition per year	Bed days per condition per year	Non bed days per condition per year
Heart condition	**10,291,000**	**30.2**	**12.6**	**17.6**
Chronic bronchitis.	6,526,000	7.5	3.6	3.9
Emphysema.	1,313,000	35.8	14.5	21.3
Asthma. ., ...	6,031,000	15.0	5.8	9.2
Total	24,161,000	—	—	—
Average	—	20.6	8.57	12.0

SOURCES: (1) Prevalerrce of Chronic *Circulatory Comditions: United* States, *1972,* Washington, D. C.: National Center for Health Statistics, 1975 (80).
(2) Prevalence of *Selected* Chronic Respiratory Conditions: United States, 1970, Washington, D. C,: National Center for Health Statistics, 1973 (81).

The discount rate approximates the yield that is foregone by investing in the project under consideration instead of using the funds in other ways. The other reason for discounting is that people prefer to realize benefits now rather than to postpone them to some future date. OTA's analysis of influenza vaccination discounts health effects, as well as costs, occurring over time (86,126).

It is important to note that discounting concerns time and is distinct from inflation, which concerns the level of prices. OTA's analysis takes account of changes in the price level by expressing all costs in terms of **1978** dollars.

The discount rate used in the base case is 5 percent, the rate generally used in recent analyses of medical programs (125). The rate considered appropriate for society's perspective is lower than that considered appropriate for an individual's perspective, because society would likely value more highly than an individual programs yielding benefits that stretch into the future, perhaps across generations. Although actual money market rates are the result of many factors **and do not represent true discount rates, it is noteworthy that U.S. bond yields during the 1950's and early 1960's,** when inflation rates were low, ranged from **2** to 4 percent **(34).** The sensitivity analysis substitutes a discount rate of zero to test the direction of the effect of a lower rate.

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References

References*

1. **Advisory Committee for Immunization Practices, "Influenza Vaccine 1980-81, " recommendation of the Public Health Service Immunization Practices Advisory Committee,** *Morb.& Mort. Wkly. Rpt.* 29:225-228, May 16, 1980.
2. Ailing, D. W., Blackwelder, W. C., and Stewart-Harris, C. H., "A Study of Excess Mortality During Influenza Epidemics in the United States, 1968-1976," *Amer. J. Epidem.* 113:30-43, *1981.*
3. Arrow, K., "Uncertainty and the Welfare Economics of Medical Care, " *Am. Econ. Rev.* 53:941-973, *1963.*
4. Arthur D. Little, *Estimated Economic Costs of Selected Medical Events Known or Suspected To Be Related to the Administration of Common Vaccine, Final Report,* written for the National Center for Health Services Research, Office of Health Research, Statistics, and Technology, DHEW, contract No. 233-78-3013, Dec. 31, 1979.
5. Bachmayer, H., "Split and Subunit Vaccines, " in *Influenza: Virus, Vaccines, and Strategy,* P. Selby (cd.) (New York: Academic Press, 1976).
6. Badger, G. F., Dingle, J. H., Feller, A. E., et al., "A Study of Illness in a Group of Cleveland Families, V. Introduction and Secondary Attack Rates as Indices of Exposure to Common Respiratory Diseases in the Community, " *Am. J. Hyg.* 58:179-182, *1953.*
7. Banford, C. R., Sibley, W. A., and Laguna, J. F., "Swine Influenza Vaccination in Patients With Multiple Sclerosis, " *Arch. Neurol.* 35:242-243, 1978.
8. Barker, W. H., and Mullooly, J. P., "Impact of Epidemic Type A Influenza in a Defined Adult Population, " *Amer. J. Epidem.* 112:798-811, December 1980.
9. _____ "Influenza Vaccination of Elderly Persons: Reduction in Pneumonia and Influenza Hospitalizations and Deaths, " *J. A.M.A.* 244:2547-2549, *1980.*
10. Bisno, A. L., Griffin, J. P., Van Epps, K. A., et al., "Pneumonia and Hong Kong Influenza: A Prospective Study of the 1968-1969 Epidemic, " Am. J. Med. *Sci.* 261:251-263, 1971.
11. Boucher, D. W., Contreras, G., and Furesz, J., "Persistence of Influenza Serum Antibodies in Humans Following Immunization With a Bivalent A/Victoria and A/New Jersey Vaccine," Can. Med. *Assn. J.* 120:799-803, 1979.
12. Britten, S. **A.,** "Contributions of the Armed Forces Epidemiological Board to Military Progress," *Milit. Med.* 130:149-157, *1965.*
13. **Bureau of the** Census, "Consumer Income, " *Curr. Pop. Rpts.* series **P-60, No. 105** (Washington, D. C.: U.S. Department of Commerce, 1977).
14. _____, "Consumer Income, " *Curr. Pop. Rpts.* series P-60, No. 114 (Washington, D. C.: U.S. Department of Commerce, 1978).
15. _____, "Consumer Income, " *Curr. Pop. Rpts.* series **P-60, No. 118 (Washington, D. C.: U.S. Department of Commerce, March 1979).**
16. **Bush,** J. W., Chen, M. M., and Patrick, D. L., "Health Status Index in Cost Effectiveness: Analysis of a PKU Program, " in *Health Status Indexes: Proceedings of a* Conference, R. L. Berg (cd.) (Chicago: Hospital Research and Educational Trust, 1973).
17. California Medical Association, *California Relative Value Studies,* 5th cd., adopted by the California Medical Association Council, San Francisco, Calif., May 10, 1969.
18. Chen, M. M., Bush, J. W., and Patrick, D. L., "Social Indicators for Health Planning and Policy Analysis, " *Pol. Sci.* 6:71-89, 1975.
19. Chen, M. M., Bush, J. W., and Zaremba, J., "Effectiveness Measures, " in *Operations Research in Health Care—A Critical Analysis,* L. Shuman, R. Speas, and J. Young (eds.) (Baltimore: Johns Hopkins University Press, 1975).
20. Couch, R. B., Kasel, J. A., Cate, T. R., et al., "Influenza Research Center, " progress report (Houston, Tex.), contract No. 1 AI 92611, No. 1, National Institute for Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md., May 1, 1980.
21. Couch, R. B., Webster, R. G., Kasel, J. A., et al., "Efficacy of Purified Influenza Subunit Vaccines and Relation to the Major Antigenic Determinants on the Hemagglutinin Molecule, " *J. Infec. Dis.* 140:553-558, *1979.*
22. Delorme, L., and Middleton, P. J., "Influenza A Virus Associated With Acute Encephalopathy, ' *Am. J.* Dis. Child. 133:822-824, 1979.
23. Dolin, R., Wise, T. G., Mazur, M. H., et al., "Immunogenicity and Reactogenicity of Influenza A/New Jersey/76 Virus Vaccines in Normal Adults, " *J. Infec. Dis.* 136 (% uppl.):435-442, 1977.

'NOTE: References for appendix A, appendix C, and appendix D are listed separately at the end of each appendix.

24. Donikian, M. A., McKee, J., and Greene, L. C., "Challenge Versus Natural Infection As An Index of Protection After Influenza Immunization," *Develop, Biol. Standard.* 39:149-154, 1977.
25. Douglas, R. G., Bentley, D. W., Betts, R. F., et al., "Clinical Evaluation of Respiratory Viral and Bacterial Vaccines in Children and Adults," progress report (Rochester, N.Y.), contract No. N01-A1-22503, report No. DAB-VDP-05-123, National Institute for Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md., Jan. 21, 1980.
26. Dowdle, W. R., Centers for Disease Control, DHHS, Atlanta, Ga., personal communication (letter), Feb. 23, 1981.
27. Dowdle, W. R., Coleman, M. T., and Gregg, M, D., "Natural History of Influenza Type A in the United States, 1957-1972, " *Prog. Med. Vi.* 17:91-135, 1974.
28. Dowdle, W. R., Millar, J. D., Schonberger, L. B., et al., "Influenza Immunization Policies and Practices in Japan, " *J. Infec. Dis.* 141:258-264, 1980.
29. Dowdle, W. R., Mostow, S. R., Coleman, M. T., et al., "Inactivated Influenza Vaccines, 2. Laboratory Indices of Protection, " *Post. Med. J.* 49:159-163, *1973.*
30. EastWood, L. M., Jennings, R., Milner, R. D. G., and Potter, C. W., "Reactogenicity and Immunogenicity of a Surface-Antigen-Absorbed Influenza Virus Vaccine in Children," *J. Clin. Path.* 32:534-537, 1979.
31. Egerer, R. M., Blichfeldt, E. D., Wentworth, B. B., and Wilcox, K. R., "Impact of Swine Influenza Vaccine on Serum Antibody, " *Am. J. Epidem.* 109:81-87, 1979.
32. Eknoyan, G. and Dillamn, R. O., "Renal Complications of Infectious Diseases," *Med. Clin. N, Am.* 52:979-1003, 1978.
33, Ennis, F. A., "Production and Distribution of Vaccine Following Emergence of A New Viral Strain," in *Influenza: Virus, Vaccines, and* Strategy, P, Selby (cd.) (London and New York: Academic Press, 1976).
34. Federal Reserve System (Board of Governors), *Banking and Monetary Statistics 1941-1970* (Washington, D. C.: Board of Governors of the Federal Reserve System, September 1976).
35. Fenner, F., "The Pathogenesis and Frequency of Viral Infections of Man, " *Pharmac. Ther.* 4:57-80, 1979.
36. Ferry, B. J., Evered, M. G., and Morrison, E. I., "Different Protection Rates in Various Groups of Volunteers Given Subunit Influenza Virus Vaccine in 1976, " *J. Infec. Dis.* 139:237-241, 1979.
37. Fisher, C. R., "Difference by Age Groups in Health Care Spending," *Hlth. Fin. Rev.* 2:65-90, spring 1980.
38. Fitzpatrick, G., Neutra, R., and Gilbert, J. P., "Cost-Effectiveness of Cholecystectomy for Silent Gallstones," in *Costs, Risks, and Benefits of Surgery*, J. Bunker, B. Barnes, and F. Mosteller (eds.) (New York: Oxford University Press, 1977).
39. Fuchs, V. R., "Health Care and the United States Economic System: An Essay in Abnormal Physiology, " *Milbank Mere, Fund Qtrly.* 1(2):211-237, April 1972.
40. Ganz, P. A., Shanley, J. D., and Cherry, J. D., "Responses of Patients With Neoplastic Diseases to Influenza Virus Vaccine, " *Cancer* 42:2244-2247, 1978.
41. Gaus, C. R., Cooper, B. S., and Hirshman, C. G., "Contrasts in HMO and Fee-For-Service Performance, " Soc. Sec. *Bull.* 39:3-14, May 1976.
42. Gibson, R., "National Health Expenditures, 1979, " *Hlth.* Care Fin, *Rev.* 2:1-36, summer 1980.
43. Glezen, W. P., Paredes, A., and Taber, L. H., "Influenza in Children, " *J. A.M.A. 243: 1345-1349, 1980.*
44. Gross, P. A., "Reactogenicity and Immunogenicity of Bivalent Influenza Vaccine in One- and Two-Dose Trials in Children: A Summary, " *J. Infec. Dis.* 136(suppl.):616-625, 1977.
45. Gross, W. L., Raverns, K. G., and Hansen, H. W., "Meningoencephalitic Syndrome Following Influenza Vaccination," *J. Neurol.* 217:219-222, *1978.*
46. Herron, A., Dettleff, G., Hixon, B., et al., "Influenza Vaccination in Patients With Rheumatic Disease," *J. A.M.A.* 242:53-56, 1979.
47. Hoffman, P. C., and Dixon, R. E., "Control of Influenza in the Hospital," *Ann, Int. Med.* 87:725-728, *1977.*
48. Horowitz, L., "Urticaria Subsequent to Administration of Influenza Vaccine, " *South.* Med. *J.* 72:1334-1335, 1979.
49. Hoskins, T. W., Davies, J. R., Smith, A. J., et al., "Assessment of Inactivated Influenza-A Vaccine After Three Outbreaks of Influenza A at Christ's Hospital, " *Lancet* 1(8106):33-35, Jan. 6, 1979.
50. Howells, C. H. L., Vesselnova-Jenkins, C. K., Evans, A. D., et al., "Influenza Vaccination and Mortality From Bronchopneumonia in the Elderly," *Lancet* 1(7903):381-383, Feb. 15, 1975.

51. Jennings, R., Clark, A., Oxford, J. S., et al., "Reactogenicity and Immunogenicity of Whole and Ether-Tween-Split Influenza A Virus Vaccines in Volunteers," *J. Infec. Dis.* 138:577-586, *1978.*
52. Jordan, W. S., Denny, F. W., Badger, G. F., et al., "A Study of Illness in a Group of Cleveland Families, XVII. The Occurrence of Asian Influenza," *Am. J. Hyg.* 68:190-212, *1958.*
53. Kaplan, M. M., and Webster, R. G., "The Epidemiology of Influenza," *Sci. Am, 237: 88-106, 1977.*
54. Kaplan, R. M., Bush, J. W., and Berry, C. C., "Health Status: Type of Validity and the Index of Well-Being," *Health Serv. Res.* 4:478-507, 1976.
55. Kavet, J., "Influenza and Public Policy," doctoral thesis submitted to the Harvard School of Public Health, Boston, Mass., Apr. 17, 1972.
56. _____, "A Perspective on the Significance of Pandemic Influenza," *Am. J. Public Health* 67:1063-1070, *1977.*
57. _____, "Vaccine Utilization: Trends in the Implementation of Public Policy in the U. S.A.," in *Influenza: Virus, Vaccines, Strategy,* P. Selby (cd.) (New York: Academic Press, 1976).
58. Keane, W. R., Helderman, J. H., Luby, J., et al., "Epidemic Renal Transplant Rejection Associated with Influenza A Victoria," *Proc. Dialysis Transpl. Forum* 8:232-235, 1978.
59. Kendal, A. P., Joseph, J. M., Kobayashi, G., et al., "Laboratory-Based Surveillance of Influenza Virus in the United States During the Winter of 1977-78," *Am. J. Epidem.* 110: 449-461, 1979.
60. Knight, V., Couch, R. B., Douglas, R. G., et al., "Serological Responses and Results of Natural Infectious Challenge of Recipients of Zonal Ultracentrifuged Influenza A2/Aichi/2/68 Vaccine," *Bull. W.H.O.* 45:767-811, 1971.
61. LaMontagne, J. R., *Summary of a Workshop on Influenza B Viruses and Reye's Syndrome,* National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md., July 30-31, 1979.
62. Laraya-Cuasay, L. R., DeForest, A., Huff, D., et al., "Chronic Pulmonary Complications of Early Influenza Virus Infection in Children," *Am. Rev. Resp. Dis.* 116:617-625, 1977.
63. Lournis, D. B., Blumenfeld, H. L., Ellis, J. T., et al., "Studies on Influenza in the Pandemic of 1957-1958, II. Pulmonary Complications of Influenza," *J. Clin. Invest.* 38:213-265, 1958.
64. Marine, W. M., "General Discussion I,"). *Infec. Dis.* 136(suppl.): *555-562, 1977.*
65. Marine, W. M., and Stuart-Harris, C., "Reactions and Serologic Responses in Young Children and Infants After Administration of Inactivated Monovalent Influenza A Vaccine," *J. Pediat.* 88:26-30, *1976.*
66. Marks, J. S., and Halpin, T. J., "Guillain-Barré Syndrome in Recipients of A/New Jersey Influenza Vaccine," *J. A.M.A.* 243:2490-2494, *1980.*
67. Masurel, N., and Andre, F. E., "Antibody Response Against Current H1N1 Influenza Virus After Vaccination With Last Season's Trivalent Vaccine," *Lancet* 1:144-145, *1978.*
68. McMillen, M. A., Cerra, F. B., Balish, T., et al., "Swine Influenza Vaccination in a Dialysis and Transplant Population," *J. Dialysis* 2:507-522, *1978.*
69. Meibalane, R., Sedmak, G. V., Sasidharan, et al., "Outbreak of Influenza in a Neonatal Intensive Care Unit," *J. Pediat.* 91:974-976, *1977.*
70. Meiklejohn, G., Eickhoof, T. C., Graves, P., et al., "Antigenic Drift and Efficacy of Influenza Virus Vaccines, *1976-1977,* " *J. Infec. Dis.* 138:618-624, *1978.*
71. Meyer, H. M., Hopps, H. E., Parkman, P. D., et al., "Review of Existing Vaccines for Influenza," *Am. J. Clin. Pathol.* 70:146-152, *1978.*
72. Molteni, R. A., "Group A B-Hemoytic Streptococcal Pneumonia, " *Am. J. Dis. Child.* 131:1366-1371, 1977.
73. Monto, A. S., Davenport, F. M., Napier, J. A., et al., "Effect of Vaccination of a School-Age Population Upon the Course of an A2/Hong Kong Influenza Epidemic, " *Bull. W.H.O.* 41:537-542, *1969.*
74. _____, "Modification of an Outbreak of Influenza in Tecumseh, Michigan by Vaccination of Schoolchildren," *J. Infec. Dis.* 122:6-25, *1970.*
75. Mostow, S. R., "Current Perspectives of Influenza," *Cleveland Clin. Qtrly.* 42:63-69, *1975.*
76. Muller, C. and Otelsburg, J., "Carrier Discretionary Practices and Physician Payment Under Medicare Part B," *Med. Care* 17:650-666, 1979.
77. Murray, D. L., Imagawa, D. T., Okada, D. M., et al., "Antibody Response to Monovalent A/New Jersey/8/76 Influenza Vaccine in Pregnant Women," *J. Clin. Micr.* 10:184-187, 1979.
78. National Center for Health Statistics, *Heart Conditions and High Blood Pressure: United States, July 1957-June 2958* (Washington, D. C.: DHEW, February 1960).
79. _____ *Out-of-Pocket Cost and Acquisition of Prescribed Medicine, United States 1973,* DHEW pub. No. HRA 77-1542 (Hyattsville, Md.: DHEW, June 1978).
80. _____, Prevalence *of* Chronic Circulatory

Conditions: United States, 1972 **(Washington, D. C.: NCHS, 1975).**

81. _____ *Prevalence of Chronic Respiratory Conditions: United States, 1970* **(Washington, D. C.: NCHS, 1973).**

82. **National Institute of Allergy and Infectious Diseases,** "Amantadine: Does it Have a Role in the Prevention and Treatment of Influenza?" transcript of proceedings of an NIH Consensus Development Conference (Bethesda, Md.: National Institutes of Health, Oct. 15, 1979).

83. National Office of Vital Statistics, *Vital Statistics of the United States, 1955,* vol. 1, table L (Washington, D. C.: DHEW, 1957).

84. _____, *Vital Statistics of the United States, 1955,* (suppl.) table 6 (Washington, D. C.: DHEW, *1965).*

85. Noble, G., Corey, L., Hoke, C. H., et al., "An Open Field Trial of Live Attenuated Influenza A/England/42/72 Vaccine, " *Society for Epidemiologic Research: Abstracts,* pp. **466-467.**

86. Office of Technology Assessment, U.S. Congress, *A Review* of *Selected Federal Vaccine and Immunization Policies,* GPO stock No. 052-003-00701-1 (Washington, D. C.: U.S. Government Printing Office, September 1979).

87. _____, *Assessing the Efficacy and Safety of Medical Technologies,* GPO stock No. *052-003-00832-1* (Washington, D. C.: U.S. Government Printing office, September 1978).

88. _____ *Compensation for Vaccine-Related Injuries,* GPO stock No. *052-003-00788-6* (Washington, D. C.: U.S. Government Printing Office, November 1980).

89. _____, *The Implications of Cost-Effectiveness Analysis of Medical Technology/Background Paper No. 1: Methodological Issues and Literature Review,* GPO stock No. 052-003-00780-1 (Washington, D. C.: U.S. Government Printing Office, September 1980).

90. Opinion Research Corp., *A Study of the Impact of the 1978-79 National Influenza Immunization Program on Specific Physician Groups, Final Report,* conducted for the Bureau of Health Education, Centers for Disease Control, by Opinion Research Corp., Princeton, N. J., HEW contract No, 200-79-0932, November 1979.

91. Ortbals, D. W., and Lienhaber, H., "Comparison of Immunogenicity of a Whole Viron and a Subunit Influenza Vaccine in Adults," *J. Clin. Micr.* 8:431-434, *1978.*

92. Ortbals. D. W., Liebhaber. H.. Presant. C. A.. et al., "Influenza Immunization of Adult Patients With Malignant Diseases, " *Ann. Int. Med.* 87:552-557, *1977.*

93. **Osardoo,** E. O., Berlin, B. S., Popli, S., et al., "Antibody Responses to Influenza Vaccination in Patients With Chronic Renal Failure, " *Kidney Int.* 14:614-618, *1978.*

94. Paisley, J. W., Bruhn, F. W., Lauer, B. A., et al., "Type A2 Influenza Viral Infections in Children," *Am. J. Dis. Child.* 132:34-36, *1978.*

95. Parkman, P. D., Hopps, H. E., Rastogi, S. C., et al., "Summary of Clinical Trials of Influenza Virus Vaccine in Adults," *J. Infec. Dis. 136* (suppl):722-730, *1977.*

96. Perry, H. D., Mallen, F. J., Grodin, R. W., et al., "Reversible Blindness in Optic Neuritis Associated With Influenza Vaccination, " *Ann. Ophtham.* 11(3) :545-550, 1979.

97. Public Health Service, *Briefing and Discussion on Influenza A/U. S. S. R./1977 (H1N1), December 22, 2978* (Washington, D. C.: DHEW, Jan. **5, 1978).**

98. _____, *Conference on Influenza A/U. S. S. R./ 1977 (H1N1), January 30, 1978,* summary report (Washington, D. C.: DHEW, Feb. 14, 1978).

99. _____, *Influenza Virus Vaccine Workshop, January 12, 1978,* summary report and conclusions (Washington, D. C.: DHEW, Jan. **20, 1978).**

100. _____, *Secretary's Conference on Influenza, July 26, 1978,* summary report (Washington, D. C.: DHEW, Aug. **7, 1978).**

101. _____ *Secretary's Conference on Influenza,* summa'ry report (Washington, D. C.: DHEW, Mar. *6, 1979).*

102. _____ *Summary Report of Conference on Influenza' Vaccine Activity for 1977-78* (Washington, D. C.: DHEW, Mar. 21, 1977).

103. _____ *Surgeon General's Meeting on Influenza, February 12, 2979,* summary report (Washington, D. C.: DHEW, Feb. 23, 1978).

104. _____ *Surgeon General's Meeting on Influenza Immunization, January* **22, 1980,** summary report (Washington, D. C.: DHEW, March 1980).

105. Pyhala, R., "Protection by a Polyvalent Influenza Vaccine and Persistence of Homologous and Heterologous HI Antibodies During a Period of Two Epidemic Seasons, " *J. Hyg. Carob.* 84:237-245, 1980.

106. Reismann, J. L., and Singh, B., "Conversion Reactions Simulating Guillain-Barrē Paralysis Fol-

lowing Suspension of the Swine Flu Vaccination Program in the U. S.A.," *Aust. & N.Z.J. Psych.* 12:127-132, 1978.

107. Retaillaiu, H. F., Curtis, A. C., Starr, G., et al., "Illness After Influenza Vaccination Reported Through a Nationwide Surveillance System, 1976-77," *Am. J. Epidem.* 111:270-278, 1980.
108. Richardson, W. C., et al., "The Seattle Prepaid Health Care Project: Comparison of Health Services Delivery" (Seattle: School of Public Health and Community Medicine, University of Washington, January 1977).
109. Ristow, S. C., Douglas, R. G., and Condemi, J. J., "Influenza Vaccination of Patients With Systemic Lupus Erythematosus," *Ann. Int. Med.* 88:786-789, *1978.*
110. Schild, R. A., Luedke, D. N., Kasai, G., et al., "Antibody Response to Influenza Immunization in Adult Patients With Malignant Disease," *Cancer* 44:1629-1635, *1979.*
111, Schoenberg, B. S., "Epidemiology of Guillain-Barre Syndrome," *Adv. Neurol.* 19:249-260, 1978.
112. Schoenberger, L. B., Bregman, D. J., Sullivan-Bolyai, J. Z., et al., "Guillain-Barré Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-77," *Amer. J. Epidem.* 110:105-123, *1979.*
113. *Serie, C.*, Barme, M., Hannoun, C., et al., "Effects of Vaccination on an Influenza Epidemic in a Geriatric Hospital," presented at the International Symposium on Influenza Immunization (II), *Develop. Biol. Standard* 39:317-321, *1977.*
114. Shepard, D. S., and Zeckhauser, R. J., "The Choice of Health Policies With Heterogeneous Populations," in *Economic Aspects of Health,* V. R. Fuchs (cd.) (Chicago: University of Chicago Press, forthcoming).
115, Silver, H. G., and Weinerman, B. H., "Impaired Serum Antibody Response to Inactivated Influenza **A and B Vaccine** in Cancer Patients," Can. *Med. J.* 119:733-738, *1978.*
116. Smith, J. W. G., "Vaccination Strategy," in *Influenza: Virus, Vaccines, Strategy,* P. Selby (cd.) (New York: Academic Press, 1976).
117. Sparks, J. P., "Influenza Vaccination Policy" (letter), *Lancet* 1(8111):317, Feb. 10, 1979.
118. Stiver, H. G., Graves, P., Eickhoff, T. C., et al., "Efficacy of Hong Kong Vaccine in Preventing 'England' Variant Influenza A in 1972," *N. Eng. J. Med.* 289:1267-1271, *1973.*
119. Sullivan, R. J., Dowdle, W. R., Marine, W. M., et al., "Adult Pneumonia in a General Hospital," *Arch, Int. Med.* 129:935-942, *1972.*
120. Sumaya, C. V., and Gibbs, R. S., "Immunization of Pregnant Women With Influenza A/New Jersey/76 Virus Vaccine: Reactogenicity and Immunogenicity in Mother and Infant," *J. Infec. Dis.* 140:141-146, *1979.*
121. Tecson, F., and Bornstein, B., "Influenza Vaccination and Lupus Erythematosus" (letter), *Ann. Int. Med.* 89:574, *1978.*
122. Tolsma, D. D., and Millar, J. D., "Costs and Accomplishment of the United States National Influenza Immunization Program, 1976," presented at the Eighth International Scientific Meeting of the International Epidemiologic Association Symposium on Epidemiologic Aspects of Cost-Effectiveness Studies, San Juan, Puerto Rico, Sept. 19, 1977.
123. *U.S. Immunization Survey, 1979,* vol. I, prepared by Opinion Research Corp. for Bureau of Health Education, Centers for Disease Control, Atlanta, Ga., August 1979.
124. *U.S. Immunization Survey,* Centers for Disease Control, based on data from Bureau of the Census (Washington, D. C.: DHEW, 1971, 1972, 1973, 1974, 1975, 1976, 1977, 1978).
125. Weinstein, M. C., "Estrogen Use in Postmenopausal Women—Costs, Risks, and Benefits," *N. Eng. J. Med.* 303:308-316, *1980.*
126. Weinstein, M. C., and Stason, W. B., *Hypertension: A Policy Perspective* (Cambridge, Mass.: Harvard University Press, 1976).
127. Zeckhauser, R., and Shepard, D., "Where Now for Saving Lives?" *Law & Contemp. Prob.* 40(4):11, *1976.*

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