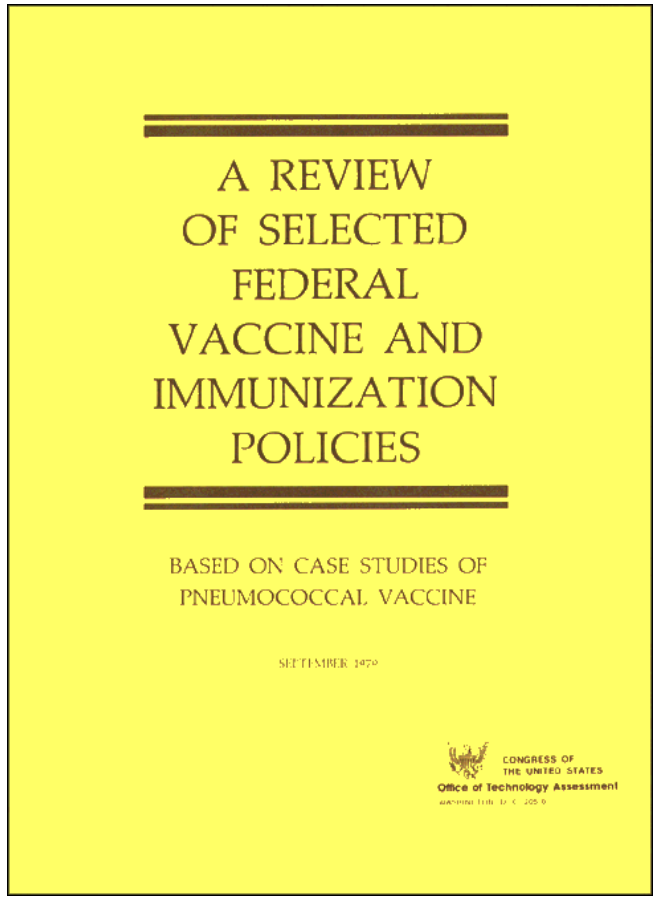
A Review of Selected Federal Vaccine and Immunization Policies, Based on Case Studies of Pneumococcal Vaccine

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FOREWORD

This work originated in April 1978 as a background study in OTA'S Congressional Fellowship Program. The study initially was limited to an analysis of the benefits and costs of pneumococcal vaccine, with particular emphasis on vaccine reimbursement under Medicare for the elderly. As a result of encouragement by several reviewers, the scope of investigation was broadened substantially to include three other areas of vaccine policy concerns: research, development, and production; safety and efficacy; and 1iability. Cost-effectiveness analysis was selected to assess benefits and costs, and the entire report was incorporated into a larger OTA study entitled *Cost-Effectiveness of* Medical Technologies. This report is the first of six documents to be published as a part of the larger cost-effectiveness study.

A Review of Selected Federal Vaccine and Immunnization Policies was prepared by OTA staff in consultation with several authorities in the relevant subject areas. The authors' professional backgrounds include training in pubic health, pharmacy, economics, law, medicine, public administration, public policy, and political science. Consultants included representatives from pharmaceutical companies, including Eli Lilly and Company, Merck Sharp and Dohme, and Lederle Laboratories; Government agencies, including the Bureau of Biologics (BOB), Center for Disease Control (CDC), National Institute of Allergy and Infectious Diseases (NIAID), National Center for Health Statistics (NCHS), and Bureau of the Census; and academic institutions, in particular, Duke University, Harvard University, the University of Pennsylvania, and the University of California at San Francisco.

Drafts of the report were reviewed by members of two OTA advisory bodies: the Health Program Advisory Committee and the Cost-Effectiveness of Medical Technologies Advisory Panel. Various drafts also were reviewed by approximately so other individuals representing a wide range of professional disciplines. We were grateful for these many contributions to the work.



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GLOSSARY OF TERMS

Active immunity: Protection against a disease resulting from the production of antibodies in a host (i.e., person or animal) that has been inoculated with an antigen.

Ambulatory medical care: Medical goods and services rendered outside of a hospital or other inpatient health care facility, including such items as physician office visits, outpatient laboratory diagnostic services, and outpatient prescription drugs.

Anaphylaxis: An unusual or exaggerated allergic reaction that often involves breathing difficulties and irregular heart beats, and sometimes causes death.

Antibiotic: A specific type of chemical substance that can be administered to fight infections in humans or animals. Most antibiotics are produced from micro-organisms; some can be produced synthetically. Examples of commonly used antibiotics are penicillin and tetracycline.

Antibody: A specific type of protein produced in humans or animals that combines with—and thereby diminishes or prevents harmful effects caused by—a specific antigen.

Antibody titer: The quantity, usually measured in the blood, of a specific type of antibody present in a host (i. e., person or animal). A certain antibody titer is needed to protect the host against a specific antigen.

Antigen: A specific type of substance, usually a protein or carbohydrate, that when introduced into the body of a human or animal stimulates the production of specific types of antibodies. Some antigens are made from particular micro-organisms and are used to produce active immunity against the disease(s) that these micro-organisms produce (e.g., an antigen made from measles virus is used to produce active immunity against measles).

Antigenicity: Potency as an antigen.

Antiserum: Blood serum containing antibodies from animals that have been inoculated with bacteria or their toxins. When administered to other animals or humans, antiserum produces passive immunity.

Antitoxin: A specific type of protein that neutralizes a specific toxin; a serum containing antitoxins.

Asplenia: Absence of the spleen, usually because of surgical removal.

Attenuated: Rendered less virulent; a term used to describe micro-organisms that have been altered so that they can be used to stimulate antibody production without producing disease.

Attributable risk: The arithmetic or absolute difference in incidence rates (e.g., of a disease) between two groups of subjects, usually an experimental (or exposed) group and a control (or unexposed) group.

Bacteremia: The presence of bacteria (e.g., pneumococci) in the circulating blood stream, an indication of severe bacterial infection.

Biologics (biological products): Medicinal preparations made from living organisms and their products. Examples include serums, vaccines, toxoids, and antitoxins.

Controlled clinical trial: An experimental method often used to evaluate the safety and efficacy of an experimental medical intervention. In a controlled clinical trial, human or animal subjects are assigned in accordance with predetermined rules either 1) to an experimental group (in which subjects receive the experimental intervention), or 2) to a control group (in which subjects do not receive the experimental intervention, but usually receive a placebo or a standard intervention instead). If the predetermined rules specify that the subjects are assigned to groups randomly, the result is a randomized controlled clinical trial.

Cost-effectiveness ratio: A ratio that expresses the cost (usually in dollars) associated with obtaining one unit of a measurable effect (e. g., a year of healthy life).

Discount rate: A factor used in economic analysis to reduce to present value costs and effects that occur in future years. Discounting is based on two premises: 1) individuals prefer to receive benefits today rather than in the future, and 2) resources invested today in alternative programs could earn a rate of return over time.

Duty to warn: A legal duty, based on theories of strict liability (see below), that requires a manufacturer to provide appropriate warning to the users of its "unavoidably dangerous" products (e. g., dynamite, Pasteur rabies vaccine) about the inherent, foreseeable risks associated with use of these products. In recent court cases involving injury produced by nondefective and properly administered vaccines, courts have held the vaccine manufacturer liable for failure to discharge its duty to warn the plaintiff (an injured vaccinee) about the inherent, though statistically remote, risks of vaccination.

Effectiveness: Same as efficacy (see below) except that it refers to ". . . average conditions of use. "

Efficacy: The probability of benefit to individuals in a defined population from a medical technology

applied for a given medical problem under ideal conditions of use.

Epidemiology: The study of the frequency, distribution, and determinants of; morbidity and mortality from; and the impact of interventions on diseases and disabilities in defined populations.

Guillain-Barre Syndrome (GBS): A neurological disorder of unknown etiology which is characterized by paralysis that begins in the legs and later involves the trunk of the body, arms, and neck. GBS has been observed rarely to follow certain types of vaccinations, most notably, swine flu. It is a transient condition in about 90 percent of those afflicted, leaves residual paralysis in about 5 to 10 percent, and is fatal in about 5 percent.

Herd immunity: The resistance of a group or population, based on the immunity of a high proportion of individual members of the group, to invasion and spread of an infectious agent.

High-risk group or population: A group comprised of persons who are more likely than those in the general population to contract or die from a certain medical problem (e. g., pneumococcal pneumonia), either because 1) they possess certain conditions (e.g., chronic lung disease), or 2) they have been exposed to the agent that causes the medical problem (e.g., pneumococci).

Immunity: See ***actiue immunity,*** *passive immunity,*

Immunization: See *vaccination.*

Immunogenicity: Relative ability to produce immunity.

Incidence rate: The rate at which new cases of a disease occur in a defined population over a defined period of time,

Isolate: A population of living micro-organisms that have been isolated from a sample of body fluid or tissue, e.g., blood, sputum.

Medical technology: The drugs, devices, and medical and surgical procedures used in medical care, and the organizational and supportive systems within which such care is provided.

Micro-organisms: Microscopic plants or animals, e.g., bacteria, fungi, molds, viruses.

Morbidity: Illness, injury, impairment, or disability.

Morbidity rate: The rate at which morbidity occurs, a term often used in epidemiologic studies in which the rate of disability or impairment resulting from a certain disease or injury is calculated for a defined population.

Mortality: Death.

Mortality rate: The rate at which mortality occurs; a term often used in epidemiologic studies in which the rate of death resulting from a certain disease or injury is calculated for a defined population.

Passive immunity: Protection against a disease derived from the injection of antibodies produced by another host (i. e., person or animal).

Pneumococcal pneumonia: Pneumonia caused by pneumococci.

Pneumococcus *(Streptococcus pneumonia):* A form of bacterium belonging to the streptococcal family. There are 83 known serotypes of pneumococci.

Pneumonia: A disease of the lungs characterized by inflammation and consolidation, which is usually caused by infection or irritation.

Polysaccharides, capsular pneumococcal: The complex sugars which make up the capsule that surrounds a pneumococcus bacterium. The composition, hence antigenicity, of capsular polysaccharides varies with each of the 83 serotypes of pneumococci.

Prevalence rate: The number of people in a defined population who have a disease at a given point in time.

Quality-adjusted life year (QALY): One year of life adjusted for various types and degrees of disability to yield one year of healthy life. QALYs are sometimes used to measure in common terms the effects on morbidity and mortality of health care interventions or programs.

Risk: The probability (among a defined population or for an individual) of occurrence of an untoward outcome (e. g., GBS) resulting from use of a particular medical technology (e. g., swine flu vaccine) when applied for a given medical problem under specified conditions of use.

Safety: A judgment of the acceptability of risk in a specified situation.

Serology: The study of antigen-antibody reactions in the test tube.

Serotype: A specific type, as determined by the kinds and combinations of antigenic components present in the cell, of a particular micro-organism (e. g., Type 3 pneumococcus).

Serum: See antiserum.

Sickle-cell anemia: A hereditary, genetically determined hemolytic anemia, which is characterized by joint pain, arthritis, acute attacks of abdominal pain, ulcerations of the lower extremities, and sickle-shaped red blood cells; and which occurs almost exclusivelyin Negroes.

Strict liability: A theory of legal liability that can be used to hold a manufacturer legally responsible for harm produced by one of its products that is unavoidably unsafe, no matter what precautions are taken (e.g., dynamite, the Pasteur rabies vaccine). Strict liability may attach even in the absence of wrongful intent or negligence on the part of the manufacturer, In cases involving socially useful, but dangerous products, some courts have ruled that liabilit$_y$ for unavoidable injury does not attach if a product which produces an injury was accompanied by appropriate warnings to the user re-

garding the product's inherent risks. (See duty to *warn.)*

Toxin: A protein substance, produced in some cases by disease-producing micro-organisms, which is highly toxic for other living organisms. Some toxins are antigenic.

Toxoid: A toxin that has been modified to reduce or eliminate its toxicity, but to retain its antigenicity. Solutions or suspensions of toxoids are administered to produce active immunity.

Vaccine: A preparation that contains live, attenuated, or killed micro-organisms for their antigenic components. Upon being administered, a vaccine can stimulate antibody formation and produce active immunity.

Vaccination: The process of administering a vaccine; a term often used interchangeably with the word immunization, although vaccination does not always confer immunity.

GLOSSARY OF ACRONYMS

ACIP – Advisory Committee on Immunization Practices
AHA – American Hospital Association
ASTHO – Association of State and Territorial Health Officials
BC – Blue Cross
BCA – benefit-cost analysis
BOB – Bureau of Biologics (FDA)
BOD – Bureau of Drugs (FDA)
BS – Blue Shield
CDC – Center for Disease Control (HEW)
CEA – cost-effectiveness analysis
CFR – Code of Federal Regulations
CHAP – Child Health Assessment Program
CMA – California Medical Association
CM – Consumer Price Index
DHEW – Department of Health, Education, and Welfare
DOD – Department of Defense
DPT – diphtheria, pertussis, and tetanus toxoids
DVS – Division of Vital Statistics, (NCHS)
EPSDT – Early and Periodic Screening, Diagnosis, and Treatment (Program)
FDA – Food and Drug Administration (HEW)
FR – Federal Register
GAO – U.S. General Accounting Office
GBS – Guillain-Barre Syndrome
HCFA – Health Care Financing Administration (HEW)
HCIFC – House Committee on Interstate and Foreign Commerce (U. S. Congress);
HDS – Hospital Discharge Survey (NCHS)
HEW – Department of Health, Education, and Welfare
HIP – Health Insurance Plan of Greater New York
HIS – Health Interview Survey (NCHS)
HMO – Health Maintenance Organization
HPRS – Health Program Reporting System (ASTHO)
HSA – Health System Agencies
IBNP – incurred-but-not-reported (claim)
IND – investigational new drug application
ISO – Insurance Services Office
LRTI – lower respiratory tract infection
MMWR – Morbidity and Mortality Weekly Report
MSD – Merck Sharp and Dohme
NAMCS – National Ambulatory Medical Care Survey (NCHS)
NCHCT – National Center for Health Care Technology (HEW)
NCHS – National Center for Health Statistics (HEW)
NCHSR – National Center for Health Services Research (HEW)
NDA – new drug application
NIAID – National Institute of Allergy and Infectious Diseases (NIH)
NIH – National Institutes of Health (HEW)
NNHS – National Nursing Home Survey (NCHS)
OASDHI – Old-Age, Survivors, Disability and Health Insurance Program (SSA)
OMB – Office of Management and Budget
ORC – Opinion Research Corporation
OTA – Office of Technology Assessment (U.S. Congress)
PHS – Public Health Service (HEW)
PKU – Phenylketonuria
PMA – Pharmaceutical Manufacturers Association
PMS – postrnarketing surveillance
PPB – planning, program, and budgeting
PP1 – patient package insert
PSRO – Professional Standards Review Organization
QALY – quality-adjusted life year
RMSF – Rocky Mountain Spotted Fever
SSA – Social Security Administration
USE – United States Code
VA – Veterans Administration
VDC – Vaccine Development Committee (NIAID)

SUMMARY

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SUMMARY

INTRODUCTION

The Federal Government is the single most important determinant of this Nation's commitment to vaccine research, development, and use. Since 1902, Congress has enacted laws and Federal agencies have established regulations designed to ensure the availability of safe and effective vaccines. Public moneys have been used to support vaccine development and to purchase vaccines for public immunization programs.

For a number of reasons, various authorities have called for an assessment of the effects of Federal policies and regulations on the development, evaluation, supply, and use of vaccines in this country. [1] First, during the past 10 years, the number of vaccine manufacturers and licensed vaccine products has declined markedly. Some authorities fear that this decline may portend a decline in the commitment or capacity of the U.S. pharmaceutical industry to develop and supply vaccines needed to protect the American public.

Second, there are longstanding debates over both the adequacy of the procedures used by the Federal Government to help ensure vaccine safety and efficacy and the impact of Federal safety and efficacy regulations on the willingness of vaccine manufacturers to develop new products. Some industry representatives argue that Federal safety and efficacy requirements go beyond what is necessary to protect the public and add needlessly to manufacturers' production costs. Some, particularly consumer representatives, however, counter that to ensure the safety and efficacy of vaccine products in general use, the Federal Government should evaluate such products more comprehensively.

Third, in recent years, Government efforts to allocate limited public health resources more efficiently have intensified. Some attempts have been made, for example, to incorporate formal cost-effectiveness analysis (CEA) into the health program decisionmaking process regarding funding. The usefulness of this analytical tool as an aid in deciding how to allocate Federal health resources, however, remains a matter of speculation and considerable controversy.

Finally, in light of recent court cases broadening vaccine manufacturers' liability, there exists a great deal of uncertainty as to whom the courts will hold liable for rare serious injuries resulting from nondefective and properly administered vaccines. This uncertainty appears to be undermining congressional and vaccine manufacturers' support for large-scale public vaccination programs. Widespread publicity of the potential, though

[1] In March 1977, for example, the Department of Health, Education, and Welfare (HEW) published *Reports and Recommendations of the National Immunization Work Groups* (U.S. Ex. Br., DHEW, 1977). In this document, a number of problems related to vaccine development and use were delineated. Also presented were a number of alternatives to the Federal Government's existing vaccine policies. An HEW report to Congress made more recently, *Liability Arising Out of Immunization Programs* (U. S. Ex. Br., DHEW, 1978), focused on vaccine liability issues.

[2] In 1978, for example, Congress refused to fund a Russian flu immunization program as large as the one proposed by the Department of Health, Education, and Welfare (HEW).

statistically remote, dangers associated with nondefective vaccines may be eroding overall public confidence in the safety of vaccine products.

Problems, issues, and policy options in four areas of Federal vaccine-related policies are discussed below: 1) vaccine research, development, and production; 2) vaccine safety and efficacy; 3) cost-effectiveness of vaccination and implications for reimbursement; and 4) liability and compensation for vaccine-related injuries.

VACCINE RESEARCH, DEVELOPMENT, AND PRODUCTION

Federal vaccine policies in the civilian sector are established by at least three agencies within the Department of Health, Education, and Welfare (HEW): the National Institute of Allergy and Infectious Diseases (NIAID), the Bureau of Biologics (BOB), and the Center for Disease Control (CDC). (See figure 1.) These three agencies collaborate infor-

Figure 1.—Federal Establishments With Vaccine-Related Responsibilities

Two departments within the Federal Government have responsibilities related to vaccine research and development. The Department of Health, Education, and Welfare (HEW) facilitates the development and use of vaccines for civilian populations, and the Department of Defense (DOD) develops vaccines against pathogens that pose particular health hazards for military populations.[1] No Federal agency engages in vaccine production for commercial use.

Three agencies at HEW fund or supervise activities related to vaccines: 1) the National Institute of Allergy and Infectious Diseases (NIAID), 2) the Bureau of Biologics (BOB), and 3) the Center for Disease Control (CDC). For the most part, these executive branch agencies interact only on an informal basis in specific instances, when, for example, their respective jurisdictional responsibilities or scientific investigations overlap. There is no official mechanism for these agencies to coordinate their policies or activities. Hence, it is difficult for any one agency to assess the impact of its actions on either the action of other agencies or on the behavior of vaccine manufacturers.

The National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), Public Health Service, funds vaccine research and development programs. Mostly, NIAID funds basic research and epidemiologic research, in which investigators attempt to assess the incidence, prevalence, morbidity and mortality of a disease. Such NIAID-sponsored research is often conducted by investigators in academic or government institutions. For some vaccines, such as pneumococcal, NIAID funds clinical testing. In FY 1976, NIAID spent a total of $68 million on vaccine-related research. Of this amount, approximately $45 million was spent on basic research and $23 million on applied research (Jordan, 1977).

The Bureau of Biologics (BOB) of the Food and Drug Administration (FDA), Public Health Service, is responsible for ensuring the safety and efficacy of vaccine products to be used either in clinical trials or by the American public. In FY 1977, BOB spent a total of $7.5 million. About $2.1 million of this amount was spent on product-related research, and the remaining $5.4 million was used to finance BOB's regulatory and product control activities (Jordan, 1977).

The Center for Disease Control (CDC), Public Health Service, in Atlanta, Ga., has a number of vaccine-related responsibilities. In addition to surveying and reporting the incidence, prevalence, morbidity, and mortality rates associated with selected infectious diseases, CDC coordinates the distribution of Federal funds to State and local health departments participating in federally sponsored immunization programs. It also operates a voluntary adverse reaction reporting system through which it receives voluntarily submitted case reports concerning adverse reactions to vaccines. Such case reports are submitted by health professionals who administer vaccines in public immunization programs and by some vaccine manufacturers.

[1] In addition, executive branch departments other than HEW and DOD sometimes help work on specific problems associated with Federal vaccine programs. The Justice Department, for example, is working at present on liability cases associated with the 1976 swine flu program.

really when the need arises, but for the most part, they establish policies independently for their respective areas of responsibility.

The Federal Government shares with the pharmaceutical industry the responsibility for researching and developing new and improved vaccines. Most often, the Government either finances or conducts basic and epidemiologic research on vaccines and target diseases, while pharmaceutical companies concentrate mostly on product development and clinical testing.

The Federal Government is totally dependent on pharmaceutical manufacturers for production and supply of vaccines used in public immunization programs. This dependence has created concern among some vaccine authorities, particularly in Government, because during the past few decades, the number of American pharmaceutical companies producing vaccines has declined substantially.

During the past 12 years alone, the number of licensed vaccine manufacturers active in this country has dropped from 37 to 18, a 50-percent decrease. During the same period, the number of licensed vaccine products has plummeted from about 380 to about 150, a 60-percent decrease. Only eight American pharmaceutical companies actually produce vaccines, and these companies hold about 70 percent of the approximately 150 current vaccine product licenses.

The exact reasons for the decline in the number of commercial vaccine manufacturers are unknown, although a number of possible contributing factors can be identified. Relative to the markets for other prescription items, the $98 million **vaccine** market is small. This limited sales market may not support a large number of competitive producers. Further, low profits, high capital investment requirements, extensive Federal regulations, and unpredictable vaccine liability risks may be contributing to the decline in number of vaccine manufacturers.

So far, there has been no major production or supply problem with any commonly used vaccine in this country, but there are some indications that potential problems may arise. There are no active manufacturers, for example, of 11 of the 51 currently licensed types of vaccines, including Rocky Mountain Spotted Fever (RMSF) vaccine. Further, the United States is dependent on a single American pharmaceutical company for each of 19 vaccine products, including poliovirus vaccine. The supply of a vaccine with only one licensed manufacturer easily could be interrupted or terminated because of technical production problems or changes in a firm's marketing plans.

ISSUE A:
The extent and nature of Federal Government intervention needed to ensure sufficient levels of vaccine research, development, and production

Federal policies affect virtually every aspect of vaccine activity in the private sector. The collective short- and long-range effects of Federal Government policies on the behavior of vaccine manufacturers, however, is not known. Some Federal policies, such as those regarding financing of vaccine research and development, may stimulate vaccine manufacturers to develop and market new products. NIAID financing, for example, appears to have been a major factor in the development of pneumococcal vaccine. Other policies, such as the use of Federal standards for vaccine safety and efficacy, when combined with low profit margins and high liability risks, though, may discourage **vaccine** manufacturers. Further, the Federal Government purchases for public immunization programs approximately so percent of the doses of vaccines distributed in the United States.

For certain vaccines, therefore, Federal purchases determine both market size and selling price. Lastly, the Federal Government now contractually assumes legal responsibility for warning potential vaccine recipients in public immunization programs about the unavoidable risks of vaccinations. The legal and economic implications of the Federal Government's assumption of this responsibility are undetermined.

The Federal Government is committed to encouraging vaccine research, development, evaluation, and use. The absence of any formal mechanism for NIAID, BOB, and CDC to work in close collaboration, however, may contribute to a less than unified Federal effort to promote vaccine development and use. If Congress decides that available evidence regarding the decline in American pharmaceutical manufacturers commitment to vaccine research, development, and production warrants immediate action it could pursue at least one of three major options.

OPTION A-1:

Establish a permanent interagency body within HEW to:

- **Develop priorities for facilitating and coordinating vaccine research, development, and evaluation in the public sector;**
- **Monitor vaccine research, development, and production in the private sector; and**
- **Report to Congress periodically.**

Such a body could be composed of representatives from the Government establishments primarily responsible for vaccine research, development, evaluation, purchase, distribution, and promotion. Consumers and representatives from the vaccine research communities in academe and the pharmaceutical industry also could be included.

If given adequate resources and authority, an interagency body could help to establish comprehensive and unified Government policies regarding the allocation of public funds for vaccine research, development, evaluation, and use. Otherwise, it might merely add an unnecessary layer of bureaucracy.

OPTION A-2:

Establish either a small- or large-scale Federal vaccine production program.

The establishment of a Federal vaccine production program, either small or large, could decrease the Federal Government's total dependence on the pharmaceutical industry for vaccine production and supply and increase its control over the availability of vaccines.

A small Government program, designed to produce only "orphan" and experimental vaccines, would help ensure the availability of special-purpose vaccines not produced by the private sector. A small program probably would not substantially affect industry's profits from large-scale production programs, because industry would continue to be the major producer of commonly used vaccines.

By establishing a large-scale vaccine production program, the Federal Government would substantially control the availability of most vaccines in this country. In theory, therefore, it could ensure the production of commonly used vaccines (e.g., poliovirus vaccine) that currently have only one commercial manufacturer. Possibly, though, a large-scale Government production program might erode manufacturers' vaccine profits,

leading to a reduction in the pharmaceutical industry's commitment to vaccines. This ultimately might lead to a situation in which the Federal Government would be the sole producer of common I y used vaccines.

OPTION A-3:

Subsidize vaccine production by private industry.

Instead of establishing its own production program to ensure the availability of vaccines, the Federal Government could subsidize the production of selected products by vaccine manufacturers. Federal subsidy could be provided to vaccine manufacturers either in the form of direct contracts for production or as a condition of Government vaccine purchases.

Acceptance of this option by both the Government and vaccine manufacturers would eliminate any need for the Government to establish its own vaccine production facilities. If no manufacturer accepted Government subsidy, however, some vaccines would still not be produced.

VACCINE SAFETY AND EFFICACY

The Federal Government has regulated the quality of vaccines in this country for 77 years. During this period, the standards, procedures, and criteria used to evaluate vaccine quality have become quite rigorous. Existing Federal laws and regulations require vaccine manufacturers to test their products for several characteristics, including purity, sterility, and potency.

During the past 20 years, the Federal Government has increasingly emphasized the evaluation of vaccines' clinical efficacy and safety. Since the early 1960's, the Federal Government has required vaccine manufacturers to test their experimental products in prelicensing clinical trials. In addition, in its evaluation of some vaccines, the Government has placed increased emphasis on the vaccines' ability to produce a desired level of antibodies.

Federal responsibility for licensing vaccines and other biological products has resided with the Food and Drug Administration's (FDA) Bureau of Biologics (BOB) since 1972. BOB imposes strict standards for the premarketing assessment of vaccine safety and efficacy. Premarketing evaluations, however, have at least three limitations. The premarketing evaluation of the safety and efficacy of pneumococcal polysaccharide vaccine illustrate these 1 imitations.

First, premarketing clinical trials have inherent limitations, particularly with respect to the evaluation of vaccine safety. For one thing, the number of subjects who receive a vaccine in a clinical trial is quite small relative to the number of persons who receive the vaccine once it is marketed. In the case of pneumococcal vaccine, the total number of vaccinees in premarketing clinical trials was 23,000. Further, in most clinical trials, subjects are observed for adverse reactions for only a short period of time. As a result of these inherent limitations, rare adverse reactions or reactions with insidious onsets seldom, if ever, are observable in premarketing vaccine clinical trials.

Second, the Federal requirement that a vaccine be tested in prelicensing clinical trials can lead American vaccine manufacturers to conduct their clinical trials among foreign populations. This situation arises when the incidence of a disease is so low in the United States that manufacturers cannot conduct affordable or acceptable domestic clinical

trials. The use of data from clinical trials conducted in foreign countries can be problematic. The validity of using findings from studies conducted among foreign subjects **as** the basis for projections concerning levels of vaccine safety and efficacy in the United States may be questioned. Without foreign clinical trial data, however, evaluations of the safety and efficacy of some experimental vaccines might not be possible,

Altogether, 70 percent of the vaccinees in clinical trials BOB used to evaluate the safety and efficacy of pneumococcal vaccine were foreign subjects. Several foreign trials of pneumococcal vaccine were conducted among South African gold miners and New Guinean potato farmers, because the high incidence rate of pneumococcal pneumonia among these two populations permitted a statistically significant assessment of the vaccine's ability to prevent this disease.

Third, in some cases, bioethical problems or economic constraints may limit clinical testing of vaccines among high risk groups. To conduct an acceptable clinical trial, investigators both must withhold an experimental, but potentially lifesaving, vaccine from high risk control subjects and must vaccinate high risk experimental subjects who may be more prone to develop or less able to tolerate severe adverse reactions. Furthermore, the cost of conducting a clinical trial among high risk persons with similar medical problems can be substantial; there is some difficulty in locating specialized populations and investigators may have to pay for subjects' medical care during a trial. For these reasons, a vaccine might never be tested in clinical trials among persons with medical problems that constitute official indications for the vaccine's use.

FDA-approved indications for use of pneumococcal vaccine, for example, include chronic heart, lung, or kidney disease, but prior to Iicensure, the safety and efficacy of this vaccine were not specifically evaluated in clinical trials among people with one or more of these medical problems. The FDA-approved indications statement was based on findings from at least two studies that demonstrated that bacteremic pneumococcal pneumonia patients with one or more of these chronic medical problems died more frequently than did those without such problems.

Certain limitations of premarketing vaccine safety and efficacy evaluations might be overcome if more comprehensive data were collected regarding adverse reactions to vaccine products in general use. BOB has proposed regulations that would establish its authority to require vaccine manufacturers to submit to FDA selected types of reports regarding adverse reactions. At the present time, vaccine manufacturers are not required to submit such reports to any Federal agency. Implementation of these regulations would likely increase the number of case reports of adverse reactions, but case reporting by itself would not permit comprehensive postmarketing evaluation of vaccine safety.

ISSUE B:

The value and potential implications of establishing an active, possibly mandatory, postmarketing surveillance (PMS) system to assess the safety, conditions of use, and possibly efficacy, of licensed vaccines

Perceptions of the need for strengthening postmarketing surveillance of adverse reactions to licensed vaccines depend, first, on one's perception of the adequacy of the current premarketing safety requirements, and second, on one's confidence in the Government's ability to develop an effective PMS system.

BOB does have authority to remove a vaccine product from the U.S. market if available evidence suggests that the product is either unsafe or inefficacious. What BOB ap-

pears to lack, however, is any mechanism to collect comprehensive data on which to base its evaluations or with which to calculate the incidence of adverse reactions. Currently, BOB's postmarketing evaluations of licensed vaccines must be based largely on case reports that are voluntarily submitted by physicians to medical journals, to manufacturers, or to Federal agencies such as CDC or FDA.

To permit the collection of more comprehensive data regarding the safety of licensed vaccine products, CDC established last year a vaccine adverse reaction surveillance system. Reports concerning adverse reactions to vaccines administered under public immunization programs are voluntarily submitted, primarily by State and local health departments, to CDC. This system is very new, so it cannot yet be evaluated. Because it relies on voluntarily submitted case reports, though, CDC's system will not generate data needed to calculate the incidence of serious adverse reactions to particular vaccines.

Congress could await assessment of CDC's new voluntary case reporting system and take no action to strengthen the Federal Government's postmarketing vaccine surveillance mechanism. Alternatively, to permit the collection of data that could be used to evaluate selected vaccines more comprehensively, it could choose one or both of the following options.

OPTION B-1:

Authorize FDA to require vaccine manufacturers to conduct postmarketing surveillance of adverse reactions to specific vaccines and intensify Federal efforts to encourage voluntary reporting of such reactions by private sector physicians and clinics.

If given appropriate authority, FDA could require vaccine manufacturers to use their sales representatives, as well as practicing physicians, pharmacists, and nurses, to collect reports of adverse reactions to their licensed vaccine products. Further, FDA could require manufacturers systematically to report data collected concerning adverse reactions to either BOB or CDC. Such data then could be analyzed and used as a basis for BOB's evaluation of the safety of selected vaccines on the market.

Requiring manufacturers to file these reports, however, might diminish pharmaceutical manufacturers' commitment to vaccine research, development, and production. Some manufacturers might perceive such a requirement as an unacceptable economic and regulatory burden. Furthermore, the Federal Government at present has no effective means by which to compel private sector physicians to report the number and types of vaccinations they administer, let alone the number of adverse reactions to these vaccinations.

OPTION B-2:

Convert CDC's passive, voluntary case reporting system to an active, mandatory postmarketing vaccine surveillance system to monitor reactions to vaccines used in public immunization programs.

Congress could authorize HEW to undertake active postmarketing surveillance of selected vaccines administered under federally sponsored immunization programs. CDC could require State and local health departments participating in public vaccination programs to maintain records of the number of doses of vaccines administered and to solicit information regarding adverse reactions.

A system of active and mandatory postmarketing surveillance of vaccines administered in federally sponsored immunization programs would permit the collection of more comprehensive data regarding the safety and efficacy of licensed vaccines than will be collected under CDC's passive, voluntary case reporting system or under a PMS system as described in Option B-1. An active and mandatory postmarketing vaccine surveillance system coordinated by CDC, however, probably would require more resources than CDC's voluntary, case reporting system. Mandatory PMS activities also might be a disincentive for local and State public health clinics to participate in federally sponsored public immunization programs.

COST-EFFECTIVENESS ANALYSIS OF VACCINATION PROGRAMS

At present, the Federal Government promotes the use of at least eight immunizing agents. Seven of these agents are used to prevent common childhood diseases: measles, mumps, rubella, diphtheria, tetanus, polio, and pertussis. The remaining agent is used to prevent influenza primarily in adults or children with certain medical problems.

Every 1 to 2 years, Congress is asked to continue its financial commitment to federally financed immunization programs. Congress can base its funding decisions regarding these programs on a variety of criteria, including a general belief in the need for Government intervention to promote vaccine use, the effectiveness of prior and existing immunization programs, and the costs of continuing these programs.

One criterion that Congress has not often used to make its funding decisions is the cost-effectiveness of a given type of vaccination. Cost-effectiveness analysis (CEA) is an economic analytical tool that provides a systematic framework for comparing the economic efficiencies of two or more programs or procedures in achieving a given goal.

OTA conducted a CEA in which it calculated the net changes in costs and effects that would result from vaccination against pneumococcal pneumonia instead of continuing the present situation in which pneumonia is treated if it occurs. More than just an economic assessment of pneumococcal vaccination, OTA's investigation was designed to help illustrate the potential utility and limitations of using CEA to help allocate funds for Federal health programs in general and vaccination programs in particular.

In OTA's analysis, the net health effects and net medical care costs associated with a one-time pneumococcal vaccination program conducted in 1978 were assessed. Vaccination proved to be more cost-effective among the elderly than among any other age group. The results also showed that while vaccination would be slightly more expensive than treatment of pneumococcal pneumonia, vaccination would yield health benefits that could not be derived from treatment.

General Applications of CEA

ISSUE C:

The degree to which CEA could be useful in allocating Federal funds for vaccination and other health programs

As illustrated by OTA's analysis of pneumococcal vaccination, CEA might be useful to Congress and the executive branch in allocating funds for vaccine-related programs ranging from research and development programs to public immunization programs. CEA also might be used to help guide reimbursement decisions. Potential users of this

type of analysis include the National Institute of Allergy and Infectious Diseases (NIAID), the Center for Disease Control (CDC), the Health Care Financing Administration (HCFA), the Advisory Committee on Immunization Practices (ACIP), and health planning agencies.

Despite its potential utility, this type of formal economic analysis has major limitations. It does not necessarily or easily take into account social values, moral judgments, legal implications, or political realities; it does not easily or commonly address issues of equity and distribution. Furthermore, the use of this type of analysis may serve to narrow the range of options considered to those that are most easily quantified.

If the present situation relative to the use of CEA in Federal vaccination and other health programs continues, the use of this technique will remain informal and voluntary, and in some cases, prohibited. Selection of the following option would likely increase the Federal Government's use of CEA.

OPTION C-1:

Federal agencies could include formal CEA in the process of allocating funds for vaccination and other health programs.

In theory, the judicious use of CEA could lead to better selection of economically efficient programs to reduce health care costs or improve health status. No reasonable estimate, however, can be made of the potential reduction in overall health care costs that might result from such use. One of the potential dangers of greater application of CEA, is that it might lead to use of this technique when, in fact, such use is unnecessary or inappropriate. To minimize this danger, it would be important for policy makers to keep in mind CEA's limitations.

At present, the utility of CEA in allocating health care resources has not been fully assessed. Mandating the use of CEA at this time probably is premature and might lead to misallocation of funds. OTA is currently conducting an assessment of CEA as a method of evaluating medical technologies and will publish a report entitled The Cost-Effectiveness *of Medical Technologies* in the summer of 1980.

CEA and Its Relationship to Reimbursement for Vaccinations

ISSUE D:

Whether the Medicare law should be amended to permit reimbursement for preventive vaccinations

Only two preventive vaccines are currently marketed for general use by persons over the age of 65: influenza vaccine and pneumococca] vaccine. In 1976 and 1978, Congress appropriated funds for influenza vaccination programs; it has not funded pneumococcal vaccination programs. Traditionally, the Federal Government chooses for its public immunization programs vaccines that help prevent selected childhood diseases, most of which are communicable.

Under existing law, Medicare is authorized to pay for the treatment of influenza and pneumococcal pneumonia, but not for vaccinations to help prevent these diseases. In a cost-benefit analysis of influenza vaccination, health benefits and potential cost-savings were demonstrated. In OTA's analysis, vaccination against pneumococcal pneumonia was shown to be most cost-effective among the elderly. To allow Medicare to pay for preventive vaccinations, Congress must amend the Medicare law.

OPTION D-1:

Amend the Medicare law to permit reimbursement for preventive vaccinations.

Congress could amend the 1965 Amendments to the Social Security Act to permit Medicare to pay for preventive immunizations. At the same time, it could establish or allow HEW to establish criteria for determining which specific immunizing agents should be included in the Medicare benefit package, e.g., agents that help prevent diseases that particularly affect the elderly, agents that have been proved both safe and efficacious, agents that have been shown to be cost-effective.

Both influenza and pneumococcal vaccines would likely meet all three of these criteria. If an additional criterion were that an agent not be included in publicly financed immunization programs, however, influenza vaccine would not be included in the package.

The impact of Medicare reimbursement on the elderly's demand for vaccination has not been determined. If the price of vaccination is a barrier to demand, then reimbursement by itself might increase such demand. It is possible, however, that Medicare reimbursement would need to be supplemented with other Federal efforts, such as a consumer health information program, to increase demand for vaccinations. Regardless of its effect on demand, Medicare reimbursement would shift the cost of vaccination from elderly vaccinees to the Federal Government. The net cost of providing vaccinations through public immunization programs, however, might be lower than that of providing vaccinations through reimbursement to private sector physicians.

CEA Methodology and Data

ISSUE E:

Whether the Federal Government should seek to overcome methodological problems of CEA and problems related to the availability of data for CEAs

There are a number of generic difficulties associated with CEA methodology. One is that the models used to relate costs to outcomes vary from one study to another. This limits the comparability of the results of such studies. Another problem is that there is no widely agreed upon health status index that can be used to measure the health effects of medical interventions. In OTA's analysis of pneumococcal vaccination, the health status index used to measure the effects of vaccination on morbidity and mortality was quality-adjusted life years (QALYs). While the use in OTA's analysis of weights based on the results of surveys may represent a methodological advance, a great deal of work in improving health status indexes used in CEAs still remains to be done.

In the course of conducting its analysis of pneumococcal vaccination, OTA found that securing appropriate data for the analysis was a significant problem. Clearly, the time required to conduct CEAs and the rigor of the results of such analyses depend heavily on the availability of certain types of data. Exploration and resolution of key data problems, therefore, would seem to be prerequisites for any routine Government use of CEA.

OPTION E-1:

Federal agencies, including HEW, could begin to develop standardized and refined CEA methodology and basic data sets for CEAs.

The legislation creating the National Center for Health Care Technology (NCHCT) permits the Center to conduct CEAs and to develop general methodology. To force analysts to confront some of the methodological weaknesses or areas of disagreement in CEA, NCHCT could conduct pilot evaluations of certain medical technologies. Data problems could be addressed jointly by NCHCT, the National Center for Health Services Research (NCHSR), and the National Center for Health Statistics (NCHS).

To the extent that these agencies are able to overcome methodological and data problems, the feasibility of conducting CEAs, and using the results might increase. Improvements and standardization of data sets, though, could be expensive. Further, there might be some difficulty in attempting to improve the state of the art of CEA, while at the same time standardizing major aspects of it. To help overcome this, considerable flexibility in setting and revising methodological standards would be necessary.

LEGAL LIABILITY AND COMPENSATION FOR VACCINE-RELATED INJURIES

All vaccines, even when properly manufactured and administered, may pose risks to vaccinees. Permanent disability or death from vaccination, however, occurs only rarely. In general, the societal benefits of vaccination greatly outweigh the risks. For a very small number of vaccinees, however, the risks of vaccination exceed the benefits.

Under the existing legal liability system, persons injured as a result of vaccination must go to court and establish fault for their injury in order to receive compensation. To establish fault, the plaintiff (injured person) generally sues one or more of the participants in the vaccination process, e.g., a party that manufactures, distributes, pays for, encourages the use of, or administers the vaccine.

The major vaccine liability issue at present does not involve injury caused by negligence on the part of vaccine manufacturers or physicians, i.e., defective vaccine products or improper vaccine administration. Rather, it involves the inherent, unavoidable, though statistically remote, risk of vaccine-induced severe injury or death. In legal terminology, vaccines, though socially useful, are “unavoidably dangerous” products. Parties involved in the vaccination process attempt to avoid liability for inevitable injury by warning potential vaccinees about the existence of unavoidable risks.

In three major cases in the past 11 years, plaintiffs have won large judgments against vaccine manufacturers for injuries caused by nondefective and properly administered vaccines. One court argued that compensation for injury should be borne by the vaccine manufacturer as a cost of doing business, with costs passed on to the general public in the form of price increases. In essence, this court ruled that because no other mechanism to compensate injured vaccinees existed in society, the vaccine manufacturer should pay. While adopting a more explicit insurance rationale for compensating injured vaccinees, Federal appellate courts in these cases have shown an increased tendency to develop some doctrinal basis for their decisions on where liability for injury should rest.

Current case law has placed ultimate liability for breach of the “duty to warn” vaccinees about the inherent risks of vaccines on vaccine manufacturers. At present, the

duty to warn is being contractually transferred by manufacturers to HEW, which in turn is attempting to transfer this responsibility to State and local health agencies participating in public immunization programs. It remains unclear whether transfer of the duty to warn can be accomplished to the satisfaction of a court. There is no definite way to predict whether a court will find HEW's informed consent statements and the way in which they are given to be adequate; nor is there any way to predict, in the event that a court finds the duty to warn has not, been discharged, whom the court will hold liable.

The duty to warn raises ethical issues in public immunization programs. On the one hand, warnings are supposed to provide information on vaccine risks and benefits so that informed individuals can decide whether to be vaccinated or not. On the other hand, the Federal Government is an active promoter of vaccination programs, and the overwhelming majority of States and other territorial jurisdictions have mandatory childhood vaccination laws. In at least some cases, therefore, the vaccinee's ability to give informed consent to vaccination is moot.

Furthermore, the uncertainty surrounding appropriate methods of discharging the duty to warn already appears to have had two major impacts on vaccination programs. First, some vaccine manufacturers' willingness to produce and supply vaccines has been affected by the uncertainty over the price and even availability of liability insurance. Second, the highlighting of severe adverse reactions and associated liability problems has shaken the American public's confidence in the general safety of vaccines.

ISSUE F:

The extent, if any, to which the Federal Government should assume legal responsibility for compensating vaccinees injured in public immunization programs

Developing Federal mechanisms to compensate individuals who are injured as a result of vaccination in public immunization programs can be based on two rationales: 1) that the Government has a social responsibility to compensate individuals harmed as a result of their participation in vaccination programs intended in many instances to benefit, not only the individual vaccinee, but society as a whole; and 2) that liability insurance problems are having an adverse effect on public immunization programs.

If the Federal Government takes the position that responsibility for compensating injured vaccinees will be determined by the courts, then it will be doing its best to avoid compensating the injured. Legal discharge of the duty to warn would mean that there would be no liability or compensation for injury.

If HEW successfully defends its current position that underlying responsibility for the duty to warn still rests with vaccine manufacturers, manufacturers' increased liability costs will be passed on to the Federal Government and other purchasers of vaccines in the form of higher vaccine prices. It is also conceivable that some manufacturers will stop participating in public immunization programs. Some, as one former major vaccine manufacturer did, might withdraw from vaccine production altogether.

HEW's assuming responsibility to develop an informed consent statement and its requirement that State and local health agencies use this statement probably will absolve the latter agencies of liability. This absolution likely will have a positive impact on State and local health agency participation, but probably will not have a significant impact on their actual liability. Because of the procedural problems in suing Government agencies and the "deep pockets" of manufacturers, injured vaccinees probably will continue to focus their lawsuits on vaccine manufacturers.

Because the Federal Government is heavily involved in all phases of vaccine development, quality assurance, promotion, and use, it could develop approaches for more easily compensating injured vaccinees that do not rely solely on the judicial process. A central element of each of the two options presented below is easier access to compensation for vaccine-related injury.

OPTION **F-1:**

Assume responsibility for defending all claims of vaccine-induced injury incurred in public immunization programs and maintain authority to sue negligent parties.

This model is analogous to that used in the swine flu program. Under this option, the Federal Government would become the primary defendant in legal actions involving claims of injury sustained as a result of participation in public vaccination programs. The Federal Government would assume liability for the duty to warn, but would retain the right to *sue other* parties for injuries caused by negligence. This approach would somewhat insulate manufacturers from the expense of defending lawsuits. Manufacturers' costs incurred in assisting the Government in the preparation and defense of lawsuits, however, would remain.

With the Federal Government as the primary focus of claims for compensation, flexibility in the Government's posture with regard to the kinds of proof that would be needed to obtain compensation would be possible. For example, although foreseeability is a fundamental concept in assigning legal liability, in the swine flu program, Guillain-Barre Syndrome (GBS) was not initially a foreseeable consequence of immunization. In its processing of swine flu-related injuries, the Federal Government apparently is relaxing this condition and relying more on finding causation between alleged injury and swine flu inoculation. If the Federal Government were to adopt a similar approach in the future, compensation would depend less on whether an adequate warning had been given than on whether significant injury had occurred as a result of immunization.

Immediate and direct costs to the Government would increase under this option because of the administrative expense of processing, evaluating, and defending claims, and because of the compensation costs for successful litigants. Long-term costs, however, might or might not increase, because liability insurance costs are handled as business costs and passed on to the purchasers of vaccines. Indirect "costs" such as decreased public participation in public immunization programs might be less, because this would represent a positive approach, or at least not a passive one, to the problem of injured vaccinees.

While this approach might be an improvement for the class of injured vaccinees in terms of their chance of receiving compensation, it might not be an improvement for the rare individual who successfully maneuvers the current litigation process and wins a large award. The tradeoff between more awards of less individual worth and high individual awards, though, is typical of the kinds of tradeoffs that would have to be made between continuing the current situation and developing a more compensation-oriented system.

OPTION F-2:

Establish a federally operated program to compensate vaccinees injured as a result of being vaccinated in public immunization programs.

A frank compensation approach could range from modification of the current legal liability system, to integration into existing social insurance programs, to melding with approaches that have similar bases for compensation, such as that for compensating persons injured in medical experimentation.

To establish a Federal compensation system, four principal issues would have to be addressed. First, criteria for the selection of vaccinees eligible for Federal compensation would have to be established. Compensation could be limited, for example, to persons whose injuries result from vaccines whose use the Government promotes to a substantial degree.

Second, the types and severity of injury qualifying a vaccinee for compensation would have to be established. Some test of causality and a cutoff point on the severity of injury that would be compensated would have to be established.

Third, limits to compensation would have to be established. Under a Federal compensation system, which is oriented away from the adversary process toward the assumption of societal responsibility for injury, some general standards or levels of compensation would have to be established. The system could be structured to pay for injured persons' needs as they occur.

Fourth, financing mechanisms would have to be created or selected. The limited number of injuries arising out of public immunization programs means that a free-standing compensation system probably would not be warranted. Any specific approach would need clarification, public debate, and compromise.

The advantages and disadvantages of establishing a federally operated compensation program would depend largely on the specific program adopted, but in many respects might parallel those cited in Option F-1. Court costs to the Federal Government probably would be less under this option than under Option F-1, but administrative costs probably would be higher. In addition, injured vaccinees might have easier access to compensation under this option.

SCOPE OF THE STUDY

This study adresses four areas of concern regarding Federal vaccine policies: 1) the impact of Federal policies on the commitment of American pharmaceutical manufacturers to conduct vaccine research and develop and supply vaccines, 2) the adequacy of Federal vaccine safety and efficacy requirements, 3) the potential utility and limitations of cost-effectiveness analysis (CEA) in decisions regarding the allocation of Federal funds for vaccination and other health programs, and 4) vaccine liability and compensation issues that have arisen in connection with nondefective, properly administered vaccines used in public immunization programs.

No attempt was made to address all areas of Federal vaccine and immunization policies. Thus, for example, the study did not include an in-depth analysis of the administration or effectiveness of federally sponsored immunization programs, and consequently, did not include an examination of the roles of State and local health departments participating in such programs.

Furthermore, the study was limited to an examination of vaccine policies for the civilian population. Concerns regarding the vaccine-related activities of the Department of Defense (DOD), therefore, were not addressed.

To illustrate salient issues in the first three policy areas cited above, case studies based on recent events and experience with polyvalent pneumococcal capsular polysaccharide vaccine were developed. This vaccine, which is the newest vaccine on the U.S. market, can be used to help prevent pneumococcal pneumonia. It is described in more detail in figure 2.

Vaccine liability and compensation problems have not arisen specifically in connection with pneurnococcal vaccine, in part, because its use has not been actively promoted by the Federal Government. To illustrate these issues, therefore, OTA reviewed recent vaccine liability case law, principles underlying the pricing of vaccine manufacturers' liability insurance, and experience with adverse reactions under the swine flu and other federally sponsored immunization programs.

Most of the issues discussed in connection with pneumococcal vaccine are applicable to other types of vaccines. Some issues, however, may not have been comprehensively illustrated as a result of using only one vaccine in these case studies. Court cases involving liability for injury caused by nondefective poliovirus and swine flu vaccines most likely have implications for all vaccinations.

This report pertains on] y to vaccines for human use.

ORGANIZATION OF THE REPORT

This report has seven chapters. Following chapter 1, which is an introduction and summary to the entire report, case studies based on experiences with pneumococcal vaccine are presented in chapters 2, 3, and 4. In chapter 2, the impact of Federal financing on the research and development of this vaccine is discussed; chapter 3 contains a description and analysis of the procedures the Federal Government used to evaluate the safety and efficacy of this vaccine; and in chapter 4, OTA's cost-effectiveness analysis (CEA) of pneumococcal vaccination is presented. Chapter 5 contains a review of recent vaccine liability court cases, principles that underlie the pricing of liability insurance, and liability experience under the 1976 swine flu immunization program.

Findings from the case studies of pneumococcal vaccine and the review of liability topics are summarized in chapter 6. These findings are used to introduce more general discussions of selected issues in each of the four major policy areas addressed in this report.

Congressional or executive branch options to address the issues discussed in chapter 6 are presented in chapter 7. In some cases, the options are mutually exclusive, in others, they are not. The implications of maintaining the status quo, along with the pros and cons of each option, are discussed.

The history of pneurnococcal research and pneumococcal vaccine development prior to 1967 is described in appendix 1.1. Appendixes which follow this contain technical reference material for chapters 2, 3, 4, and 5.

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Figure 2.—Pneumococcal Diseases and Polyvalent Pneumococcal Polysaccharide Vaccine—cont.

pneumococcal pneumonia permit physicians to treat many patients without hospitalization.

Unfortunately, two problems have arisen in connection with antibiotic treatment of pneumococcal diseases. First, in a substantial number of cases, the use of antibiotics fails to prevent death caused by bacteremic pneumococcal pneumonia. In spite of receiving appropriate antibiotic therapy, as many as 17 to 30 percent of patients with bacteremic pneumococcal pneumonia have been reported to die from their disease (Austrian, 1964).

Second, in some instances, certain types of pneumococci have become resistant to antibiotics. The development of resistant strains has been reported in South Africa (Jacobs, 1978), New Guinea (Hansman, 1971), and the United States (U.S. Ex. Br., CDC, 1977). So far, resistance to at least eight antibacterial agents has been demonstrated. The development of resistant strains of pneumococci reduces the overall effectiveness of available antibiotics in the treatment of pneumococcal diseases.

Polyvalent Pneumococcal Polysaccharide Vaccine

Recent efforts to develop a vaccine to help prevent pneumococcal pneumonia were stimulated in part by findings regarding the limitations of antibiotic therapy. These efforts, culminating nearly 70 years of basic and clinical research, proved successful. On November 21, 1977, the Food and Drug Administration (FDA) issued Merck Sharp and Dohme, an American pharmaceutical manufacturer, a license to market its 14-valent pneumococcal capsular polysaccharide vaccine (PNEUMOVAX). In August 1979, FDA issued Lederle Laboratories a license to market a similar product (PNU-IMUNE).

Pneumococcal vaccine, which appeared on the U.S. market in February of 1979 is composed of purified polysaccharides from the capsules of 14 different types of pneumococci. When injected into humans, these 14 capsular polysaccharides stimulate the formation of serum antibodies that provide immunity against 14 types of pneumococcal organisms. The duration of immunity conferred by the vaccine is unknown. Some researchers estimate that the period of protection lasts for at least 3 years; others claim that it may last a lifetime (Weibel, 1977).

In premarketing clinical tests, pneumococcal vaccine appeared to be relatively safe. While minor reactions such as pain or erythema (redness at the injection site) were fairly common, no deaths and few serious adverse reactions to the vaccine were reported. Since the vaccine has been on the market, however, a few cases of more severe transient adverse reactions have occurred (Broome, 1978; Uhl, 1978; Semel, 1979). Pneumococcal vaccine does not contain live organisms and therefore cannot itself cause pneumococcal infection.

The 14 types of pneumococci represented in the vaccine reportedly account for approximately 80 percent of pneumococcal infections in children and adults (Austrian, 1977). In premarketing clinical trials, pneumococcal vaccine produced an acceptable increase in serum antibody titers in at least 80 percent of the subjects tested. In some studies, at least an 80-percent reduction in the incidence of pneumococcal pneumonia occurred among vaccinees (Austrian, 1976; Smit, 1977). In other studies, however, the reduction of disease among vaccinees was less (Riley, 1977).

FDA-approved indications for use of the 14-valent vaccine specify prevention of pneumococcal pneumonia or bacteremia in individuals over 2 years of age who are at high risk of developing and dying from these pneumococcal infections. High risk individuals include those with chronic physical conditions (such as heart, lung, or kidney disease, diabetes, or cirrhosis of the liver); those in chronic care facilities; those convalescing from severe diseases; and those over 50 years old.

2.

A CASE STUDY: FINANCING THE RESEARCH AND DEVELOPMENT OF PNEUMOCOCCAL VACCINE

2.

A CASE STUDY: FINANCING THE RESEARCH AND DEVELOPMENT OF PNEUMOCOCCAL VACCINE

A glance at the record makes one point indisputable: new vaccine development in the U.S.A. has been second to none, and we must have been doing many things right.

Maurice R. Hilleman, Ph. D., D. SC.
Director, Merck Institute for Therapeutic Research
November 14, 1976[1]

Never take your vaccine supply system for granted,

Harry M. Meyer, Jr., M.D.
Director, Bureau of Biologics
November 13, 1976[1]

BACKGROUND AND INTRODUCTION

During the past few years, concern has been expressed about the decline in the number of American pharmaceutical companies engaged in the research, development, and production of vaccines. Some authorities have speculated that the capacity of the pharmaceutical industry to develop and produce needed vaccines has dwindled to the point that increases in Federal funding for vaccine research and development—and, possibly, even Government production of certain vaccines that the industry drops—soon may be necessary (Krugman, 197'7).

Since the early 1940's, there has been a definite decline in the number of licensed vaccine manufacturers and licensed vaccine products in this country. (See figures 3 and 4.) Furthermore, the number of licensed vaccine products per licensed manufacturer also has declined. (See figure 5.) Possible reasons for the general decline since the 1940's, including the discovery and widespread use of antibiotics, are discussed briefly in appendix 2.1.

No full investigation of the causes of the decline in the number of vaccine manufacturers or of its potential effect on vaccine research, development, and production in this country has been made. Similarly, there has been no comprehensive assessment of the net effect of various Federal vaccine policies and regulations on industry behavior. The effect of the following Federal actions on the pharmaceutical industry's willingness to develop

'Statement presented at the National Immunization Conference sponsored by the National Institutes of Health, Bethesda, Md., Nov. 13 and **14, 1976,**

Figure 3.—Total Number of Vaccine Manufacturing Establishments Licensed in the United States by Year (1903-79)[1]



The number of licenses shown on this graph represents the net number of active vaccine *establishment* licenses for each year. Totals for each year were calculated by tallying a running total of the number of vaccine *establishment* licenses issued over time and subtracting the number of vaccine *establishment* licenses revoked over time.

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, 1979.

Figure 4.—Total Number of Vaccine Products Licensed in the United States by Year (1903-79)[1]



[1]The number of licenses shown on this graph represents the net number of active vaccine *product* licenses for each year. Totals for each year were calculated by tallying a running total of the number of vaccine *product* licenses issued over time and subtracting the number of vaccine *product* licenses revoked over time.

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, 1979

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and produce vaccines, therefore, is unknown: NIAID's funding of certain types of vaccine research and development, BOB's evaluating vaccine safety and efficacy, CDC's purchasing of vaccines for public immunization programs, and HEW's handling of vaccine liability and compensation issues.

In order to assess the impact of Government actions on industry behavior, it is important to know what general factors influence individual pharmaceutical manufacturers' decisions to enter, stay in, expand within, or withdraw from the vaccine business. From selected readings and from interviews with representatives of the pharmaceutical industry and certain government agencies, the following influences on individual pharmaceutical manufacturers' decisions to conduct vaccine research, development, and production can be identified:

1. The size of the potential market for a given vaccine product.
2. The availability of company personnel and facilities needed to engage in vaccine research, development, and production.
3. The cost and complexity of complying with Federal regulations concerning vaccine safety and efficacy.
4. The manufacturer's ability to predict potential costs of liability for harm produced through the use of vaccines.
5. The availability of Government financing for vaccine research and development, and possibly, production.
6. The manufacturer's ability to establish adequate selling prices for vaccine products.
7. The public need for a given vaccine and the extent to which this need is being met by other manufacturers.

Since 1968, the number of licensed manufacturing establishments that produce vaccines in this country has droppped about 50 percent—from about 37 to 18. The number of licensed vaccine products has dropped about 60 percent—from 385 to around 150. The impact of this recent decline on the U.S. pharmaceutical industry's ability to develop and produce supplies of vaccines commensurate with public need is unknown. The apparently diminishing commitment—and possibly capacity—of the American pharmaceutical industry to research, develop, and produce vaccines, however, may be reaching levels of real concern.

At the present time, there are 26 licensed vaccine establishments. Only 18 establishments actually produce vaccines for sale in the United States. Eight of the 18 establishments are American pharmaceutical companies. These eight companies hold 100 (70 percent) of the 143 vaccine product licenses in this country; foreign-based establishments hold 24 (17 percent); and two State governments and one American university hold the remaining 19 (13 percent). (See table 1.)

The 143 vaccine products currently licensed in the United States can be assigned on the basis of product content to about 51 different categories. Altogether, these products are intended to provide immunity against about 23 different types of infections. (See table 2.) For 20 (40 percent) of the 51 currently licensed types of products, there is only one manufacturer licensed in the United States. (See table 3.)

Eight American pharmaceutical companies collectively hold 100 current product licenses[2] for 51 different types of vaccines. Fifty-five of these licenses are being used to

[2]In table 4, 10 products are subsumed under one license (polyvalent bacterial vaccines with "no U.S. standard of potency").

Table 1 .–Vaccine Manufacturing Establishments Currently Licensed in the United States (1979)

Category and name of establishment	Number of product licenses
American pharmaceutical companies	
1. Connaught Laboratories, Inc..	15
2. Cutter Laboratories (includes Hollister-Stier)	3
3. Delmont Laboratories, Inc..	1
4. Eli Lilly and Company	9
5. Lederle Laboratories.	20
6. Merck Sharp and Dohme.	12
7. Parke, Davis and Company.	18
8. Wyeth Laboratories, Inc....	12
Subtotal	100 (70%)
Foreign institutions	
1. Connaught Laboratories, Ltd.	5
2. Glaxo Laboratories, Ltd.	1
3. institute Sieroterapico Vaccinogeno Tuscano Sclavo	10
4. Pfizer, Ltd.	4
5. Recherche et Industrie Therapeutiques S.A.	1
6. Swiss Serumand Vaccine Institute Berne	2
7. Wellcome Foundation, Ltd. Wellcome Research Laboratories	1
Subtotal	24 (17%)
State governments	
1. Bureau of Laboratories, Michigan Department of Public Health	9
2. Massachusetts Public Health Biologic Laboratories	9
Subtotal	18 (13%)
American universities	
1. University of Illinois	1
Subtotal	(< 1 %)
Grand total	143(1OO%)

SOURCE OTA's Interpretation of data provided by the Bureau of Biologics. 1979

Table 2.—Diseases Against Which There Are Currently Licensed Immunizing Agents in the United States (1979)

General population (7 diseases)	Special populations (16 diseases)
Diphtheria	Adenovirus
Pertussis	Anthrax
Polio	BCG
Measles	Cholera
Mumps	Gas gangrene
Rubella	Influenza
Tetanus	Meningococcal diseases
	Plague
	Pneumococcal pneumonia
	Rabies
	Rocky Mountain Spotted Fever
	Smallpox
	Staphylococcal disease
	Typhoid
	Typhus
	Yellow Fever

SOURCE OTA's interpretation of data provided by the Bureau of Biologics 1979

Table 3.—Vaccine Products With Only One Manufacturing Establishment Currently Licensed in the United States (1979)

	Type of product	Number of establishments holding product license: American pharmaceutical companies	Foreign-based institutions	American universities	State governments
1	Adenovirus and influenza virus vaccines combined alumlnum phosphate adsorbed	1			
2	Adenovirus vaccine	1			
3	Anthrax vaccine adsorbed				1
4	Diphtheria tetanus toxoids, pertussis vaccine adsorbed, poliomyelitis vaccine	1			
5	Diphtheria, tetanus toxoids, pertussis poliomyelitis vaccines adsorbed	1			
6	Gas gangrene polyvalent antitoxin	1			
7	Measles and mumps virus vaccines, live	1			
8	Measles and rubella virus vaccine, live	1			
9	Measles-smallpox vaccine. live.	1			
10	Measles. mumps, and rubella virus vaccine, live	1			
11	Mumps virus vaccine, live	1			
12	Pertussis vaccine adsorbed	1			
13	Plague vaccine . . .	1			
14	Poliomyelitis vaccine adsorbed	1			
15	Polyvalent bacterial antigens with "no U.S. standard of potency"	1			
16,	Polyvalent bacterial vaccines with "no U.S. standard of potency" . . .	1			
17	Rabies vaccine	1			
18	Rocky Mountain Spotted Fever vaccine	1			
19	Rubella and mumps virus vaccine, live . . .	1			
20.	Yellow Fever vaccine ., ...	1			
	Totals.	19	—	—	1

SOURCE OTA s interpretation of data provided by the Bureau of Biologics. 1979.

market 31 types of products. Twenty of the 51 currently licensed types of vaccines have no producer. Eighteen have only one producer, 7 have two producers, 2 have three producers, and 4 have four or more producers. (See table 4.) If technological or marketing problems were to cause a shutdown of production, it is conceivable that certain types of vaccine products might become unavailable—at least for a period of time. (See appendix 2.2.)

New types of products have been introduced at a rate of three to seven products every 5 years since 1940. (See table 5.) American pharmaceutical companies have introduced about 42 (82 percent) of the 51 currently available types of vaccines. (See appendix 2.3.)

Several factors may have contributed to the recent decline in the number of licensed vaccine establishments and products. First, in 1972, the Licensing Branch of the Food and Drug Administration's (FDA) Bureau of Biologics (BOB) launched a concerted effort to remove inactive vaccine product licenses. Second, rather than comply with new standards for product safety and efficacy issued by FDA in 1972, many licensed establishments may have opted to cease vaccine production. Third, in recent years, manufacturers have been faced with a static vaccine market and increasing production costs. Finally, vaccine manufacturers' liability for the infrequently occurring injury produced by vaccination has been broadened.

The focus in this chapter is on issues pertaining to the manner in which Federal Government policies influence pharmaceutical manufacturers' decisions to undertake vaccine

Table 4.—Commercial Availability in the United States of Vaccine Products Manufactured by American Pharmaceutical Companies (1979)[a]

Type of product	Number of American corporations licensed to market the product in the United States	Number of American corporations actually market ing the product in the United States	Number of foreign establishments licensed to market the product in the United States
1. Adenovirus and influenza virus vaccines combined aluminum phosphate adsorbed	1	None	None
2. Adenovirus vaccine	1	None	None
3. Antirabies serum	1	1	1
4. Anthrax vaccine adsorbed[b]	None	None	None
5. BCG vaccinec	None	None	2
6. Cholera vaccine	4	2	1
7. Diphtheria antitoxind	1	1	1
8. Diphtheria and tetanus toxoids	2	None	None
9. Diphtheria and tetanus toxoids	2	None	None
10. Diphtheria and tetanus toxoids and pertussis vaccine adsorbedd	6	4	1
11. Diphtheria and tetanus toxoids adsorbedd	4	3	1
12. Diphtheria toxoid[b]	3	None	1
13. Diphtheria toxoid adsorbed[b]	2	None	1
14. Diphtheria, tetanus toxoids, pertussis vaccine adsorbed, poliomyelitis vaccine	1	None	None
15. Diphtheria, tetanus toxoids and pertussis, poliomyelitis vaccines, adsorbed	1	None	None
16. Gas gangrene polyvalent antitoxin	1	None	None
17. Influenza virus vaccine	5	4	None
18. Measles and mumps virus vaccine, live	1	1	None
19. Measles and rubella virus vaccine, live	1	1	None
20. Measles virus vaccine, live, attenuated	2	2	None
21. Measles-smallpox vaccine, live	1	None	None
22. Measles, mumps, and rubella virus vaccine, live	1	1	None
23. Meningococcal polysaccharide vaccine, Group A	2	2	None
24. Meningococcal polysaccharide vaccine, Group C	2	2	None
25. Meningococcal polysaccharide vaccine, Groups A and C combined	2	2	None
26. Mumps virus vaccine, live	1	1	None
27. Pertussis vaccine	4	1	None
28. Pertussis vaccine adsorbedb	1	None	None
29. Plague vaccine	1	1	None
30. Pneumococcal vaccine, polyvalent	2	2	None
31. Poliomyelitis vaccine	2	None	1
32. Poliomyelitis vaccine adsorbed	1	None	None
33. Poliovirus vaccine, live oral trivalent	1	1	1
34. Poliovirus vaccine, live oral, Type 1	1	None	1
35. Poliovirus vaccine, live oral, Type 2	1	None	1

Table 4.—Commercial Availability in the United States of Vaccine Products Manufactured by American Pharmaceutical Companies (1979)'–cont.

Type of product	Number of American corporations licensed to market the product in the United States	Number of American corporations actually marketing the product in the United States	Number of foreign establishments licensed to market the product in the United States
36. Poliovirus vaccine, live oral, Type 3 ..	1	None	1
37. Polyvalent bacterial antigens with "no U.S. standard of potency"	1	1	None
38. Polyvalent bacterial vaccines with" no U.S. standard of potency"	1	1	None
39. Rabies vaccine[f]	1	1	None
40. Rocky Mountain Spotted Fever vaccine	1	None	None
41. Rubella and mumps virus vaccine, live	1	1	None
42. Rubella virus vaccine, live	1	1	2
43. Smallpox vaccine[b]	3	2	1
44. Staphylococcus toxoid ...	1	1	1
45. Tetanus and diphtheria toxoids adsorbed (for adult use)[b]	5	4	None
46. Tetanus toxoid[b]	7	3	2
47. Tetanus antitoxin	3	None	2
48. Tetanus toxoid adsorbed[d]	6	5	2
49. Typhoid vaccine	2	1	None
50. Typhus vaccine[e]	3	1	None
51. Yellow Fever vaccine	1	1	None
Totals	100	55	24

[a]Includes 2 serums and 11 antitoxin products.
[b]Product license held also by one State government laboratory.
[c]Product license held by one American university.
[d]Product licenses held also by 2 State government laboratories.
[e]One of the two American pharmaceutical companies licensed to market this measles vaccine in the United States plans to remove the product from interstate commerce in 1980.
[f]The one American pharmaceutical company that currently markets rabies vaccine plans to stop marketing it if another company is licensed for this product.
SOURCE: OTA's interpretation of data provided by the Bureau of Biologics and the eight American vaccine manufacturers, 1979.

Table 5.— Number of New or Improved Types of Currently Licensed Vaccine Products Introduced in the United States in 5-Year Intervals Since 1940a

5-year time interval	Number of new or improved types of vaccine products introduced
1975-1979	4
1970-1974	6
1965-1969	3
1960-1964	7
1955-1959	4
1950-1954	6
1945-1949	6
1940-1944	3
Before 1940	10
Total	49

[a]Only 49 of the currently licensed 51 types of licensed products are included. Polyvalent bacterial antigens and polyvalent bacterial vaccines with "no U.S. standard of potency" are excluded.
SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, 1979.

research, development, and production activities. Specifically examined is NIAID's role vis-a-vis private industry in financing the research and development of a polyvalent pneumococcal polysaccharide vaccine. Findings from this case study and issues related to the development and overall impact of Federal Government policies on private sector vaccine research, development, and production activities, are presented in chapter 6. Possible options for congressional action are presented in chapter 7.

EARLY PNEUMOCOCCAL VACCINE RESEARCH AND DEVELOPMENT (1881-1966)[3]

Pneumococcal vaccine research and development efforts prior to 1967 were uncoordinated, poorly funded, and not highly visible. Like other basic scientists, early pneumococcal researchers, mostly in academe and private industry, worked with no single leader or coordinated research plan. In the late 1800's and early 1900's, communication among pneumococcal researchers was limited to periodic publications in scientific and clinical journals and infrequent personal exchanges. Research funds, although provided by a variety of sources, were generally scarce.

In the late 1940's, based upon the clinical safety, efficacy, and immunogenicity data generated by such researchers as Lloyd Felton, Colin M. MacLeod, Paul Kaufman, and Michael Heidelberger, E. R. Squibb and Sons developed and marketed two 6-valent pneumococcal capsular polysaccharide vaccines. One vaccine, formulated for use in adults, contained polysaccharide Types 1, 2, 3, 5, and 8; the other vaccine, intended for use in children, contained Types 1, 4, 6, 14, 18, and 19.

Neither of Squibb's vaccines ever gained widespread acceptance. Physicians in the early 1950's chose to rely on newly introduced antimicrobial agents (penicillin, sulfonamides, chlortetracycline, and chloramphenicol) to treat bacterial pneumonia, rather than to help prevent this disease through immunization. In 1954, therefore, Squibb terminated its production of pneumococcal vaccine. The Biologics Control Agency (then the Laboratory of Biologics Control of the National Microbiologic Institute, NIH) withdrew without prejudice Squibb's license to produce these vaccines, and the company subsequently abandoned all of its pneumococcal vaccine research and development programs.

After this, with increasing reliance on antibiotic treatment therapy, perceptions of the need for the development of a pneumococcal polysaccharide vaccine generally diminished until Robert Austrian and Jerome Gold produced data between 1952 and 1962, showing that, despite antibiotic treatment, the mortality rate for bacteremic pneumococcal pneumonia was still high (Austrian, Gold, 1964). In their study at Kings County Hospital in Brooklyn, N. Y., these researchers found that 10 types of pneumococci accounted for at least 70 percent of pneumococcal pneumonia cases. Of patients treated for bacteremic pneumococcal pneumonia with penicillin or other antibiotics, 17 percent died. Among patients over 50 years of age, the mortality rate was 28 percent; and among individuals with complicating illnesses such as heart disease, stroke, and pulmonary emphysema, the mortality rate was 30 percent.

In addition, other investigators found that the emergence of antibiotic resistant strains of pneumococci was becoming a significant problem in the treatment of pneumococcal diseases (Dixon, 1967). These findings sparked renewed interest in the development of a pneumococcal vaccine.

[3]For a more extensive review of private sector pneumococcal vaccine research and development efforts prior to 1967, see app. I .1,

FEDERAL GOVERNMENT PARTICIPATION IN THE RESEARCH AND DEVELOPMENT OF PNEUMOCOCCAL VACCINE (1967-79)

Federal Government participation in the research and development of a polyvalent pneumococcal polysaccharide vaccine dates from 1967. At the strong and insistent urging of Robert Austrian, the National Institute of Allergy and Infectious Diseases (NIAID), one of the 11 Institutes at the National Institutes of Health (NIH), in 1967, committed itself to providing substantial Federal funds for the research and development of a pneumococcal polysaccharide vaccine.

There were three reasons underlying NIAID's decision, based on the recommendation of its Vaccine Development Committee (VDC), to provide funding for research and development of a pneumococcal vaccine (Davis, 1967):

1. For some years prior to 1967, NIAID had been considering initiating a goal-oriented, contract-supported program to develop bacterial vaccines.
2. The work of Austrian and other researchers demonstrated that pneumococcal diseases had not been conquered by antibiotics and that the development of a safe and effective vaccine against these diseases was technically feasible.
3. After contacting the Pharmaceutical Manufacturers Association (PMA), NIAID concluded that no pharmaceutical company was interested at the time in developing a pneumococcal vaccine on its own.

The Federal Government traditionally has financed a significant amount of basic and epidemiologic research on vaccines through the provision of grants to basic researchers.[4] Some basic and epidemiologic research also has been financed by the pharmaceutical industry. Prior to 1967, the Federal Government had funded vaccine product development and clinical testing,[5] but the primary source of funding for this was the private sector, specifically, individual pharmaceutical companies expecting to develop a marketable product.

On the basis of the size of NIAID's financial commitment to pneumococcal vaccine in 1967, it would appear that this agency perceived a need for greater Federal involvement in financing vaccine research and development than had been called for in the past. Between 1968 and 1976, NIAID spent an estimated $6.5 million for basic research on the pneumococcus and for development and testing of pneumococcal vaccines. Of this amount, $2. o million was allocated to basic research on the pneumococcus and epidemiologic research of pneumococcal diseases, and $4.5 million was devoted to the development and testing of pneumococcal vaccines.

The objectives of this NIAID-sponsored research were these (Horton, 1973):

1. To assess the predominant types of pneumococci causing illness and to determine the incidence of pneumococcal disease among certain high risk populations;
2. To develop serological procedures to enhance the diagnosis of pneumococcal disease and to facilitate the collection of essential data that characterize the antigenic potential of pneumococcal vaccines;
3. To evaluate pneumococcal (monovalent and polyvalent) vaccines in clinical trials for clinical efficacy, safety, and immunogenicity; and

[4]NIAID continues today to provide substantial funds for basic, epidemiologic, and clinical research. Most researchers who receive Federal funds work in academe, although some work in private industry.

[5]For example, it was heavily involved in field testing of polio, measles, and rubella vaccines. In the 1960's, NIAID's Vaccine Development Branch, and in the 1940's, the Commission on Influenza of the Armed Forces supported substantial product development and clinical testing activities.

4. To stimulate the commercial production and eventual licensure of a safe, highly purified, polyvalent pneumococcal vaccine.

NIAID-funded research began in 1968. That year NIAID contracted with Austrian and other researchers in academe and private medical practice to conduct epidemiologic studies to determine the incidence of pneumococcal disease and to establish the distribution of the most common serotypes of pneumococci producing these diseases. NIAID also contracted with Austrian at the University of Pennsylvania and later with Gerald Schiffman at the State University of New York at Brooklyn to develop serological methods of diagnosing pneumococcal disease and measuring antibody responses.

In addition to funding basic research, NIAID awarded a contract to Eli Lilly and Company, a pharmaceutical manufacturer, to develop an experimental polyvalent pneumococcal polysaccharide vaccine for use in clinical trials. In the early 1970's, NIAID also contracted with clinical investigators in academe and private practice to conduct U.S. clinical trials of pneumococcal vaccine. For two of the studies, one at Kaiser Permanence Medical Center in San Francisco, Calif., and another at the Dorothea Dix Hospital in Raleigh, N. C., Austrian served as principal investigator. ' In another study, which was partially funded by NIAID, the clinical efficacy, safety, and immunogenicity of an 8-valent pneumococcal vaccine were evaluated in children with sickle-cell disease and hyposplenic function (Ammann, 1977).

Since 1974, NIAID has been collaborating in at least 30 clinical studies involving the use of polyvalent pneumococcal vaccine in special populations at high risk, such as those with sickle-cell disease or inadequate splenic function. NIAID does not provide direct funding for such studies, but it does provide both staff time for coordination of study activities and use of contract laboratory facilities. In addition, it facilitates researchers' access to manufacturer-supplied vaccines.

INDUSTRY PARTICIPATION IN THE RESEARCH AND DEVELOPMENT OF PNEUMOCOCCAL VACCINE (1967-79)

Following the termination of Squibb's pneumococcal vaccine research, development, and production programs in the 1950's, little additional work on pneumococcal polysaccharide vaccines was done by the pharmaceutical industry until 1968, when Eli Lilly began preparing vaccines under contract from NIAID.

Prior to accepting the NIAID contract, Lilly had not been working independently on the development of a pneumococcal vaccine, but was involved in the manufacture of other vaccines and was attempting to develop a vaccine to prevent common respiratory infections. Thus, Lilly's decision to undertake the task of developing and producing experimental pneumococcal polysaccharide vaccine may have been influenced by the company's involvement in other vaccine-related activities. This decision, however, also may have been influenced by the availability of Federal funds for pneumococcal vaccine development. Lilly had also accepted NIAID funds in the 1960's to develop rubella vaccine.

Lilly eventually produced thousands of doses of monovalent and polyvalent vaccines of purified polysaccharide Types 1-9, 12, 14, 18, 19, 23, and 25. According to some Government officials, though, Lilly's pneumococcal vaccine researchers encountered

'NIAID-sponsored studies, along with other clinical trials and studies designed to assess the safety and efficacy of experimental polyvalent pneumococcal vaccines, are described in ch. 3 and in app. 3.6.

substantial problems during the first 18 months of their contract (U.S. Ex. Br., NIAID, 1970).

As Lilly was producing experimental pneumococcal vaccines, company officials were considering dropping the bulk of Lilly's vaccine research, development, and production programs. Apparently, the company's vaccine-related activities were not as profitable as its activites in other product areas. Specific problems related to vaccines included these (Johnson, 1978):

1. The vaccine market did not appear to be growing. Vaccine use at the time was largely aimed at preventing certain childhood diseases, and at least four producers competed for shares of the existing vaccine market. Because the U.S. birth rate was declining, the childhood disease vaccine market was expected to decl inc.
2. Vaccine research was expensive and required substantial investments in technology and human resources. Prescription drug products manufactured in tablet or capsule form were often less expensive to produce than vaccines and usually generated higher profits.
3. Documenting the efficacy of a vaccine in the United States was difficult and expensive. This was especially true for pneumococcal vaccine, a product designed to treat a disease whose incidence even today remains difficult to assess and for which accurate diagnostic techniques can be expensive and difficult to perform.[7]
4. Proving the quality of each batch of vaccines manufactured, as required by Federal regulations, was expensive. Samples of each batch had to be tested for safety, purity, and potency, and additional samples had to be sent for confirmation testing to the Food and Drug Administration (FDA).

Discouraged by such problems, in 1975, Lilly stopped producing experimental pneumococcal vaccines. Soon thereafter, in March 1976, Lilly also terminated most of its other vaccine research, development, and production programs. Lilly continues to produce only those vaccine products, such as rabies vaccine, which no other manufacturer makes.

In 1970, about 2 years after Lilly began work on pneumococcal vaccine under NIAID contract, Merck Sharp and Dohme intensified its own efforts to develop a pneumococcal vaccine. A leading vaccine innovator, developer, and producer, Merck had committed itself earlier to the task of developing and producing a meningococcal poly - saccharide vaccine for the U.S. Army. The company may have decided to invest in developing a pneumococcal polysaccharide vaccine because of the similarity of the research techniques and resources needed for this undertaking (Hilleman, 1978).

Working without direct Federal funding, Merck reportedly spent an estimated $6 million between 1970 and 1978 to develop a marketable pneumococcal polysaccharide vaccine. In the early 1970's, the company conducted independent clinical trials among gold miners in South Africa, demonstrating the safety and efficacy of its vaccine among tested populations (Smit, 1977). Levels of safety and efficacy for Merck's vaccine in these trials were comparable to those found for Lilly's product, which was used by Austrian in concurrent clinical trials among gold miners in South Africa (Austrian, et al., 1976).

Encouraged by these clinical trial results, Merck applied to FDA in 1976 for a license to manufacture and market its polyvalent pneumococcal capsular polysaccharide vac-

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'These diagnostic techniques are described in app. 3.5.

cine.[8] The company was issued a product license on November 21, 1977, and in February 1978, began marketing its 14-valent vaccine known as PNEUMOVAX.

A third company that recently pursued development of a pneumococcal polysaccharide vaccine is Lederle Laboratories. For the past 70 years, Lederle has been a relatively active vaccine reseacher and producer. It currently holds 19 product licenses and produces 10 vaccine products. Lederle is the sole producer of live poliovirus vaccine in the country.

According to an official company spokesman, Lederle began developing a pneumococcal vaccine in 1970 (Stessel, 1978), possibly in response to NIAID's initiative in spearheading basic research and development. Like Merck's, Lederle's work on pneumococcal vaccine was done without NIAID funding. Lederle's application for a pneumococcal vaccine product license was approved by FDA in August 1979. Lederle named its vaccine PNU-IMUNE.

THE ROLE OF FEDERAL FINANCING IN THE RESEARCH AND DEVELOPMENT OF PNEUMOCOCCAL VACCINE

The Federal Government's effort to stimulate vaccine research in academe, and to a lesser extent, in industry, centers on the dispersal, primarily through NIAID, of limited Federal funds for vaccine research and development. At present, no long-term, established criteria or specific objectives appear to direct either the size or the allocation of Federal vaccine research funds. Further, the expenditure of these funds can be influenced by factors other than quantitative assessment of public need.

The case study of pneumococcal vaccine illustrates the informal, often ad hoc process by which the public and the private sectors select diseases for intervention, develop methods of treatment or prevention, and evaluate the effectiveness of their efforts. NIAID's decision to fund pneumococcal vaccine research and development was not based on a comparative, quantitative assessment of pneumococcal diseases' threat to the public's health. All private and public sector efforts devoted to the development, evaluation, and marketing of pneumococcal vaccine were conducted in the absence of the following types of data: specific rates for the incidence, prevalence, morbidity, mortality, and medical costs of pneumococcal diseases. At no point during the development of this vaccine did HEW simultaneously solicit the collective advice and counsel from three of its agencies—BOB, NIAID, and CDC—for a systematic evaluation of the need for, or potential attributes of, a pneumococcal vaccine.

Two overriding factors led to the development and eventual marketing of pneumococcal vaccine. First, one man devoted his professional career to studying the mortality resulting from pneumococcal diseases and to developing a vaccine to prevent the occurrence of these diseases. Robert Austrian, virtually singlehandledly, convinced NIAID and at least one pharmaceutical company to spend jointly $12 million to research, develop, and test the pneumococcal polysaccharide vaccine now on the U.S. market. Second, in 1967, NIAID believed that the development of a pneumococcal polysaccharide vaccine to help prevent pneumococcal diseases was technologically feasible.

At the time NIAID committed itself to providing Federal funds for polyvalent pneumococcal polysaccharide vaccine research and development in 1967, no pharmaceutical

[8] Federal Government licensure of Merck's 14-valent pneumococcal polysaccharide vaccine is discussed in ch. 3.

company had committed itself to the development of a marketable product. NIAID's financial support greatly enhanced the coordination and visibility of pneumococcal vaccine research and development efforts.

Subsequent to NIAID's involvement, at least three pharmaceutical companies, Lilly, Merck, and Lederle, either started or intensified their pneumococcal research and development programs. That either Merck or Lederle would have pursued the independent development of a pneumococcal polysaccharide vaccine had NIAID not decided to become involved appears unlikely. Although neither company received direct Federal funding for basic research or product development, Merck did receive data generated from NIAID-funded research. When it subsequently applied for licensure to market its pneumococcal vaccine, Merck was required to submit to BOB some of its own data. Data that relate to specific manufacturing processes are considered to be trade secrets and are protected from public scrutiny by patent laws, but data such as those relating to the product's safety and efficacy are made public. Lederle, therefore, was able to use some of Merck's data in the development of its own product.

Merck and Lederle, the two companies that did not receive Federal funds for pneumococcal vaccine research and development, appear to remain strongly committed to their pneumococcal and other vaccine-related activities. Somewhat ironically, Eli Lilly, the one company that received Federal financing to develop pneumococca] polysaccharide vaccine, not only has since stopped all its work on pneumococca] vaccine, but has withdrawn from the vaccine market almost entirely. As reasons for- terminating the bulk of its vaccine research, development, and production activities, Lilly cited a number of economic factors, one of which was the cost of complying with certain Federal Government regulations.

The impact of various types of Federal Government policies on the commitment of the pharmaceutical industry to the research, development, and production of vaccines has not been thoroughly studied. For the pharmaceutical industry as a whole, the impact of particular Federal vaccine policies on private sector research, development, and production should be viewed in perspective with the impact of general economic factors, e.g., the size of the vaccine market and the profitability of vaccines compared to other pharmaceutical products.

3.

A CASE STUDY: EVALUATING THE SAFETY AND EFFICACY OF PNEUMOCOCCAL VACCINE

3.

A CASE STUDY: EVALUATING THE SAFETY AND EFFICACY OF PNEUMOCOCCAL VACCINE

Obviously one can always do more and more clinical studies and, with each well done study, advance our knowledge. Even today we are still learning new things about vaccines licensed decades ago.

It is important, however, for the judgment to be made at some point that the product is ready for licensure and to weigh the benefits of delay in gaining new data against the risks to those who are deprived by this delay in being immunized and protected.

Paul D. Parkman, M.D.
Deputy Director, Bureau of Biologics
May 23, 1979

BACKGROUND AND INTRODUCTION

Investigators since the 1800's have attempted to evaluate the safety and efficacy of medical technologies and procedures (U.S. Cong., OTA, September 1978). Efforts during the first half of the 19th century were generally unsophisticated and tended to focus on safety, however, and many medical therapies at the time were not efficacious. When the ineffectiveness of many technologies was demonstrated through the application of controlled trials and statistical techniques during the latter half of the 19th century, the public's confidence in medicine sharply declined.

The concepts of safety and efficacy as applied to medical technologies and procedures have generated considerable public debate. While most people would agree that medical technologies and procedures should be safe and efficacious, there is little consensus on the types of criteria and methods that should be used to evaluate safety and efficacy.

Federal authority to regulate the quality of vaccines produced in the private sector dates from 1902, the year Congress enacted the first biologics control act. This act, the Virus Serums and Toxins Act of 1902, and pursuant regulations issued in 1903, 1909, and 1919, were incorporated into section 351 of the Public Health Service Act of 1944 and remain in force today, Current Federal authority to regulate vaccine safety and efficacy also is based on the 1962 amendments to the Food, Drug, and Cosmetic Act of 1938. Investigational new drug (IND) regulations developed from the 1962 amendments have been applied to biologics since 1963. (See appendix 3.1.)

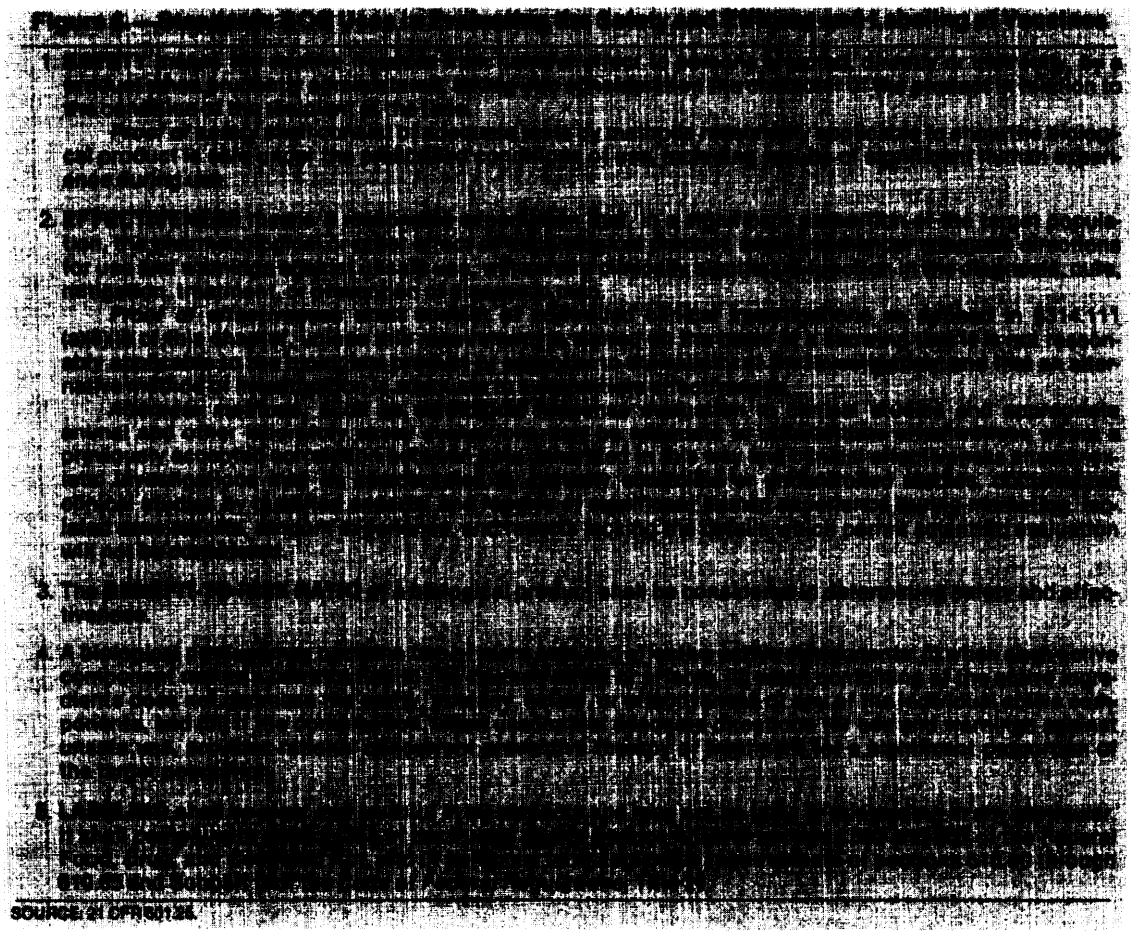
Many regulations that establish the standards and procedures that the Food and Drug Administration (FDA) uses to evaluate the safety and efficacy of investigational, as well as marketed, vaccine products were promulgated in 1972. In that year, responsibility for helping to ensure the safety and efficacy of biological products was transferred to FDA from the National Institutes of Health (NIH), which had had this responsibility for over 20 years.

The general standards that FDA's Bureau of Biologics (BOB) uses to evaluate the safety and efficacy of vaccines and other biological products are shown in figure 6. As noted in OTA's report *Assessing the Efficacy* and Safety of *Medical Technologies,* definitions of efficacy and effectiveness vary substantially, and often these terms are used interchangeably. In that OTA report, the two were differentiated as follows (U.S. Cong., OTA, September 1978):

Efficacy: The probability of benefit to individuals in defined populations from a medical technology applied for a given medical problem under ideal conditions of use.

Effectiveness: Same as efficacy except that it refers to ". . . average conditions of use. "

This OTA definition of efficacy closely parallels BOB's definition of effectiveness shown in figure 6, and efficacy so defined is the term used in this chapter.



The 10 basic steps involved in BOB's vaccine product licensure and review process are shown in figure 7. Some of the procedures and processes that BOB uses to regulate the market introduction of vaccines resemble those that FDA's Bureau of Drugs (BOD) uses to regulate therapeutic prescription drugs. (See appendix 3.2.) Like BOD, BOB can require a manufacturer to submit for its approval an investigational new drug application (IND), which must be accepted before a U.S. manufacturer is permitted to test a new product in clinical trials. Also, like BOD, BOB can waive or modify the IND requirement if it believes that available foreign clinical trial data regarding a particular product are sufficient.

Unlike BOD, however, BOB does not use the new drug application (NDA) process to permit a manufacturer to market a product; instead, it issues establishment and product licenses. Before marketing a vaccine product, a manufacturer is required to obtain two types of licenses from BOB—a general manufacturing establishment license and a license for the particular product. Both types of licenses remain valid until suspended or revoked by FDA either for a particular cause or at the manufacturer's (voluntary) request.

For detailed discussion of each of the 10 steps shown in figure 7, including the sources of statutory and regulatory authority, see appendix 3.3. The types of safety and efficacy data and information on which BOB bases its evaluations of vaccines and other biological products are described in appendix 3.4.

BOB's use of premarketing data, criteria, standards, and methods to evaluate the clinical safety and efficacy of Merck's 14-valent pneumococcal capsular polysaccharide vaccine (PNEUMOVAX) prior to licensure is described below. Issues related to the heavy reliance on premarketing clinical testing and the comparatively small emphasis on structured, systematic, and comprehensive postmarketing evaluation are discussed further in chapter 6. Options for the Federal Government to strengthen postmarketing surveillance of licensed vaccines are described in chapter 7.

TYPES OF STUDIES USED TO EVALUATE THE SAFETY AND EFFICACY OF POLYVALENT PNEUMOCOCCAL VACCINE

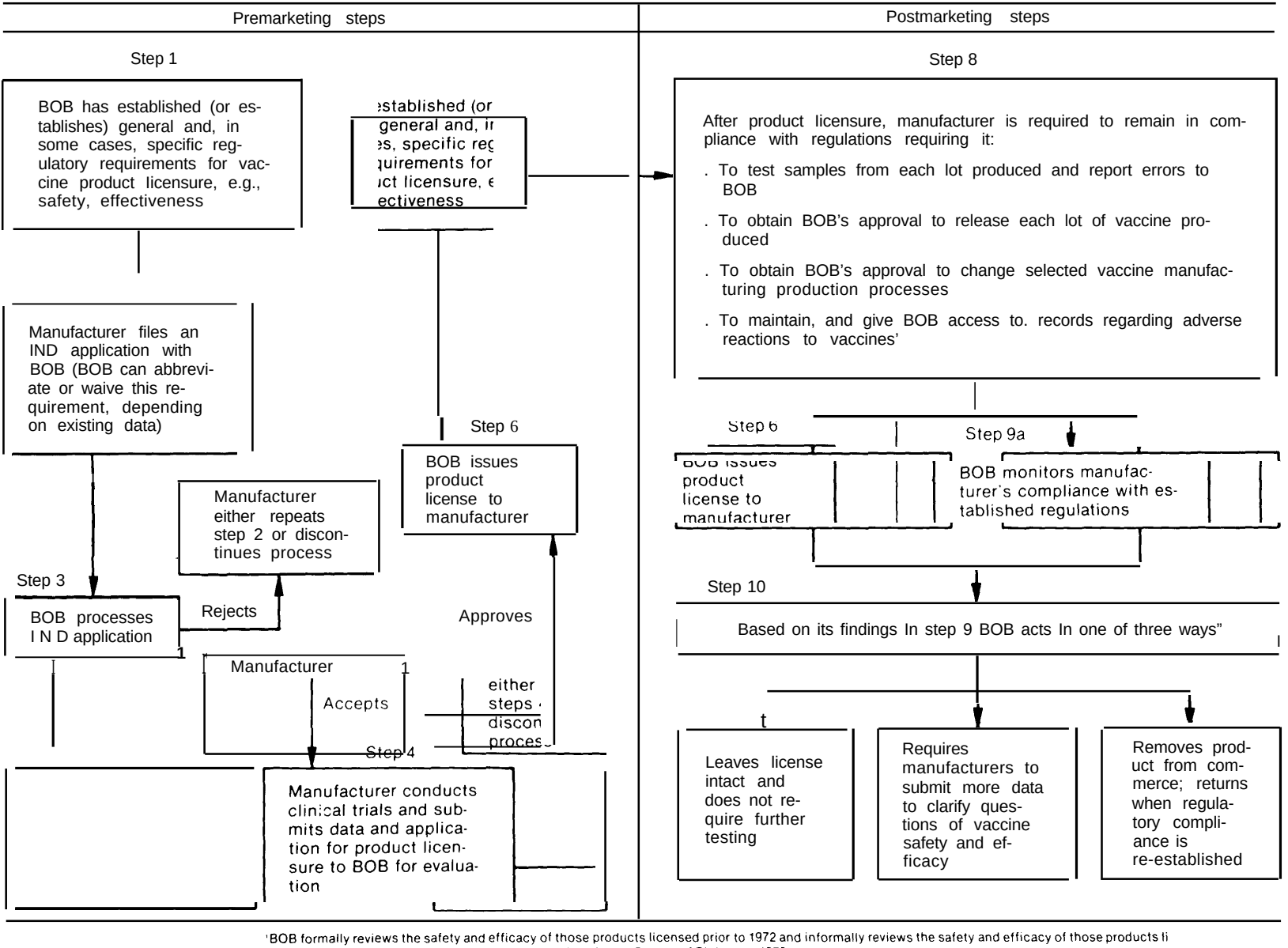
The safety and efficacy of 2-, 3-, 4-, and 6-valent pneumococcal capsular polysaccharide vaccines were demonstrated in three major clinical trials conducted independently by Lloyd Felton and G. M. Ekwurzel in the 1930's, Colin MacLeod in 1945, Paul Kaufman in 1947, and in the immunogenicity studies conducted by Michael Heidelberger in 1948. These investigations, discussed in appendix 1.1, were important benchmarks in the research and development of Merck Sharp and Dohme's (MSD) 14-valent vaccine. Because of differences in the chemical composition of the vaccines tested, however, most of these early trials did not generate data that BOB could use to evaluate the safety and efficacy of Merck's 14-valent vaccine.

To evaluate Merck's product, BOB required additional data, and for the most part, it relied on data from 26 studies conducted between 1967 and 1977. These 26 studies included three major types of investigations:

1. Epidemiologic studies to evaluate which types of pneumococci produce disease in the United States.

[1]The discussion in this chapter includes only those studies BOB used to evaluate polyvalent pneumococcal vaccine prior to licensure. Other studies of polyvalent pneumococcal vacines were conducted, but BOB did not rely on their data.

Figure 7.—BOB'S Vaccine Product Licensure Application and Review Process



'BOB formally reviews the safety and efficacy of those products licensed prior to 1972 and informally reviews the safety and efficacy of those products li
SOURCE: OTA's interpretation of information provided by the Bureau of Biologics. 1979.

2. **Immunogenicity studies** to determine pneumococcal vaccine's ability to stimulate the production of protective antibodies in humans.
3. Clinical trials to assess the level of the vaccine's clinical safety and efficacy in humans.

The three categories of studies used to evaluate the safety and efficacy of pneumococcal vaccine are described in appendix 3.5.

Altogether, the 26 studies on which BOB based its evaluation involved a total of approximately 60,000 subjects, about 23,000 (38 percent) of whom received some experimental pneumococcal vaccine. (See table 6.) Vaccines tested in these studies were 6-, 8-, 12-, 13-, or 14-valent pneumococcal polysaccharide vaccines produced in the United States by either EIi Lilly and Company or by Merck Sharp and Dohme (MSD).

Table 6.—Overview of the 26 Studies BOB Used To Evaluate Pneumococcal Vaccine

Sponsor/Study	Type of study[a]	Type of subjects	Number of subjects[b]	Year(s) of study
Industry[c]				
1. MSD (No. 315) (Smit)	Epidemiologic Efficacy Safety Immunogenicity	Foreign (South African)	983 vaccinees 2,036 controls	1973-75
2. MSD (No. 315A) (Smit)	Epidemiologic Efficacy Safety Immunogenicity	Foreign (South African)	718 vaccinees 1,493 controls	1974-76
3. MSD (No. 497)[d]. .	Immunogencity	Domestic	26 vaccinees	1977
4. MSD (No. 378)[e]. .	Immunogenicity in children	Foreign (Chilean)	4,000 vaccinees	1976
5. MSD(NO. 378D)[e]	Immunogenicity in children	Foreign (Chilean)	31 vaccinees	1976
6. MSD(NO. 337)[e]. .	Immunogenicity in children	Foreign (Chilean)	37 vaccinees	1976
7. MSD (No. 384)[f]. .	Immunogenicity Efficacy	Domestic	25 vaccinees	1976
8. MSD (No. 431)[f]. .	Immunogenicity Efficacy	Domestic	17 vacinees	1975
9. MSD (No. 482)[f]. .	Immunogenicity Efficacy	Domestic	13 vaccinees	1976
10. MSD (No. 454)[f]. .	Immunogenicity Efficacy	Domestic	23 vaccinees	1977
11. MSD9	Immunogenicity Safety	Domestic	20 vaccinees	1967
12. MSD/Papua[h] (Riley)	Epidemiologic Efficacy Safety Immunogenicity	Foreign (New Guinean)	5,946 vaccinees 6,012 controls	1973-76
13. Lederle (BB-IND 685) (Mufson).	Immunogenicity	Domestic	150 vaccinees 150 controls	1976
Subtotals . .	Epidemiologic (3 studies) Efficacy and Safety (8 studies) Immunogenicity (13 studies)	Foreign (6 studies) Domestic (7 studies)	11,989 vaccinees (foreign, 11, 715; domestic, 274) 9,691 controls (foreign, 9,541; domestic. 150)	1973-77

Footnotes appear at end of table

Table 6.—Overview of the 26 Studies **BOB Used To Evaluate Pneumococcal Vaccine—cont.**

Sponsor/Study	Type of studya	Type of subjects	Number of subjectsb	Year(s) of study
Government				
1. Austrian (Kaiser)	Efficacy Safety Immunogenicity	Domestic	6,850 vaccinees 6,750 controls	1972-76
2. Coulehan	Epidemiologic	Domestic	219 cases (no vaccinees)	1976
3. Austrian.	Immunogenicity	Domestic	21 vaccineesi	1976
4. Bentley.	Epidemiologic Immunogenicity	Domestic	110 vaccinees	1974
5. Ammann.	Efficacy Safety Immunogenicity	Domestic	178 vaccinees 106 controls	1977
Subtotals . .	Epidemiologic (2 studies) Efficacy and Safety (2 studies) Immunogenicity (4 studies)	Domestic (5 studies)	7,159 vaccinees 6,856 controls	1972-77
Academe				
1. Finland and Barnes	Epidemiologic	Domestic	12,049 cases (no vaccinees)	1935-74
2. Kaiser and Schaffner. . . .	Epidemiologic	Domestic	64 cases (no vaccinees)	*1968-72*
3. Shaperaand Matsen.	Epidemiologic	Domestic	62 cases (no vaccinees)	1961-70
4. Seeler.	Epidemiologic	Domestic	23 cases (no vaccinees)	1972
Subtotals. .	Epidemiologic (4 studies)	Domestic (4 studies)	12,198 cases (no vaccinees)	1935-77
Other				
1. Lund (Danish Government) .	Epidemiologic	Foreign	Unknown[k]	1955-70
2, Austrian (Chamber of Mines of South Africa. .	Epidemiologic (3 studies) Efficacy and Safety (3 studies) Immunogenicity (3 studies)	Foreign (South African) (3 studies)	4,000 vaccinees 8,000 controls	1972-76
Subtotals. .	Epidemiologic (4 studies) Efficacy and Safety (3 studies) Immunogenicity (3 studies)	Foreign (4 studies)	4,000 vaccinees 8,000 controls	1955-76

Footnotes appear at end of table

Table 6.—Overview of the 26 Studies BOB Used To Evaluate Pneumococcal Vaccine—cont.

Sponsor/Study	Type of study[a]	Type of subjects	Number of subjects[b]	Year(s) of study
SUBTOTALS	Epidemiologic (13 studies) Efficacy and Safety (8 studies) Immunogenicity (20 studies)	Foreign (10 studies) Domestic (16 studies)	23,148 vaccinees (foreign, 15,715; domestic, 7,433) 24,547 controls (foreign, 1 7,541; domestic, 7,006) 12,417 cases	1935-77
TOTALS	Epidemiologic, Efficacy and Safety, Immunogenicity (26 studies)[j]	Foreign and Domestic (26 studies)[j]	60,112 subjects	1935-77

[a] In "Efficacy" studies cited, investigators measured the reduction in the incidence of pneumococcal disease among vaccinees in controlled clinical trials
[b] Some epidemiologic studies listed report only cases of pneumococcal pneumonia. In these studies, there were no vaccinated or control subjects
[c] Except for the study by Lederle, all these studies were funded entirely or partially by Merck Sharp and Dohme (MSD).
[d] The results of Merck's immunogenicity study No. 497 were not published.
[e] The results of these Merck immunogenicity studies were reported by Borgon
[f] The results of these Merck immunogenicity studies were reported by Weibel
[g] The results of this Merck study were not published.
[h] This study was cosponsored by Merck Sharp and Dohme and the Department of Public Health, Papua, New Guinea.
[i] All these U.S studies were funded or assisted in some way by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).
[j] Austrian conducted vaccine immunogenicity studies involving over 1,000 vaccinees under contract with NIAID. The extent to which data from these investigations were used by BOB was not ascertained for this report.
[k] The total number of cases reported in Dr. Lund's investigation were not calculated for this report.
[l] This number refers to major studies In some studies, two or three types of investigations, (e.g., epidemiologic, efficacy and safety, and immunogenicity) were conducted.

SOURCE OTA's interpretation of data provided by the Bureau of Biologics, Merck Sharp and Dohme, the National Institute of Allergy and Infectious Diseases, and principal investigators of included studies, 1979.

Ten of the 26 studies were conducted in foreign countries: five in South Africa, three in Chile, one in New Guinea, and one in Denmark. Foreign studies involved about 33,000 subjects (55 percent of the total study population), including some 16,000 vaccinees (70 percent of the total vaccinated).

Primary sponsors were Merck Sharp and Dohme (the first vaccine manufacturer licensed to produce pneumococcal vaccine in the United States), the National Institute of Allergy and Infectious Diseases (NIAID), and the Chamber of Mines of South Africa. Other sponsors included academic institutions in the United States, the Danish Government, and the Department of Public Health, Papua, New Guinea.

RESULTS OF PREMARKETING CLINICAL TRIALS OF PNEUMOCOCCAL VACCINE[2]

Clinical Safety

The types of adverse reactions produced by vaccines can be categorized as follows:

Local reactions: These reactions include pain, redness, and swelling at the vaccine injection site. Such reactions do not involve other areas of the body and are usually minor.

[2] Data from the 13 epidemiologic studies of Pneumococcal pneumonia and the 20 studies BOB used to assess the immunogenicity of experimental polysaccharide polyvalnt pneumococcal vaccines are not summarized in this report. For these data, consult the references cited for each study in table **6.**

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.

Fatal reactions from the use of pneumococcal vaccine have not been reported.

The results of the eight clinical trials and one other report (Weibel, 1977) that BOB used to assess the level of safety of experimental polyvalent pneumococcal polysaccharide vaccines are presented in table 7. As shown in this table, in the five clinical trials conducted in South Africa (two by Merck, three by Robert Austrian), investigators reported quite low rates of adverse reactions. The incidence of local reactions reported in these studies was around 1 to 2 percent; fevers were not commonly reported; and no severe or fatal reaction was reported (Austrian, et al., 1976; Smit, 1977). In his investigation in New Guinea, I. D. Riley studied adverse reactions in a subpopulation of 133 vaccinees (comprising 2 percent of his total study population), and reported a 27 percent incidence of local reactions and a 7 percent incidence of mild fevers (Riley, 1977). Riley further reported that 75 percent of these 133 vaccinees experienced no adverse reactions.

In an NIAID-sponsored study among 180 vaccinees in the United States, Arthur Ammann reported only one case of mild fever (Ammann, 1977). Austrian, in another NIAID-sponsored U.S. study of 6,850 vaccinees, reported a 40 percent incidence rate of

Table 7.— Results of Premarketing Safety Studies of Pneumococcal Vaccine

	Number of vaccinees[a]		Rate of reported reactions[b]			
Sponsor	Foreign	Domestic	Local[c]	Fever	No reactions	Severe systemic
Industry[d]						
1. MSD (No. 315) (South Africa)	983		1-2 percent	Low frequency	High frequency	None
2. MSD (No. 315A) (South Africa)	718		1 percent	Low frequency	High frequency	None
3. Riley[e] (New Guinea)	5,946 (133)[a]		27 percent	7 percent (mild)	75 percent	None
4. Weibel (No. 384, 431, 454, 482) (USA)		92	86-98 percent (1 case-severe)	14-40 percent (1 case-high)	14 percent	None
Government[f]						
1. Austrian (Kaiser-USA)		6,850	40 percent	3.4 percent (mild)	60 percent	None
2. Ammann (USA)		178	Unknown	1 case (mild)	Unknown	None
Other[g]						
1, Austrian (South Africa) (3 trials)	4,000		1 percent	1 percent	99 percent	None
Subtotals	17,647	7,120				
Total	18,767					

[a]The exact number of vaccinees observed for adverse reactions in most of these studies is unknown. Numbers refer to the total number of vaccinees in each study, but in some of the studies, only some of the vaccinees may have been observed for adverse reactions. In Riley's New Guinea study, for example, only 133 of 5,946 vaccinees were observed for adverse reactions.
[b]The inconsistent manner in which data for different studies are displayed in this table reflects the manner in which clinical investigators reported these data.
[c]Local reactions include pain, redness, and swelling at the vaccine injection site.
[d]These studies were sponsored by Merck Sharp and Dohme (MSD).
[e]This study was cosponsored by Merck Sharp and Dohme and the Department of Public Health, Papua, New Guinea.
[f]These studies were sponsored at least in part by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes Of Health (NIH)
[g]These studies were sponsored by the Chamber of Mines of South Africa.

SOURCE: OTA's Interpretation of data provided by the Bureau of Biologics, Merck Sharp and Dohme, the National Institute of Allergy and Infectious Diseases, and principal investigators of included studies

local reactions and a 3 percent rate of mild fevers; 60 percent of the vaccinees in the Austrian study experienced no adverse reactions (Austrian, et al., 1976).

In a group of small Merck Sharp and Dohme studies (not clinical trials) also conducted in the United States, Robert Weibel reported much higher incidence rates of adverse reactions (Weibel, 1977). For example, among 92 vaccinees in four studies, 86 to 98 percent reported experiencing local reactions (one case was severe), and 14 to 40 percent reported fever (one case was severe).

In the eight clinical trials that generated data which BOB used to evaluate the safety and efficacy of the currently licensed pneumococcal vaccine, a total of six different vaccine products were used. These products were a 6-valent, a 12-valent, and a 14-valent pneumococcal vaccine produced by Merck Sharp and Dohme, and a 6-valent, an 8-valent, and a 13-valent vaccine produced by Eli Lilly.

Clinical Efficacy

The primary criterion investigators in the eight clinical trials used to evaluate pneumococcal vaccine's clinical efficacy was the incidence of pneumococcal pneumonia (or in some cases, bacteremia) caused by the types of pneumococci represented in the vaccine. The incidence of either pneumococcal pneumonia or bacteremia among vaccinees was compared to the incidence of such disease among control subjects. The results of these eight trials are presented in table 8.

Table 8.—Results of Premarketing Efficacy Trials of Pneumococcal Vaccine

Sponsor	Type of vaccine	Number of subjects	Reduction in the incidence of diseasea among vaccine recipients: Pneumococcal pneumonia	Pneumococcal bacteremia
Industry[b]				
1. MSD (No. 315) (South Africa)	6-valent (MSD)	983 vaccinees 2,036 controls	76 percent	Unknown
2. MSD (No. 315A) (South Africa)	12-valent (MSD)	718 vaccinees 1,493 controls	92 percent	Unknown
3. RileyC (New Guinea)	14-valent (MSD)	5,946 vaccinees 6,012 controls	Unknown[d]	Unknown
Government				
1. Austrian (Kaiser-USA)	13-valent (Lilly)	6,850 vaccinees 6,750 controls	Unknown	100 percent[f]
2. Ammann (USA)	8-valent (Lilly)	77 vaccinees 106 controls	100 percent[g]	
Other[h]				
1. Austrian (South Africa) (3 trials)	6-valent, 13-valent (Lilly)	4,000 vaccinees 8,000 controls	78.5 percent[i]	82.3 percent
Total		18,574 vaccinees 24.397 controls		

[a]Disease means either pneumococcal pneumonia or bacteremia caused by one of the types of pneumococci represented in the experimental vaccine
[b]These studies were sponsored by Merck Sharp and Dohme
[c]This study was cosponsored by Merck Sharp and Dohme and the Department of Public Health, Papua, New Guinea
[d]In this study, an 18 percent reduction in incidence of lower respiratory tract infection (LRTI) and a 22 percent reduction in overall death rate were reported
[e]These studies were sponsored at least part by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).
[f]Four cases occurred among controls, none among vaccinees.
[g]Eight cases occurred among controls, none among vaccinees
[h]These studies were sponsored by the Chamber of Mines of South Africa
[i]This reduction was reported in only one trial involving 1,493 pneumococcal vaccinees and 3.007 control subjects

SOURCE OTA'S Interpretation of data provided by the Bureau of Biologics, Merck Sharp and Dohme, the National Institute of Allergy and Infectious Diseases, and principal Investigators of included studies, 1979

In Merck study No. 315, a 6-valent vaccine was tested in South Africa. The type-specific (i.e, caused by one of the six types of pneumococci represented in the vaccine) pneumococcal pneumonia incidence rate among nearly 1,000 vaccinees in this study was 76 percent lower than the rate among 2,000 control subjects (Smit, 1977). When a 12-valent vaccine was tested in a similar clinical trial in South Africa, MSD No. 315A, a 92 percent reduction in the incidence rate of type-specific pneumococcal pneumonia was reported (Smit, 1977).[3]

In three South African clinical trials sponsored by the Chamber of Mines of South Africa and conducted by Austrian, a total of 4,000 test subjects were vaccinated with polyvalent pneumococcal vaccines made by Eli Lilly, and 8,000 subjects were used as controls (Austrian, et al., 1976). BOB used two findings from these trials to evaluate the clinical efficacy of the vaccine. First was the finding in one trial involving a 13-valent vaccine that the incidence rate for type-specific putative pneumococcal pneumonia was 78.5 percent lower among 1,493 vaccinees than the rate among 3,007 controls. Second was the finding that, when data were combined from all three trials, the incidence rate of type-specific pneumococcal bacteremia among the 4,000 vaccinees was 82.3 percent lower than the rate among the 8,000 controls; 10 cases of type-specific bacteremia occurred in pneumococcal vaccinees, while 113 cases occurred among control subjects.

In Riley's New Guinea study, cosponsored by Merck and the Papua Department of Public Health, about 6,000 persons received an experimental 14-valent pneumococcal vaccine, and another 6,000 persons received a placebo (Riley, 1977). Investigators in this clinical trial did not measure the difference between vaccinees and controls in the incidence of type-specific pneumococcal pneumonia or bacteremia. Instead, they measured the difference in the incidence of lower respiratory tract infection (LRTI). The incidence of LRTI among pneumococcal vaccinees was only 18 percent lower than the incidence among control subjects.

In the NIAID-sponsored clinical trial conducted by Austrian at the San Francisco Kaiser Permanence Medical Center, 6,850 test subjects received experimental 13-valent pneumococcal polysaccharide vaccine, and 6,750 control subjects received a placebo vaccine (Austrian, May 28, 1976). The attack rate of respiratory disease caused by the types of pneumococci represented in the vaccine was too low in the experimental and control groups to yield statistically significant data regarding the clinical efficacy of the vaccine in preventing pneumococcal pneumonia. BOB, however, did use incidence data for pneumococcal bacteremia to help assess the efficacy of the vaccine. Four cases of bacteremia occurred in the control population, and no cases occurred in the test population.

In another NIAID-sponsored trial, also conducted in San Francisco, Ammann administered an 8-valent pneumococcal polysaccharide vaccine made by Eli Lilly to 77 children with sickle-cell disease. He then compared the incidence of pneumococcal infections among these children to that among 106 unvaccinated children with sickle-cell disease (Ammann, 1977). During a 2-year followup period, Ammann found eight cases of pneumococcal disease among the unvaccinated controls and no cases among vaccinees.

The studies BOB used to evaluate the clinical safety and efficacy of pneumococcal vaccine prior to licensure are described in detail in appendix 3.6.

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[3]The diagnosis of pneumococcal pneumonia initially was made on the basis of clinical criteria (e.g., cough, fever, purulent, rusty, or bloody sputum, rales, bronchial breathing, and localized chest pain on percussion). In any test subject having three or more of these symptoms or signs, investigators conducted a chest X-ray and collected samples for further laboratory diagnostic study. Typing of pneumococci was performed using the Quellung reaction. Sera were tested for antibodies by a standard radioimmunoassay.

BOB'S PRELICENSING EVALUATION OF PNEUMOCOCCAL VACCINE

Based on its analysis of data from the studies discussed above, BOB issued the statements below regarding the public need for, as well as the safety and efficacy of, Merck's 14-valent pneumococcal capsular polysaccharide vaccine (PNEUMOVAX). These statements were contained in BOB's summary of its basis for approving licensure of this product (U.S. Ex. Br., BOB, 1977):

Public Need

Pneumococci cause serious disease in individuals of all ages. As individuals mature over *50* years, the attack rate of pneumococcal disease increases. Individuals who have had their spleens removed or have malfunctioning spleens, as seen in excessive hemolytic states such as sickle-cell anemia, are particularly at risk to severe and overwhelming pneumococcal disease. Despite antimicrobial therapy, approximately **5-10%** of individuals who have pneumococcal pneumonia and/or bacteremia succumb to their disease. In addition, antimicrobial therapy and other supportive measures still have not reduced the morbidity and mortality of pneumococcal meningitis below 50%. Further, there are now appearing, with increasing regularity, pneumococcal strains with decreased sensitivity to penicillin and other acquired resistance to many other antibiotics. *Thus, prevention of* ***this disease seems worthwhile.***

Environmental Impact Analysis Report

The cost of producing the vaccine, the waste products from the vaccine, and the cost of the vaccine are not considered to have a deleterious environmental impact. It is anticipated that a favorable environmental impact upon the Nation's health will be induced by the vaccine.

Safety

Adverse reactions such as local swelling, pain or erythema, occur in approximately *5-15%* of vaccine recipients. These reactions are considered minor and do not interfere with the benefit/risk provided by this vaccine for the patient.

In clinical trials of this product, as well as comparable products made by Eli Lilly and Company under contract for the National Institute of Allergy and Infectious Diseases, and capsular polysaccharides made by E. R. Squibb & Sons, Inc., and individual investigators in the 1930's and 1940's, approximately 20,000-30,000 individuals have been vaccinated. There have been no reports of immediate or long range toxic effects.

There are no deleterious effects of this capsular polysaccharide vaccine when injected in appropriate doses in laboratory animals. At very high doses (at least logarithms in excess of the human dose) or extraordinarily low doses (two logarithms less than the human dose), a suppressive effect upon the specific immune response to the polysaccharide may be induced. This phenomenon has not been observed with pneumococcal capsular polysaccharides in humans or following disease with the individual types of organisms.

Efficacy

Indications for use: For the prevention of pneumococcal pneumonia and/or bacteremia in individuals older than 2 years of age.

The mechanism by which the vaccine exerts its protective effect is the induction of serum antibodies. . . . individuals less than 2 years of age, pregnant women, or individuals with primary or treatment-induced immunodeficiency states may not respond with sufficient amount of antibody to have the protective immunity . . .

> . . . antibody response to each type is not inhibited by their polyvalent formulation. The antibody response has been shown to be the protective moiety and can be induced with regularity in at least 80-100% of all vaccine recipients over the age of 2 years. A similar response occurs in those well into the 70's and 80's as well as healthy individuals who do not have spleens or have malfunctioning spleens, such as seen in excessive hemolytic states as sickle-cell anemia and in individuals who have chronic alcoholism as a disability.

The Code of *Federal Regulations* contains the following mandate (21 CFR 601 .25):

> The benefit-to-risk ratio of biological product shall be considered in determining safety and efficacy.

After BOB separately analyzed data regarding the safety and efficacy of pneumococcal vaccine, it considered these data together to determine the relative benefits and risks of the vaccine under anticipated conditions of use. The potential benefits of pneumococcal vaccine, BOB apparently believed, outweighed its risks.

On the basis of BOB's evaluation, on November 21, 1977, FDA issued Merck Sharp and Dohme a license to market its 14-valent pneumococcal capsular polysaccharide vaccine (PNEUMOVAX). FDA-approved statements for the package insert of Merck's product are shown in figures 8 (Public Need), 9 (Safety), and 10 (Efficacy). Presumably, the same statements will appear on the package insert for Lederle's new polysaccharide pneumococcal vaccine (PNU-IMUNE), which FDA licensed on August 15, 1979.

POSTMARKETING DATA REGARDING THE SAFETY AND EFFICACY OF PNEUMOCOCCAL VACCINE

Merck's 14-valent pneumococcal vaccine (PNEUMOVAX) appeared on the U.S. market in February of 1978. The company reported that between February and September of 1978, roughly 1.6 million doses of this vaccine were distributed in the United

Figure 8.—FDA-Approved Statements Regarding the Public Need for Pneumococcal Vaccine (PNEUMOVAX)

Pneumococcal infection is a leading cause of death throughout the world and a major cause of pneumonia, meningitis, and otitis media. The exact incidence of pneumococcal infection is not known. On the basis of the limited epidemiological data obtained from studies in municipal hospitals where the incidence might be higher than that found in the average population, it is estimated that there are annually 200,000 to 1,000,000 cases of pneumococcal pneumonia in the United States, and between 13,200 and 66,000 deaths resulting therefrom. Thus, the attack rate for pneumococcal pneumonia is estimated to be between 1 and 5 cases per 1,000 persons per year, and death is *estimated* to occur in about 1 of 15 cases. Based on these same data, about 25 percent of all persons with pneumococcal pneumonia develop bacteremia. Death occurs in about 28 percent of these bacteremic patients more than 50 years of age.

In the United States, pneumococcal meningitis occurs principally in young children with annual rates of about 3 to 11 per 100,000 children less than 5 years old. Within the first 2 years of life, about 15 to 20 percent of all children develop otitis media caused by pneumococci, and 50 percent of all children develop such illness within the first 10 years of life (see under INDICATIONS).

Invasive pneumococcal disease causes high morbidity and mortality in spite of effective antimicrobial control by antibiotics. These effects of pneumococcal disease appear due to irreversible physiologic damage caused by the bacteria during the first 5 days following onset of illness, and irrespective of antimicrobial therapy. Older persons, individuals with chronic debilitating diseases, and persons with absent or impaired splenic function, including those with homozygous sickle-cell anemia and sickle thalassemia, are especially susceptible to severe pneumococcal disease.

SOURCE: Package Insert, PNEUMOVAX, Merck Sharp and Dohme, 1979.

Figure 9.—FDA-Approved Statements Regarding the Safety of Pneumococcal Vaccine (PNEUMOVAX)

PRECAUTIONS

Any febrile respiratory illness or other active infection is reason for delaying use of PNEUMOVAX, except when, in the opinion of the physician, withholding the agent entails even greater risk.

Caution and appropriate care should be exercised in administering PNEUMOVAX to individuals with severely compromised cardiac and/or pulmonary function in whom a systemic reaction would pose a significant risk.

Patients who have had episodes of pneumococcal pneumonia or other pneumococcal infection in the preceding 3 years may have high levels of pre-existing pneumococcal antibodies which may result in increased reactions to PNEUMOVAX, mostly local but occasionally systemic. Caution should be exercised if such patients are considered for vaccination with PNEUMOVAX.

Available data suggest that revaccination before 3 years may result in more frequent and severe local reactions at the site of injection, especially in persons who have retained high antibody levels (see DOSAGE AND ADMINISTRATION).

Children under 2 years of age may not obtain a satisfactory antibody response to some pneumococcal capsular types. Therefore, the vaccine should not be used in this age group.

ADVERSE REACTIONS

Local erythema and soreness at the injection site, usually of less than 48 hours duration, occurs commonly; local induration occurs less commonly. In a study of PNEUMOVAX (containing 14 capsular types) in 26 adults, 24 (92 percent) showed local reaction characterized principally by local soreness and/or induration at the injection site within 2 days after vaccination.

Low grade fever (less than 100.9° F) occurs occasionally and is usually confined to the 24-hour period following vaccination. Although rare, fever over 102° F has been reported.

Reactions of greater severity, duration, or extent are unusual. Rarely, anaphylactoid reactions have been reported . . .

WARNINGS

Intradermal administration may cause severe local reactions.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine. Epinephrine injection (1:1000) must be immediately available should an acute anaphylactoid reaction occur due to any component of the vaccine.

Do not give PNEUMOVAX to pregnant females. The possible effects of the vaccine on fetal development are unknown.

SOURCE: Package Insert, PNEUMOVAX, Merck Sharp and Dohme, 1979

States for general use. Approximately 1.0 million doses probably were administered (Kasdin, 1979).

Neither the Federal Government nor the pharmaceutical industry systematically surveys vaccinees to determine the incidence of adverse reactions to licensed vaccines. Since Merck's pneumococcal vaccine has been in general use, however, a few reports of serious adverse reactions have voluntarily been made publicly available. Sporadic reporting in clinical literature, for example, has revealed at least three cases of severe fever associated with the use of this product (Uhl, 1978; Semel, 1979). In addition, reports vol - untarily submitted to the Center for Disease Control (CDC) by Merck Sharp and Dohme and by physicians administering the vaccine, as of September 1978, included six cases of possible anaphylaxis (severe allergic reaction), four cases of fever (1000 F), and nine cases of severe local reactions (Broome, 1978). Additional cases of adverse reactions to pneumococcal vaccine may have been reported through CDC's passive and voluntary vaccine adverse reaction monitoring system. (See appendix 3.7.)

Figure 10.—FDA-Approved Statements Regarding the Efficacy of Pneumococcal Vaccine (PNEUMOVAX)

INDICATIONS

PNEUMOVAX is indicated for immunization against pneumonia and bacteremia, caused by those types of pneumococci included in the vaccine, in all persons 2 years of age or older in whom there is an increased risk of morbidity and mortality from pneumococcal pneumonia. These include: 1) persons having chronic physical conditions such as chronic heart disease of any etiology, chronic bronchopulmonary diseases, chronic renal failure, and diabetes mellitus or other chronic metabolic disorders; 2) persons in chronic care facilities; 3) persons convalescing from severe disease; 4) persons 50 years of age or older.

Preliminary data suggest the vaccine is efficacious for preventing severe pneumonic disease and bacteremia in persons over 2 years of age with sickle-cell anemia and in individuals who have had a splenectomy or who have impaired splenic function, and in pediatric patients over 2 years of age with nephrotic syndrome. It is expected also that the vaccine will be found effective in preventing pneumococcal meningitis of bacteremic origin. However, PNEUMOVAX may not be effective in preventing infection resulting from basilar skull fracture or from external communication with cerebrospinal fluid. Studies are underway to determine the effectiveness of the vaccine for preventing pneumococcal otitis media in infants.

Presently, there are 83 known pneumococcal capsular types. However, the preponderance of pneumococcal diseases is caused by only some capsular types. For example, a 10-year (1952-1962) surveillance at a New York medical center showed that 56 percent of all deaths due to pneumococcal pneumonia were caused by 6 capsular types and that approximately 78 percent of all pneumococcal pneumonias were caused by 12 capsular types. Such unequal distribution of pneumococcal capsular types causing disease has been shown throughout the world. It is on the basis of this information that the pneumococcal vaccine is composed of 14 capsular types.

It has been established that the purified pneumococcal capsular polysaccharides induce antibody production and that such antibody is effective in preventing pneumococcal disease. PNEUMOVAX consists of 14 different capsular polysaccharides which represent at least 80 percent of pneumococcal disease isolates in the United States and Europe. Studies in humans have demonstrated the immunogenicity (antibody-stimulating capability) of each of the 14 capsular types when tested in polyvalent vaccines. Adults of all ages and children of 2 years of age or older responded immunologically to the vaccines. In a recent study of PNEUMOVAX, at least 90 percent of all adults showed a fourfold or greater increase in type-specific antibody for each vaccine capsular type . . .

The duration of protective effect of PNEUMOVAX is presently unknown, but it has been shown in previous studies with other pneumococcal vaccines that antibody induced by the vaccine may persist for as long as 5 years. Type-specific antibody levels induced by PNEUMOVAX have been observed to decline over a 20-month period of observation, but remain significantly above prevaccination levels in almost all recipients who manifest an initial response.

Because of the decline in antibody levels, revaccination may be considered. Available data suggest that revaccination should not be carried out at less than 3-year intervals so as to minimize the frequency and severity of local reactions, especially in persons who have retained high antibody levels. Long-term surveillance of antibody levels in immunized individuals is continuing . . .

WARNINGS

PNEUMOVAX will not immunize against capsular types of pneumococcus other than those contained in the vaccine (see above).

If the vaccine is used in persons receiving immunosuppressive therapy, the expected serum antibody response may not be obtained.

Children less than 2 years of age do not respond satisfactorily to the capsular types of PNEUMOVAX that are most often the cause of pneumococcal disease in this age group. Accordingly, PNEUMOVAX is not recommended in this age group.

Patients with Hodgkin's disease who have received extensive chemotherapy and/or nodal irradiation have been shown to have an impaired antibody response to a 12-valent pneumococcal vaccine. Because, in some intensively treated patients, administration of that vaccine depressed pre-existing levels of antibody to some pneumococcal types, PNEUMOVAX is not recommended at this time for patients who have received these forms of therapy for Hodgkin's disease.

SOURCE: Package Insert, PNEUMOVAX, Merck Sharp and Dohme, 1979.

In 1978, Nicholas Fiumara and George Waterman conducted a field study of the licensed 14-valent pneumococcal vaccine among 13,336 senior citizens and patients rehabilitating in various health care centers in Massachusetts (Fiumara, 1979). According to the investigators, vaccinees were monitored for adverse reactions for 48 hours subsequent to vaccination. During this observation period, nursing staffs in health care facilities reportedly recorded complaints that vaccinees volunteered about local reactions (at the site of injection) and took each vaccinee's body temperature twice daily. Reactions were reported in about 6 percent of 12,529 vaccinees: About 5.3 percent (715) experienced local reactions (soreness), and about 0.7 percent (92) had fevers, most of which *were* quite mild (100 ^{0} to **100.90** F). It is difficult to determine from the literature report of this study the extent to which vaccinees were monitored for severe systemic reactions to the vaccine, but no such reactions were reported.

Since pneumococcal vaccine has been marketed, at least five reports of vaccine failure have appeared in the medical literature (Overturf, 1979; Minor, 1979; Giebink, 1979; Preheim, 1978; Ahonkhai, 1979). In each of these reports, a person vaccinated with the licensed 14-valent product developed a pneumococcal infection caused by one of the types of pneumococci represented in the vaccine. Some of these vaccinees were healthy, although at least three had sickle-cell disease, one had Hodgkin's disease, and one had no spleen.

By themselves, these cases do not provide a sufficient data base for a comprehensive postmarketing evaluation of the vaccine's efficacy. In premarketing clinical trials, pneumococcal vaccine was shown to be about 80 percent effective. These newly reported cases may merely represent the 20 percent of vaccinees that would not be expected to be effectively protected by the vaccine. These cases may, however, represent vaccine failures that were not expected and may indicate that the vaccine is less efficacious, at least in high risk populations, than the 80 percent level projected on the basis of efficacy data from premarketing clinical trials. Further postmarketing clinical research is needed to more fully assess the efficacy of this vaccine in general use among healthy, as well as high risk, vaccinees.

One postmarketing literature report regarding the efficacy of Merck's new vaccine resulted in a change in the wording of the FDA-approved package insert. In August 1978, George Siber and associates reported a demonstrated impaired antibody response to pneumococcal vaccine in 53 patients previously treated for Hodgkin's disease (a form of cancer in the lymph glands) (Siber, 1978). As a result of this finding, BOB and Merck Sharp and Dohme agreed that the following language should be added to the vaccine's package insert:

> Patients with Hodgkin's disease who have received extensive chemotherapy and/or nodal irradiation have been shown to have an impaired antibody response to a 12-valent pneumococcal vaccine. Because, in some intensively treated patients, administration of that vaccine depressed pre-existing levels of antibody to some pneumococcal types, PNEUMOVAX is not recommended at this time for patients who have received these forms of therapy for Hodgkin's disease.

As mentioned in chapter 2, the National Institute of Allergy and Infectious Diseases (NIAID) is currently facilitating approximately 35 studies of the safety, Clinical efficacy, and immunogenicity of pneumococcal polysaccharide vaccines in specialized populations. NIAID is not funding these studies directly; instead, it is providing the assistance of its professional staff to researchers (mostly in academe) who wish to test some aspect of the vaccine. This Institute also finances antibody assays for these studies through a contract with a laboratory at the State University of New York (SUNY), Downstate Med-

ical Center, Brooklyn. It also is coordinating the dispersement to clinical investigators of pneumococcal vaccines, often donated, from the manufacturer.

Since licensure of the new 14-valent pneumococcal vaccine, NIAID has facilitated about 25 investigations of the vaccine's use among high risk populations: 8 involve splenectomized persons, 9 involve children with sickle-cell disease, 9 involve patients with various forms of cancer, and 13 involve patients with other types of medical problems.[4] These studies combined involve a total of about 2,800 subjects. Results from these studies will be made public, and some data will be available in the fall of 1979.

The Bureau of Biologics (BOB) since licensure has continued to seek and coordinate information regarding pneumococcal vaccine's safety and efficacy (Robbins, 1979). For example, BOB has sponsored three workshops at which new scientific data relating to the vaccine's safety, immunogenicity, and clinical efficacy were presented and discussed by prominent researchers. Further, BOB has incorporated selected new scientific and clinical findings into its evaluation and labeling requirement of the licensed product (e.g., regarding vaccination of patients with Hodgkin's disease). To coordinate information received from practitioners regarding adverse reactions to the vaccine, BOB participates in a voluntary arrangement with CDC, Merck Sharp and Dohme, and NIAID. Many, if not most, of BOB's postmarketing product evaluation activities result from the professional concerns and incentives of BOB's scientific personnel, rather than from statutory or regulatory authority or responsibility.

In Johannesburg, South Africa, Michael Jacobs and associates studied the emergence of new strains of pneumococci that are resistant to certain antibiotics (Jacobs, 1978). In particular, these investigators reported resistance to some antibiotics among Types 6A and 19A pneumococcal isolates. Antibiotic-resistant Type 6B pneumococci also have been reported (U.S. Ex. Br., CDC, 1979). Increasing numbers and growing patterns of types of pneumococci that are resistant to antibiotics enhance the usefulness of the new vaccine. Type 6A is represented in the vaccine, but Types 6B and 19A are not. Vaccine Type 19F, however, probably would confer protection against most infections caused by Type 19A. Type 6A would likely protect against Type 6B infections. Jacobs has suggested that extensive antibiotic resistance among types of pneumococci not currently in the licensed vaccine could serve as a criterion for altering the vaccine's composition.

LIMITATIONS OF PREMARKETING EVALUATIONS OF THE SAFETY AND EFFICACY OF PNEUMOCOCCAL VACCINE

Inherent Limitations of Premarketing Clinical Studies

In theory, every clinical trial is designed to assess both safety and efficacy. In fact, the degree of assessment of these two characteristics largely depends on the extent to which investigators in a particular trial focus on one characteristic or the other. Thus, reports regarding the number and types of adverse reactions to vaccines often reflect the intensity of researchers' efforts to evaluate vaccine safety.

Even when investigators design their clinical trials to emphasize the detection of adverse reactions, however, their ability to detect certain types of adverse reactions may be limited. Differences in local and systemic reaction rates reported in various studies may be influenced by a number of factors (Parkman, 1979):

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[4]Some; these studies involve two or more of these high risk populations. The total of the numbers cited for each high risk population, therefore, exceeds 25.

> Differences in local and systemic reaction rates in various studies are not unexpected; assessment of objective reactions depends, among other factors, on the timing and frequency of observation, and on subjective reactions or the judgment of the investigators.

A greater problem with evaluating the safety of vaccines in premarketing clinical trials, however, stems from the fact that most of these trials are conducted over 1- to 3-year periods (sometimes less) and usually do not involve large sample populations. As a result, reported adverse reactions to vaccines tested in premarketing clinical trials tend to be limited to acute and commonly occurring reactions. Two types of adverse reactions, in particular, frequently escape detection in premarketing clinical tests:

1. Adverse reactions that rarely occur, and
2. Adverse reactions that occur with delayed onset.

These limitations of premarketing clinical trials are illustrated in the case of pneumococcal vaccine. At least six investigations to evaluate the safety and efficacy of pneumococcal vaccines were conducted in this country. U.S. investigations included two clinical trials, Austrian's NIAID-sponsored study at the San Francisco Kaiser Permanence Medical Center (Austrian, et al., 1976), and Ammann's study in sickle-cell children (Ammann, 1977). The other four investigations, not clinical trials, were Merck studies No. 384, 431, 454, and 482 (Weibel, 1977). Differences in findings concerning adverse reactions to pneumococcal vaccine were substantial. Austrian reported that about 40 percent of his 6,850 vaccinated subjects experienced local reactions and another 3.4 percent developed a mild fever. In Merck studies No. 384, 431, 454 and 482, involving a total of 92 subjects, Weibel reported incidence rates for local reactions of 86 to 92 percent and incidence rates for fever of 14 to 40 percent. Ammann reported only one case of mild fever among the 180 vaccinees in his study. Austrian and Ammann each used different vaccines produced by Eli Lilly, and Weibel used vaccines manufactured by Merck Sharp and Dohme.

The total number of vaccinees involved in premarketing clinical trials of pneumococcal vaccine, including 15,715 foreign subjects and 7,433 domestic subjects, was about 23,000. (See table 6.) Vaccine safety was evaluated in about 18,800 vaccinees. (See table 9.) Relative to the size of sample populations used to evaluate other vaccines prior to marketing, the population of 23,000 vaccinees who received pneumococcal vaccine in premarketing testing is large. Yet as one BOB official commented (Parkman, 1979):

> Clearly, one cannot reliably predict six possible cases of anaphylaxis in about one million vaccinees on the basis of an experience with **23,000.**

Data from studies involving 23,000 vaccinees cannot be used alone as the basis for predictions of the incidence of rare adverse reactions that might result if pneumococcal vaccine were to be used, for example, in a large public immunization program.

Vaccine Testing Among Foreign Populations

In accordance with the law and FDA regulations, a vaccine manufacturer must demonstrate the efficacy of a new vaccine product in clinical trials before FDA will license the product. To demonstrate **a** new vaccine's clinical efficacy, investigators must test the product in a defined population in which the incidence or prevalence of the target disease can be measured.

Because of the relatively low reported incidence of pneumococcal pneumonia in the United States (1 to 5 cases per 1,000 persons per annum), assessment of pneumococcal vaccine's clinical efficacy in this country would have been very time-consuming and ex-

Table 9.-Number of Subjects Involved in Premarketing Safety Studies of Pneumococcal Vaccine

Sponsor	Vaccinees		Controls	
	Foreign	Domestic	Foreign	Domestic
Industry[a]				
1. MSD (No. 315) (South Africa)	983	—	2,036	—
2. MSD (No. 315A) (South Africa)	718	—	1,493	—
3. Riley[b] (New Guinea)	5,946	—	6,012	—
4. Weibel (No. 384,431,454, 482) (USA)	–	92	—	
Subtotal	7,647	92	9,541	—
Government				
1. Austrian (Kaiser-USA)	—	6,850	—	6,750
2. Ammann (USA)	–	178	—	106
Subtotal	—	7,028	—	6,856
Other[d]				
1. Austrian (South Africa) (3 trials)	4,000	—	8,000	—
Subtotal	4,000	—	8,000	—
SUBTOTAL	11,647	7,120	17,541	6,856
TOTAL	18,767		24,397	

[a] These studies were sponsored by Merck Sharp and Dohme (MSD).
[b] This study was cosponsored by Merck Sharp and Dohme and the Department of Public Health, Papua, New Guinea.
[c] These studies were sponsored at least part by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).
[d] These studies were sponsored by the Chamber of Mines of South Africa.

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, Merck Sharp and Dohme, the National Institute of Allergy and Infectious Diseases, and principal investigators of included studies, 1979

pensive. For this reason, some investigators, namely, Austrian and Merck Sharp and Dohme, conducted clinical trials of pneumococcal vaccine among foreign populations with high pneumococcal pneumonia incidence rates (e. g., South African gold miners, among whom the estimated incidence is at least 90 cases per 1,000 persons per annum). The numbers of foreign and domestic subjects involved in premarketing clinical trials and other studies of pneumococcal vaccine are shown in table 10.

The wisdom of basing evaluations of pharmaceutical and biological products intended for use in the United States on the results of tests conducted among foreign populations has been debated for several years. On the one hand, testing among foreign populations may be necessary, because, as in the case of pneumococcal disease, the incidence of a targeted medical problem in the United States is either unknown or too low to permit accurate assessment of a product's clinical efficacy and safety. On the other hand, data generated in foreign-based testing may be an inadequate basis on which to evaluate the safety of a product to be used in the United States for two reasons:

1. Results obtained in safety tests conducted among subjects in foreign countries, because of culturally influenced perceptual differences and living condition variations, for example, might differ significantly from results that are yielded in similar studies among subjects who reside in the United States.
2. Foreign trials might not include or permit followup observation of vaccinees for the assessment of delayed onset or rare reactions.

Foreign trials per se are not always necessarily inadequate. As is true for clinical trials conducted in this country, each foreign investigation deserves to be evaluated independent] y.

Without premarketing clinical trials of the vaccine in South Africa, there probably would be no licensed pneumococcal vaccine in the United States today. BOB would have

Table 10.—Number of Foreign and Domestic Subjects Involved in Premarketing Clinical Trials and Studies of Pneumococcal Vaccine

	Number of subjects					
	Clinical safety and efficacy trials[a]		Epidemiologic studies[b]		Immunogenicity studies[c]	
Sponsor	Foreign	Domestic	Foreign	Domestic	Foreign	Domestic
Industry	7,647	92	299	0	4,130	274
Government	0	7,028	0	329	0	4,055[c]
Academe	0	0	0	12,198	0	0
Other	4,000	0	177		11	0
Subtotal	11,647	7,120	476	12,527	4,141	4,329
Total	18,767		13,003		8,470	

[a]Numbers include vaccinees only.
[b]Numbers refer to cases, not subjects.
[c]Some of these data are still being analyzed by the investigator.

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, Merck Sharp and Dohme, the National Institute of Allergy and Infectious Diseases, and principal investigators of included studies, 1979.

had no evidence of the vaccine's clinical efficacy, because studies of polyvalent pneumococcal vaccines conducted in the United States and New Guinea did not generate statistically significant efficacy results. Austrian's study at the San Francisco Kaiser Permanence Medical Center was rigorously designed, but not helpful in documenting efficacy of pneumococcal vaccine because of the very low incidence of pneumococcal respiratory diseases in both the experimental and control populations. Similarly, Riley's study in New Guinea was not helpful to BOB in assessing the efficacy of pneumococcal vaccine, because investigators in this study measured the reduction in the incidence of lower respiratory tract infection (LRTI), not type-specific pneumococcal disease.

To evaluate the clinical efficacy of pneumococcal vaccine, BOB had to rely heavily on data from five South African trials in which the primary emphasis was on the evaluation of vaccine efficacy. While BOB was able to rely on these trials' efficacy data, it had to view clinical safety data from these trials of pneumococcal vaccine more critically.

There would seem to be two particular limitations to the usefulness of foreign data regarding the safety of pneumococcal vaccine. First, unlike efficacy data, safety data are generated largely on the basis of vaccinees' subjective responses; the extrapolation of foreign safety data to U.S. populations, therefore, may not be valid. All 5,701 subjects involved in the South African studies (30 percent of the total) were young black male gold miners, mostly from Malawi and Mozambique. These foreign subjects very possibly might have perceived adverse reactions to the vaccine differently, or been less able or willing to complain about or report adverse reactions, than vaccine recipients in the United States. Investigators' ability to assess the rate of adverse reactions to pneumococcal vaccine also may have been hindered by the prevalence among these foreign subjects of mimicking symptoms that were not caused by the vaccine. Fever, for example, is a known possible adverse reaction to pneumococcal vaccine, and many vaccinees in South African clinical trials had fevers from infections such as malaria. Even if cases of malaria were evenly distributed between experimental and control groups, investigators' ability to establish a causal relationship between pneumococcal vaccination and fever undoubtedly was hampered.

The second problem with basing an evaluation of pneumococcal vaccine's safety on data from foreign trials is that the methods researchers in some foreign studies used to solicit reports of adverse reactions may not have permitted accurate or comprehensive assessment of such reactions. Researchers in Merck's two South African studies, No. 315 and No. 315A, used physicians, nurses, and other trained aides to observe vaccinees for

adverse reactions, but vaccinees were observed for a period of only 3 days subsequent to vaccination (Smit, 1977). No attempt to monitor vaccine recipients for delayed-onset adverse reactions was made; however, vaccinees had access to medical care throughout their participation in the study and could voluntarily report serious adverse reactions. In Riley's study in New Guinea, only 133 of 5,946 vaccinated subjects were monitored for adverse reactions (Riley, 1977).

That BOB was quite aware of the limitations of using foreign trial data to evaluate the safety of pneumococcal vaccine is evidenced by the following response to an early draft of this OTA report from one BOB official (Parkman, 1979):

> It is true that common local and febrile reactions may have been more difficult to assess under the circumstances of the South African and New Guinea trials; this was understood at the time these studies were undertaken. The primary emphasis of these trials was on the assessment of effectiveness.
>
> Certainly, however, the opportunity to also gain information on adverse reactions seemed worth the effort. In clinical trials of this sort, it is common to have a period of intensive observation when reactions are most likely to occur, and a more general surveillance directed toward followup of any unusual events which are reported to the investigators or which are reported to those physicians caring for study participants. Thus, severe reactions at the inoculation site or severe systemic reactions of frequent occurrence would have been detected in the 3-day observation period, since previous experience with these and other earlier pneumococcus vaccines indicated this to be the period in which local and systemic reactions were most likely to occur.

One possible problem with heavy reliance on short observation periods in foreign investigations is that researchers may lack the opportunity or willingness to conduct a follow-up surveillance of adverse reactions, especially after a trial has produced adequate efficacy data.

In general, studies of polyvalent pneumococcal vaccines conducted in the United States generated higher reported incidence rates of vaccine-related side effects than did those conducted in foreign countries. (See table 7.) In total, 7,120 (38 percent) of the 18,767 subjects vaccinated in safety studies were U.S. residents. (See table 10.) If BOB's assessment of the safety of pneumococcal vaccine had been based solely on data from studies involving these 7,120 domestic subjects, then the question would have arisen: Is this an adequate sample on which to base an evaluation of the safety of a product that will be administered to millions of Americans? The answer would lie in the degree of safety assessment believed necessary. Most acute, commonly occurring, local and systemic reactions probably could have been detected in a sample this size. Less common adverse reactions and any reactions with delayed onset, however, most likely would have escaped detection.

Lack of Vaccine Testing Among High Risk Populations

One should not assume from the FDA-approved pneumococcal vaccine "Indications" statement (see figure 10) that, prior to Government licensure, the new vaccine was tested for safety or efficacy among high risk individuals with the medical problems (e.g., diabetes, heart disease, or lung disease) that are listed as indications for vaccine use. No premarketing clinical trial specifically assessed pneumococcal vaccine's efficacy or safety among groups of individuals with one or more of the chronic medical problems listed as official indications for vaccine use. Most premarketing clinical trials of this vaccine were conducted among individuals in healthy populations, who, though possibly at high risk of encountering pneumococcal disease, were not necessarily at high risk of becoming

seriously ill or dying from such disease. One study, however, did assess the clinical efficacy of a pneumococcal vaccine in children with sickle-cell disease (Ammann, 1977).

Rather than data from clinical trials, the primary basis for FDA's approval of the "Indications" statement on pneumococcal vaccine's label were data from a study of mortality rates among 529 patients with bacteremic pneumococcal pneumonia. In this study, conducted at a New York hospital between 1952 and 1962, Austrian and Jerome Gold found that the incidence of mortality caused by pneumococcal pneumonia or bacterernia was higher in patients with certain types of chronic medical problems than in patients without such problems (Austrian, 1964). They also found higher mortality rates from these diseases among those over the age of 50 than among those who were younger. In another study of 325 adult subjects with pneumococcal pneumonia, similar mortality patterns were demonstrated (Mufson, 1974).

Like clinical trials, most immunogenicity studies of pneumococcal vaccine were conducted among healthy subjects. Prior to Licensure, the immunogenicity of this vaccine in specialized populations most likely to contract or die from pneumococcal disease was investigated in only two studies. In one study among a small number of subjects, it was demonstrated that the vaccine could produce good antibody responses in the elderly (Bentley, 1974). Another study demonstrated that the vaccine was immunogenic among children with sickle-cell anemia and children with inadequate spleen function (Ammann, 1977).

One reason for the lack of new vaccine testing in premarketing clinical trials among high risk individuals is that rigorous adherence to randomized controlled clinical trial standards frequently may pose ethical dilemmas for investigators. These standards require that all test subjects be assigned randomly to either an experimental group, which receives the product being tested, or a control group, which does not. Investigators must withhold an experimental vaccine (which by this time in clinical testing must already have demonstrated some degree of efficacy) from individuals at high risk of contracting and possibly dying from the potentially preventable disease, and must administer the vaccine to other high risk individuals who may be particularly susceptible to serious vaccine-induced adverse reactions. To avoid the ethical dilemma posed by withholding an experimental vaccine from someone who would likely benefit from vaccination or giving such a vaccine to someone who is at high risk of experiencing a severe adverse reaction, clinical investigators tend most often to conduct trials among healthy populations.

Economic constraints associated with conducting premarketing clinical trials also may preclude extensive testing in high risk individuals. Testing vaccines in rigorous clinical trials among specialized high risk populations may consume substantial investments in research resources and time. Sponsors of such clinical investigations sometimes pay for the medical care rendered to participating patients. Furthermore, finding concentrated high risk populations that are suitable for clinical vaccine testing is sometimes more difficult than identifying a suitable population of healthy volunteers.

At present, the requirement that a new vaccine be tested in high risk populations is determined by BOB and the vaccine manufacturer. Whether or not BOB and a vaccine manufacturer believe that clinical trial data from high risk populations are needed depends at least in part on the availability of safety and efficacy data from other types of studies. According to one BOB official, further testing of pneumococcal vaccine among individuals at high risk was not felt to be necessary (Parkman, 1978):

> This [the assessment of the pneurnococcal vaccine in clinical trials involving high risk individuals] was not a major consideration in the minds of those who planned the trials or those who evaluated them because of the general experience with inactivated vaccine in immunologically mature children and normal adults as well as in persons in these groups with a variety of conditions (e.g., diabetes, heart disease, lung disease) which indicates that they all behave in a similar fashion with regard to adverse reactions and immunologic response patterns.
>
> Thus it would not seem an economical use of resources to set up studies in which groups of, say, cardiac patients were evaluated. The exceptions to this generalization are those patient groups who, for whatever reason, are immunosuppressed. Here the consideration is efficacy, not safety. A prime example here would include patients with splenic dysfunction, this group was studied by Ammann . . .
>
> All in all, the consensus of the various groups who evaluated the data at the time of licensure both within the Bureau and among experts outside the Government was that the available information was adequate.

For- the reasons cited, FDA established indications for use of pneumococcal vaccine based primarily on a person's risk of contracting or dying from pneumococcal pneumonia, basically assuming—unless and until proved otherwise—that the vaccine would work in high risk individuals. The net result of not involving high risk persons in premarketing clinical trials, however, is this: The safety and efficacy of pneumococcal vaccine never was thoroughly evaluated prior to licensure among persons for whom the vaccine may provide the greatest benefit.

The potential implications of requiring premarketing clinical testing of a vaccine specifically among high risk individuals are unclear. To permit clinical trials to be conducted among high risk individuals, bioethical research standards might have to be modified. Furthermore, the added expense of such clinical testing, if required, might undermine vaccine manufacturers' willingness to engage in vaccine research and development. One implication of requiring such c1inical testing, however, is certain: A new vaccine's safety and efficacy among high risk individuals would be better understood.

4.

A CASE STUDY: COST--EFFECTIVENESS ANALYSIS OF VACCINATION AGAINST PNEUMOCOCCAL PNEUMONIA

4.

A CASE STUDY: COST-EFFECTIVENESS ANALYSIS OF VACCINATION AGAINST PNEUMOCOCCAL PNEUMONIA

These modes of analysis [cost-effectiveness and cost-benefit] are neither good for nothing nor good for everything, and one *cannot speak of them as wholly good or bad. It is much more useful to try to specify some conditions under which they would or would not be helpful for various purposes.*

Aaron Wildavsky
University of California
1966

BACKGROUND AND INTRODUCTION

Several factors influence the use of vaccines in this country. Public demand for vaccines is influenced by individuals' perceptions regarding personal susceptibility to disease, the likelihood of local occurrence of disease, and the value of vaccination. Demand is also influenced by physicians' knowledge about vaccinations and their perceptions about patients' needs for vaccinations. (See appendix 4.1.)

Perhaps the single most important influence on vaccine availability and use is the Federal Government. For the most part, the Federal Government promotes vaccine use through its public immunization programs, which are mainly directed toward the prevention of certain childhood diseases (e.g., measles). By purchasing and distributing selected vaccines free of charge to State and local health departments, the Federal Government reduces costs and increases the availability of vaccines to consumers. (See appendix 4.2.)

Every 1 to 2 years, Congress is asked to enact legislation that authorizes the Federal Government to continue purchasing and distributing vaccines. Congress appears to base its decisions, at least in part, on the following types of judgments:

1. The appropriate use of selected vaccines, once deemed safe and efficacious by the Food and Drug Administration (FDA), will benefit society by conferring protection against certain contagious infectious diseases.
2. Many persons at high risk of contracting a disease are not being vaccinated, and this situation is detrimental to the public's health,
3. Government has the responsibility and capability of promoting the use of certain vaccines among those high risk persons who do not get vaccinated on their own.

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In 1976 and 1978, the Federal Government established special influenza vaccination programs to promote the use of influenza vaccines intended for use by both high risk adults and children. Federally sponsored immunization programs to help prevent pneumococcal pneumonia through use of the recently licensed pneumococcal vaccine, also intended for adult use, however, have not been established. Pneumococcal vaccine has been available 11/z years, and although the Federal Government helped develop the vaccine, it has not yet actively promoted its use among individuals at high risk of contracting pneumococcal pneumonia.

Decisions regarding the extent, if any, to which the Federal Government should promote the use of pneumococcal, as well as influenza, vaccine will likely be based on criteria similar to those mentioned above. Two bodies have evaluated the new pneumococcal vaccine: the Food and Drug Administration (FDA) (see chapter 3) and the Advisory Committee on Immunization Practices (ACIP). In their deliberations, both of these bodies considered the efficacy and safety of the vaccine, the mortality produced by pneumonia and bacteremia, and the importance of certain high risk conditions. Not amassed, and hence not considered, were additional health factors such as the morbidity from pneumococcal pneumonia and medical care expenditures for vaccination or treatment.

The emphasis of this chapter is on the potential usefulness and limitations of a criterion that the Federal Government has not yet applied in allocating Federal funds for specific types of vaccinations: cost-effectiveness. Cost-effectiveness analysis (CEA) compares the costs of alternative methods of attaining a specific goal. This type of economic analysis has been used rather limitedly to help allocate health resources. (See appendix 4.3.) At least theoretically, CEA could be used to address two health policy issues: 1) the costs of using medical technologies, and 2) the relative effectiveness of using these technologies to improve health.

For illustrative purposes, OTA conducted a cost-effectiveness analysis in which it calculated the net changes in costs and effects that would result from vaccination against pneumococcal pneumonia instead of a continuing of the present situation in which pneumonia is treated if it occurs. Undertaken in light of current interest in evaluating the benefits, costs, and cost-effectiveness of new medical technologies, OTA's analysis of vaccination against pneumococcal pneumonia represents a case study of the cost-effectiveness technique.

In OTA's cost-effectiveness analysis presented below, the costs and health effects of pneumococcal vaccine, a new preventive technology, are evaluated from a societal perspective, as well as from the perspective of Medicare. Specifically addressed is whether expenditures on vaccination to help prevent pneumococcal pneumonia are a more efficient use of resources than expenditures on treatment for pneumococcal pneumonia in different subgroups of the population.

Findings from OTA's analysis and issues related to the potential utility of CEA to Federal health policymakers are presented in chapter 6. Federal options related to these issues appear in chapter 7.

MEASUREMENT OF HEALTH EFFECTS AND SOCIETAL MEDICAL COSTS OF PNEUMOCOCCAL VACCINATION

In this cost-effectiveness analysis, expected changes in health effects and medical care costs that would result from vaccination against pneumococcal pneumonia rather

than continuing reliance solely on treatment are measured. The analysis is limited to events within the medical care sector, but includes all health and cost effects within this sector. Costs incorporate both medical care expenditures and savings. Effects consist of changes in years of healthy life. The cost-effectiveness ratio represents the net societal medical cost per year of healthy life that would be gained by a vaccinated person. That ratio indicates the net change over continuation of the present situation if a person were vaccinated.

The analysis takes into account the effect of the pneumococcal vaccine only on pneumococcal pneumonia. Excluded is any possible immunity conferred by the vaccine against other pneumococcal diseases, such as pneumococcal otitis media (middle ear infection) or pneumococcal meningitis (infection in the membranes surrounding the brain and spinal cord). The efficacy of the vaccine against pneumococcal diseases other than pneumonia has not yet been assessed in clinical trials. Because of these exclusions, the cost-effectiveness ratios derived in this analysis may be conservative relative to the overall cost-effectiveness of the vaccine against all pneumococcal diseases. Furthermore, the assumption is made that pneumococcal vaccination of some individuals in the population will not produce herd immunity among the unvaccinated.

Cost-effectiveness ratios were based on a single hypothetical vaccination program conducted in June 1978. A simulation model was used to estimate the costs and effects that would result from 1978 through 2050 for two closed populations, one vaccinated and the other unvaccinated. Past rates of medical expenditures, days of illness, and mortality formed the basis of projections. (See appendixes 4.4, 4.5, and 4.6.)

Health Effects

In the analysis, the health effects of pneumococcal vaccination are expressed in quality-adjusted life years (QALYs). [1] QALYs incorporate into a single index changes in both mortality and morbidity, thus allowing comparisons between programs that mainly reduce death and those that mainly reduce illness or disability. This index allows measurement of the effects of health care interventions without attaching a monetary value to increases or decreases in days of health or years of life.

To construct QALYs, 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 .9, and a year with a major health problem might rank as only .2. QALY rankings of different degrees of health can be thought of as representing tradeoffs between more years of unhealthy life and fewer years of healthy life. (For further details on QALYs, see appendix 4.4.)

For purposes of this CEA, degrees of health were divided into four categories: death, disabilities with confinement to bed, disabilities without confinement to bed, and full functioning. Weighings for these different states were drawn from an analysis by Bush, Chen, and Patrick of a phenylketonuria (PKU) screening program: O for a year of death, .4 for a year of bed disability, .6 for a year of nonbed disability, and 1.0 for a year of full functioning (Bush, 1973). [2] The sensitivity of the results to these weights is tested in the course of the analysis.

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

[1] The term "quality-adjusted life years" was coined by Zeckhauser and Shepard, although other health analysts have used the concept. (See Zeckhauser, 1976.)

[2] These weights were derived by averaging values from the Bush, Chen, and Patrick survey. (See Bush, 1973.)

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

Costs measured in the analysis, expressed in dollars, reflect changes in societal medical care expenditures that would result from pneumococcal vaccination. Included as costs are increases or decreases in the medical expenditures incurred by all payers—patients, private third-party payers, and governments. According to OTA's analysis, total treatment costs for pneumococcal pneumonia in the United States in *1978* were an estimated $135 million. (See table 11.)

Table 11 .—Estimated Expenditures by Age Group for the Treatment of Pneumococcal Pneumonia in the United States (1978)

Age group	Estimated expenditures				
	Ambulatory care	+	Hospital costs	=	Total
2-4 years	$ 3,234,000	+	$ 8,851,000	=	$ 12,085,000
5-24 years	2,192,000	+	6,181,000	=	8,373,000
25-44 years	3,125,000	+	14,430,000	=	17,555,000
45-64 years	2,573,000	+	31,940,000	=	34,513,000
65+ years	1,733,000	+	61,560,000	=	63,293,000
Total	$12,857,000	+	$122,962,000	=	$135,819,000

SOURCE OTA.derived estimates based on data prowded by sources identified In appendix=4

Changes in costs outside of the medical care sector are excluded from the analysis. Changes in years of healthy life, in particular, may influence other sectors as changes in working days and productivity; similarly, any changes in resources used in the provision of medical care might have implications for production and expenditures on other goods and services. In benefit-cost analysis (BCA), such systemwide effects are included and expressed in dollar terms. In this cost-effectiveness analysis, systemwide ramifications are to some extent implicit in changes in QALYs. Increases or decreases in years of healthy life implicitly carry implications for economic effects, as well as for personal and social effects (e.g., changes in family life and in the age distribution of the population).

Costs in this CEA are expressed in 1978 dollars. Thus, it is tacitly assumed that future inflation will occur at the same rate in the medical care sector as in the general economy. In fact, medical prices in recent years have been rising more rapidly than the Consumer Price Index (CPI). It is unclear, however, what portion of higher medical prices is attributable to higher prices for the same services (inflation) and what portion to new or different services (changing quality and intensity). Furthermore, predicting relative price rises in different medical services, such as physician fees, hospital days, and drug-prices would be difficult.

COST-EFFECTIVENESS EQUATION AND MODEL

Cost-effectiveness ratios (C/E) for pneumococcal vaccination, expressing the net medical expenditure per year of healthy life gained by a vaccinated individual, were computed with the basic formula that appears below:[3]

[3]The formula used in this analysis is similiarto the formula used by Weinstein and Stason in their analysis of a hypertension treatment program. One difference is that the term E_i has been added to account for illnesses in extended years of life. (See Weinstein, **1976.)**

$$C/E = (C_p - C_t + C_{se} + C_i) / (E_{ly} + E_m - E_{se} - E_i) = \text{Net costs/Net effects}$$

where:

C_p = Cost of preventive vaccination
C_t = Cost of treating pneumococcal pneumonia prevented by vaccination
C_{se} = Cost of treating vaccine side effects
C_i = Cost of treating future illnesses not prevented by vaccination among vaccinees whose lives are prolonged as a result of vaccination
E_{ly} = Life years gained from vaccination
E_m = QALYs of morbidity prevented by vaccination
E_{se} = QALYs of morbidity and mortality associated with vaccine side effects
E_i = QALYs of morbidity from future illnesses 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 five different age groups: 2 to 4 years, 5 to 24 years, 25 to 44 years, 45 to 64 years, and 65 years and older. Research has not proved pneumococcal vaccine to be efficacious for children under the age of 2 (Ammann, 1977); consequently, this age group was eliminated from the analysis. The choice of the other age categories was based on variation in pneumonia incidence and divisions in available data sources.

No separate cost-effectiveness ratios were calculated for males and females or for different racial groups. When sex-specific data were available and reliable, though, these were used in the calculations. The only high risk group for which a separate cost-effectiveness ratio was calculated on the basis of empirical data was that comprised of people 65 years and older. Without question, however, ratios for other high risk groups would be important to calculate. Hypothetical cost-effectiveness ratios, based solely on assumptions, were also calculated for high risk groups.

BASE CASE AND SENSITIVITY ANALYSIS

Cost-effectiveness ratios generated in this analysis depend on assumptions about the value of several variables. The magnitude of the reduction in the incidence of pneumococcal pneumonia, for example, depends on assumptions about the duration of vaccine immunity, the efficacy of the 14-valent vaccine, and the percentage of pneumococcal pneumonia caused by the polysaccharide types in the vaccine. The calculations also depend on whether the vaccination program is assumed to be administered through the public or the private sector, which affects the cost of vaccination, and on whether serious adverse reactions, such as Guillain-Barre Syndrome (GBS), are expected to be associated with use of the vaccine.

As none of these variables or factors was certain, a base case was established in which the most likely value was assigned to each variable. Decisions regarding the assignment of values in the base case were made on the basis of such factors as the preponderance of findings from the clinical literature. (See appendixes 4.4, 4.5, and 5.1.)

For purposes of the base case analysis, the following assumptions were made:

- QALY weights of .4 for bed disability and .6 for nonbed disability on a scale of O for death and 1 for full functioning;

- Discount rate of 5 percent applied to costs and effects occurring after 1978;
- Private sector vaccine provision at a cost of $11.37 per vaccination;[4]
- 15 percent of all pneumonia as pneumococcal (Bentley, 1979; Austrian, 1979; Filice, 1979; Fraser, 1979);
- 75 percent of pneumococcal pneumonia caused by the 14 types of pneumococci against which the vaccine is effective (Austrian, May 1, 1976; Austrian, et al., 1976; Fey, 1975; Valenti, 1978);
- 80-percent rate of vaccine effectiveness against the 14 types of pneumococci represented in the vaccine (Austrian, et al., 1976; Smit, 1977);
- Vaccine side effects of one case per 100,000 persons vaccinated of severe systemic reaction and five cases per 100 of fever;[5]
- An average of 8 years' immunity provided by the vaccine (Heidelberger, 1953);
- Rate of 1978 pneumonia deaths based on death certificates with pneumonia specified as the underlying cause of death (U.S. Ex. Br., NCHS, DVS);
- Same projected rate of decline for pneumonia deaths over time as for all deaths;[6]
- Rate of 1978 age-specific hospital cases of pneumonia in which pneumonia was the first-listed diagnosis (U.S. Ex. Br., NCHS, HDS); and
- Rate of 1978 age-specific ambulatory visits for Pneumonia from the National Ambulatory Medkal "Care Survey (NAMCS), a survey of physicians (U.S. Ex. Br., NCHS, NAMCS).

The influence of selecting different values for each of these 12 variables was tested in a sensitivity analysis. For further discussion of the values assigned to variables in the base case and sensitivity analysis, see appendix 4.4.

DATA SOURCES

For **many estimates** used in OTA's analysis, data were collected from several sources and many assumptions had to be made. No reliable estimate of the incidence of pneumococcal pneumonia, for example, is available; in the analysis, two assumptions were used. One was that the percent of pneumonia caused by pneumococci is uniform throughout all age groups. Although age-specific incidence rates for pneumococcal pneumonia may indeed vary, no study has provided data on which to base empirically derived rates. The second assumption was that the severity of a case of pneumococcal pneumonia is equivalent to the severity of **an** average case of pneumonia.

Data on the incidence of pneumonia and the costs of pneumonia treatment were combined from several sources: the National Center for Health Statistics (NCHS), including the Division of Vital Statistics (DVS), the Health Interview Survey (HIS), the Hospital Discharge Survey (HDS), and the National Ambulatory Medical Care Survey (NAMCS); Blue Cross; and the HEW Medicare program. An estimate of pneumonia's ef-

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[4]This cost estimate was based on a product cost of $4.90 for a dose of the vaccine (Beck, 1978) and an injection fee of $6.47 (Schieber, 1976; CMA, 1969; U.S. Ex. Br., BLS, 1978).

[5]This estimate was based in part on data reported in premarketing clinical investigations (see ch. 3) and in part on adverse reaction case reports voluntarily submitted by physicians to Merck Sharp and Dohme, BOB, and CDC (Broome, 1978). The incidence of reported adverse reactions changes continually, and this estimate does not incorporate data generated since September 1978.

[6]This assumption was consistent with the observation that pneumonia mortality has declined at a faster rate among the young than among the elderly and avoids the mortality rates' rapidly reaching zero.

feet on individuals' health was based on data regarding the number of pneumonia deaths from NCHS's Division of Vital Statistics and the number of pneumonia illness days from HIS. HDS provided data on the number and length of hospitalizations for the treatment of pneumonia; HIS provided data on the number of hospital outpatient visits. The number of physician office visits for pneumonia came from NAMCS and HIS.

The estimate that 15 percent of all cases of pneumonia are caused by pneumococci was based primarily on an informally derived consensus among selected researchers, as well as data generated in a small study of hospitalized patients in Rochester, N.Y. **(Bentley, 1979). The range** of values used for this variable in the sensitivity analysis was derived from studies reported in the clinical literature.

To obtain estimates of the costs of treating pneumococcal pneumonia, the information regarding the utilization of pneumonia treatment facilities was matched with other data concerning the cost of treatment at each type of medical facility. Estimates of costs per inpatient day were based on costs for hospitalized pneumonia cases covered by Blue Cross under the Federal Employees Health Benefit Program (Blue Cross, 1978). Hospital outpatient costs, office visit costs, and physicians' fees were estimated on the basis of charges for physician services, lab tests, and X-rays under Medicare (Schieber, 1976), and on general charges for drugs.

For several variables in the cost-effectiveness equations, different data sets provided conflicting estimates. In such cases, the most probable value was used as the base case estimate, and alternative values were used in the sensitivity analysis. In the base case, for example, the number of pneumonia deaths (used to calculate the pneumonia mortality rate) was drawn from death certificates on which pneumonia was listed as the underlying cause of death. In the sensitivity analysis, the estimate of pneumonia mortality depends on the number of death certificates on which pneumonia was mentioned as a contributing cause of death. Similarly, in the base case, the number of inpatient pneumonia cases was based on the number of cases discharged from hospitals with pneumonia listed as the first diagnosis. Because pneumonia might have been an important factor leading to hospitalization, even in cases where it was not listed first, the number of hospital discharges with any diagnosis that listed pneumonia was used in the sensitivity analysis.

The number of pneumonia-related physician office visits reported in NAMCS was about one-half that reported in HIS. In the base case, OTA used data from NAMCS, because this survey is based on physicians' reporting of pneumonia, Physician reporting was believed to be more accurate than the HIS method of reporting, which is based on interviews of the noninstitutionalized population, who might report other respiratory diseases as pneumonia. Other HIS estimates, including hospital outpatient visits and pneumonia illness days, were halved in the base case. Although crude, this adjustment reflects the same degree of patient overreporting in HIS as was assumed for office visits. The importance of this assumption was tested in the sensitivity analysis.

Other data sources and studies used to derive estimates for pneumococcal pneumonia vaccine's cost-effectiveness are discussed in appendixes 4.4 and 4.5.

RESULTS

The results of the base case and sensitivity analysis for pneumococcal vaccination illustrate the types of information that a CEA can convey. The presentation of the results of OTA's analysis below constitutes neither advocacy of, nor opposition to, pneumococcal vaccination to help prevent pneumonia.

Most of the results are presented as "per vaccinee." Costs and effects per vaccinee are not affected by the number of people vaccinated. This relationship reflects assumptions made in the analysis that the price of vaccination is not changed by the number of people vaccinated and that people who are not vaccinated derive no herd immunity from others' vaccinations.

Base Case

Cost-effectiveness ratios for pneumococcal vaccination, derived using base case assumptions, are presented in table 12. With base case assumptions, pneumococcal vaccination against pneumonia would result in a net improvement in health (QALYs), but no savings in expenditures for any age group. Vaccination would be most cost-effective for those **65** years and older—about $1,000 per QALY gained.

Cost-effectiveness ratios for vaccination, expressing net societal medical cost per QALY gained, improve with increasing age of the vaccinee at the time of vaccination. Net medical cost per QALY gained for a vaccinee aged 2 to 4 is about $77,000. This cost drops to $55,000 for ages 5 to 24,$23,000 for ages 25 to 44,$6,000 for ages 45 to 64, and $1,000 for **ages 65 and older. As age at** the time of vaccination increases, net medical costs decline and the gain in QALYs increases. Per vaccinee net costs range from about $10 for ages 2 to 4 to about $7 for ages **45 to 64;** QALYs range from .00013 (.05 days) for ages 2 to 4, to .00118 (.43 days) for ages 45 to 64; for older ages, the gain in QALYs remains positive, but small. (See table 12.)

For all ages combined, the overall cost-effectiveness ratio per vaccinee is about $4800 per **QALY gained. This Overall ratio** illustrates by contrast the difference in the cost-effectiveness of a vaccination program that can be achieved by targeting vaccinations to specific subgroups of the population, namely, the higher cost-effectiveness of vaccinating the elderly ($1,000 per QALY) and the lower cost-effectiveness of vaccinating the very young ($77,000 per QALY).

Even when a program is not actually cost-saving, it may be deemed cost-effective. The majority of people would be willing to pay something to gain a year of healthy life, and a consensus exists that most people would willingly spend several hundred dollars

Table 12.–Per Vaccinee Cost-Effectiveness of Pneumococcai Vaccination (Base Case Results)

Per vaccinee costs and effects of vaccination	Age group					
	2-4 years	5-24 years	25-44 years	45-64 years	65+ years	All ages
Net cost[a], ...	**$10.30**	**$10.20**	**$9.70**	**$6.80**	**$4.40**	— [b]
Net effect (QALYs)[c]. . . .	.00013	.00018	.00042	.00118	.00435	—b
Cost-effectiveness ratio[d]	$77,200 / **QALY**	$55,3001 **QALY**	$22,9001 **QALY**	$5,7001 **QALY**	$1,000 / **QALY**	**$4,8001 QALY**

[a]Net cost equals the total of:
C_p = Cost of preventive vaccination
C_t = Cost of treating pneumococcal pneumonia prevented by vaccination
C_{se} = Cost of treating vaccine side effects
C_i = Cost of treating illnesses not prevented by vaccination in extended years of life
[b]Net per vaccinee costs and net per vaccinee effects for all ages combined were not calculated.
[c]Net effect (QALYs) equals the total of:
E_{ly} = Life years gained from vaccination
E_m = QALYs of morbidity prevented by vaccination
E_{se} = QALYs of morbidity and mortality associated with vaccine side effects
E_i = QALYs of morbidity from illnesses not prevented by vaccination in extended years of life
QALY = Quality-adjusted life year
[d]The age-specific cost-effectiveness ratios that are shown, expressing the net societal cost per QALY gained by vaccinated individual, were calculated on the basis of more exact numbers for net costs and effects than those that appear in this table.

for each healthy year gained (Weinstein, 1976). In terms of their economic efficiency, alternative programs or interventions with low cost-effective ratios might be more easily justified that those with high ratios (e.g., those costing over $50,000 per *QALV (Wein-*stein, 1976).

Net costs and effects of pneumococcal vaccination for the total population are shown in table 13. These numbers were calculated for illustrative purposes only. Total population costs and effects of vaccination would depend on the number of people vaccinated, which in turn might depend on such factors as the perceived threat of disease, cost of vaccine, and type of vaccine program. (See appendix 4.1.) Pneumococcal vaccination rates are difficult to predict. Most vaccines are intended primarily for children, not adults, and age-specific vaccination rates are cumulative over many years. The vaccination rates used to calculate the numbers in table 13 were the age-specific influenza vaccination rates in 197s, a nonepidemic year prior to the swine flu episode. Influenza vaccine, like pneumococcal vaccine, is targeted to high-risk adults and children, but generally confers protection for a single year or until the antigenic components of the influenza virus shift. As was assumed in base case for pneumococcal vaccinations, influenza vaccinations in 1975 were administered through the private sector.

Table 13.—illustrative Population Costs and Effects of Pneumococcal Vaccination

Population costs and effects of vaccination	Age group					
	2-4 years	5-24 years	25-44 years	45-64 years	65+ years	All ages
Net cost[b](in $1,000)	$23,500	$24,300	$42,700	$36,700	$22,600	**$150,000**
Net effect[c](QALYs).	300	440	1,870	6,400	22,400	31,400
Cost-effectiveness ratio[d].	$77,200/ QALY	$55,300/ QALY	$22,900/ QALY	$5,7001 QALY	$1,000/ QALY	$4,8001 QALY

[a]The numbers in this table were calculated for illustrative purposes only. The demand for pneumococcal vaccine cannot be predicted with any degree of certainty, so it was assumed that the percentages of people who would be vaccinated with pneumococcal vaccine would approximate the age-specific percentages of people who were vaccinated with influenza vaccine in 1975. Costs were calculated on the assumption that there would be no economies of scale; effects, on the assumption that there would be no herd immunity.

[b]Net cost equals the total of:
C_p = Cost of preventive vaccination
C_t = Cost of treating pneumococcal pneumonia prevented by vaccination
C_{se} = Cost of treating vaccine side effects
C_i = Cost of treating illnesses not prevented by vaccination in extended years of life

[c]Net effect (QALYs) equals the total of:
E_{ly} = Life years gained from vaccination
E_m = QALYs of morbidity prevented by vaccination
E_{se} = QALYs of morbidity and mortality associated with vaccine side effects
E_i = QALYs of morbidity from illnesses not prevented by vaccination in extended years of life
QALY = Quality-adjusted life year

[d]The age-specific cost-effectiveness ratios that are shown, expressing the net societal cost per QALY gained by vaccinated individual, were calculated on the basis of more exact numbers for net costs and effects than those that appear in this table.

The numbers in table 13 demonstrate the degree to which per vaccinee costs and effects of a pneumococcal vaccination program are magnified when considered for the population as a whole. Vaccinating 21.5 percent of the population age 65 and over, for example, could cost about $23 million and yield about 22,000 QALYs over the vaccinees' lifetimes. Vaccinating all age groups might have a net cost to the health system of about $150 million and would add about 31,000 QALYs.

Sensitivity Analysis

The importance of certain variables in the cost-effectiveness model is suggested by the results of the sensitivity analysis in table 14. Especially for people in younger age groups, cost-effectiveness ratios change markedly as values for particular variables are

Table 14.—Per Vaccinee Cost"Effectiveness of Pneumococcal Vaccination (Sensitivity Analysis Results)

Variable	Assigned values[a]	Per vaccinee cost per QALY by age group[a] 2-4 years	5-24 years	25-44 years	45-64 years	65+ years	All ages
QALY weightings for bed- and nonbed-disability days	Bed-day $\sqrt{.4}$ Nonbed-day $\sqrt{.6}$	$80,700	$58,400	$24,000	$6,600	$1,200	$5,500
	*Bed-day $\sqrt{.4}$ Nonbed-day $\sqrt{.6}$	*$77,200*	*$55,300*	*$2,900*	*$5,700*	*$1,000*	*$4,800*
	Bed-day $\sqrt{.4^2}$ Nonbed-day $\sqrt{.6^2}$	$76,000	$53,700	$22,000	$5,000	$900	$4,200
Discount rate applied to costs and effects occurring after 1978	No discount rate	$21,700	$17,100	$9,000	$2,700	$700	$2,700
	*5 percent	*$77,200*	*$55,300*	*$22,900*	*$5,700*	*$1,000*	*$4,800*
	10 percent	$181,800	$127,700	$46,500	$10,600	$1,600	$7,700
Cost of vaccination	$3.45	$17,900	$12,300	$4,200	**	**	**
	*$11.37	*$77,200*	*$55,300*	*$22,900*	*$5,700*	*$1,000*	*$4,800*
Percent of pneumonia that is pneumococcal	10 percent	$150,000	$101,300	$38,800	$10,800	$2,300	$8,500
	*15 percent	*$77,200*	*$55,300*	*$22,900*	*$5,700*	*$1,000*	*$4,800*
	35 percent	$23,100	$17,100	$7,000	$200	**	$700
Percent of pneumococcal pneumonia caused by types of pneumococci represented in the vaccine	50 percent	$150,800	$101,300	$38,800	$10,800	$2,300	$8,500
	*75 percent	*$77,200*	*$55,300*	*$22,900*	*$5,700*	*$1,000*	*$4,800*
	100 percent	$50,700	$37,100	$15,600	$3,300	$400	$3,000
Pneumococcal vaccine's rate of efficacy against type-specific pneumococcal pneumonia	40 percent	$275,800	$166,700	$57,200	$16,100	$3,700	$12,300
	*80 percent	*$77,200*	*$55,300*	*$22,900*	*$5,700*	*$1,000*	*$4,800*
	100 percent	$55,600	$40,600	$17,100	$3,800	$500	$3,300
Incidence of GBS as a vaccine side effect	*No GBS	*$77,200*	*$55,300*	*$22,900*	*$5,700*	*$1,000*	*$4,800*
	Same as with swine flu vaccine	$77,200	$57,800	$23,800	$5,900	$1,000	$4,900
Duration of immunity conferred by the vaccine	3 years	$393,800	$262,000	$82,100	$22,170	$4,067	$14,800
	*8 years	*$77,200*	*$55,300*	*$2,900*	*$5,700*	*$1,000*	*$4,800*
	72 years	$7,100	$3,300	$1,000	$400	$300	$500
Number of pneumonia deaths, 1978	Pneumonia mentioned on death certificate[b]	$19,700	$12,900	$6,200	$2,000	$1,000	$1,900
	*Pneumonia listed as underlying cause of death on death certificate	*$77,200*	*$55,300*	*$22,900*	*$5,700*	*$1,000*	*$4,800*
Projected decline in the pneumonia death rate, 1978-2050	Fast decline[c]	$113,500	$84,400	$35,200	$8,200	$100	$6,700
	*Same decline as the overall death rate	*$77,200*	*$55,300*	*$22,900*	*$5,700*	*$1,000*	*$4,800*
	No decline	$76,800	$55,000	$22,500	$5,700	$1,000	$4,800
Number of hospitalized pneumonia cases	*Pneumonia first-listed diagnosis on hospital discharge summary	*$77,200*	*$55,300*	*$22,900*	*$5,700*	*$1,000*	*$4,800*
	Pneumonia any-listed diagnosis on hospital discharge summary	$75,000	$53,100	***$20,900***	***$2,800***	• *	$2,700
Number of ambulatory pneumonia cases and number of pneumonia morbidity days	Higher estimates based on HIS data	$51,000	$40,700	$19,400	$5,200	$1,000	$4,400
	*Lower estimates based on NAMCS data and adjusted HIS data	*$77,200*	*$55,300*	*$22,900*	*$5,700*	*$1,000*	*$4,800*

*Base case values

**In these instances, vaccination resulted in negative costs—or savings. Such savings are not displayed, however, because they can be misleading. Actual per vaccinee effects and savings are quite small. For example, a typical per person saving is less than $5, and a per person net QALY gained is around 1 to 2 days.

[a]For information regarding the sources of the values used to generate cost-effectiveness ratios appearing in this table, see appendix 4.6. For a description of the manner in which values were selected for the base case and sensitivity analysis, see appendix 4.4. Actual calculated values were rounded off to the nearest $100.

[b]The last year data on pneumonia mentions were available was 1969. Death rates based on pneumonia mentions were calculated with 1969 data. Other data used in this study are from more recent years.

[c]Fast decline implies that 97 percent of pneumonia deaths could be eliminated within 40 years.

changed. In the sensitivity analysis, selected values were altered one at a time; the variables that were not being tested were assigned their base case values.

One critical variable in terms of its impact on the results is the average *duration of the immunity* conferred by pneumococcal vaccine. Studies have shown that vaccinated individuals maintain serum antibody levels, and thus may be protected against pneumococcal pneumonia, for at least **3** to *8* years (Heidelberger, 1953). Some scientists, however, believe that the immunity may last a lifetime (Robbins, 1978; Hill, 1978). The assumption made in the base case analysis was that the average duration of immunity is **8** years. If immunity extends beyond **8** years to lifetime protection, the cost-effectiveness of vaccination improves dramatically. For all ages combined, the overall cost of adding a QALY is reduced from **$4,800** to **$500** when the duration of immunity increases from **8** years to lifetime **(72** years). By contrast, if immunity lasts only **3** years, then the overall cost of adding a QALY increases to $14,800.

Altering the *discount rate* for costs and effects occurring after **1978** alters the results substantially as well. Using a 10-percent discount rate, instead of the 5-percent rate used in the base case, decreases the cost-effectiveness of vaccination for people from 2 and 64 years. The ratio for all ages is $4,800 per QALY gained with a 5-percent discount rate and $7,700 per QALY gained with a 10-percent rate. While the initial expense of vaccination itself occurs in 1978, most of the benefits from vaccination (i. e., reduced pneumonia treatment costs and improved health) appear in subsequent years. Thus, for those between **2** and 64 years, raising the discount rate reduces the relative level of future benefits to present costs. This effect is not so pronounced for people 65 years and older, however, because for the elderly, initial vaccination costs are soon offset by savings in pneumococcal pneumonia treatment costs. Applying a higher discount rate to effects, most of which occur in subsequent years, does decrease the gain in QALYs for people in this age group. When no discount rate is used, cost-effectiveness ratios for people of all ages improve.

Another influential variable is the initial cost of *vaccination.* The cost per dose used in the base case was $11.37, the estimated cost under private provision. Using a lower cost of $3.45,[7] the estimated cost under a public immunization program, improves the cost-effectiveness of vaccination for every age group. Pneumococcal vaccination then yields cost savings for those 45 years and older, and costs from $4,000 to $18,000 per QALY gained for those 2 to 44 years old.

As one would expect, selection of larger values for variables relating to pneumonia morbidity and treatment costs, such as *days of disability, days of hospitalization,* and *number of ambulatory visits,* improves the cost-effectiveness of vaccination.

Changing the projected *rate of decline in the pneumonia death* rate produced some unexpected results. It was expected that a faster decline would reduce the vaccine's benefits and make it less cost-effective. That result held for people aged **2** to 64, but for people **65** years and older, a faster decline improves the cost-effectiveness of vaccination. It is possible that the reduction in pneumonia treatment costs resulting from vaccination would more **than** offset increased costs and morbidity from nonpneumonia illnesses and the lesser gain in life expectancy from vaccination. With a faster decline in age-specific pneumonia death rates, cost-effectiveness ratios are less favorable for those **2** to 64 years old.

Creating a hypothetical probability of contracting a severe, rare vaccine side effect, such as *Guillain-Barre Syndrome (GBS),* produces little or no change in cost-effectiveness

[7]This figure is based on the assumption that the cost of vaccination under a public immunization program would be $1.00 (Hinman, 1978) and that the product cost of one dose of the vaccine would be $2.45 (Beck, 1978; Chin, 1978).

ratios. Treatment and disability costs associated with a case of GBS were estimated (Asbury, 1978). Even in the extreme case in which the age-specific incidence of GBS are assumed to equal those associated with swine flu vaccination, cost-effectiveness ratios for all ages remain substantially unchanged from the base case. (See discussion of GBS in appendix 5.1.)

The results show little sensitivity to different *QALY weightings* for bed- and nonbed-disability days. The lack of sensitivity to these weighings indicates that the health effects of pneumococcal vaccination arise more from postponing death than from reducing disability caused by pneumococcal pneumonia.

As expected, a higher *percentage of pneumonia that is pneumococcal,* a higher *percentage of pneumococcal pneumonia caused by vaccine types,* or greater vaccine *efficacy* against these types improves the cost-effectiveness of vaccination for all age groups. Values for these variables representing the higher boundary of the reasonable range produce cost-effectiveness ratios that are favorable not only for people 65 years and over, but for those between 45 and 64, as well.

MODIFICATION OF THE MODEL FOR THE HIGH RISK POPULATION

If data had been available, this cost-effectiveness analysis would have been performed, not only for individuals in different age groups, but also for individuals (other than elderly) at high risk for pneumococcal pneumonia. Individuals at high risk are both more susceptible to contracting pneumococcal pneumonia and more likely to suffer serious consequences from the disease. In two studies, persons with the following medical conditions were found to be at a higher risk of dying from bacteremic pneumococcal pneumonia than were those without these conditions: chronic lung disease, chronic heart disease, chronic renal failure, and diabetes mellitus or other metabolic disorders (Austrian, 1964; Mufson, 1974). As a result of these findings, the official labeling for this vaccine includes recommendations for its use particularly in people with these medical problems.

Data on the number of individuals in the population with one or more of these high risk conditions, unfortunately, are not available. Furthermore, because data are unavailable, the extent of pneumococcal pneumonia and other diseases within these groups cannot be determined. More specifically, the degree to which the types of pneumococci represented in the vaccine cause pneumonia among high risk groups is not known.

To demonstrate the importance of developing a cost-effectiveness analysis for high risk individuals, therefore, OTA designed a purely illustrative model. The high risk model was based mainly on variations of data used in the base case analysis. [a] For most of the variables used in the analysis, the assumption was arbitrarily made that the value of the variable for high risk individuals would be approximately twice the value of the variable for an "average" individual. Thus, it was assumed that the cost of medical care in extended years of life for high risk individuals would be two times greater than the cost

[a] In some cases, other data sources were used. For example, the numbers of persons at high risk in each age group were based on crude estimates derived by Joel Kavet on the percentage of the general population within different age groups with selected cardiovascular diseases, bronchopulmonary diseases, renal diseases, and metabolic diseases. (See Kavet, 1972.) For the number of pneumonia hospitalizations and hospital days among the high risk population, OTA used NCHS data for the number of hospital discharges and lengths of hospital stay for persons with pneumonia as a first-listed diagnosis and a high risk condition as another diagnosis. OTA estimated the number of pneumonia ambulatory visits among the high risk population by arbitrarily assuming that the ratio of pneumonia ambulatory visits in the high risk population to visits in the general population would be the same as the rate of pneumonia hospital discharges in the general population.

of medical care for an average person. Similarly, it was assumed that a high risk individual would have twice as many days of pneumonia illness and twice as many days of non-pneumonia illness as a member of the general population. Finally, it was assumed that a high risk individual had two times the exponential probability of dying from all causes and almost two times the exponential probability of dying from pneumonia as did an "average" person. [9] The values for individuals not at high risk were adjusted accordingly.

The results of the high risk model obviously depend on the arbitrary selection of the multipliers that were used to adjust the base case data. The model, however, does illustrate the effect that differentiating by risk status can have on the results. Results from OTA's hypothetical model are shown in table 15. In each age group, the model shows that it is more cost-effective to vaccinate a person at high risk than a person not at high risk, and in some cases, vaccinating a person at high risk may even be cost-saving.

Table 15.—Hypothetical Per Vaccinee Cost-Effectiveness Ratios[a] for High Risk Vaccineesb Compared to Ratios for Non-High Risk Vaccinees

	Per vaccinee cost per QALY by age group				
	2-4 years	5-24 years	25-44 years	45-64 years	65 + years
High risk individuals	$21,300	$17,300	$7,300	$500	—[c]
Non-high risk individuals	$92,700	$82,300	$33,300	$10,600	$1,700

[a]The age-specific cost. effectiveness ratios that are shown, expressing the net per vaccinee societal cost per QALY gamed by a vaccinated individual, were calculated on the basis of more exact numbers for net costs and effects than those that appear in this table
[b]High risk individuals are defined here as individuals with medical conditions that place them at especially high risk of contracting o dying 'rem pneumococcal pneumonia In this analysis, it was assumed that for these Individuals, medical costs, days of illness, and an exponential probability of dying were twice those for non-high risk individuals (See footnote 9 below)
[c]For this age group, vaccination would be cost-saving

MODIFICATION OF THE SOCIETAL MODEL FOR MEDICARE

The discussion in the preceding sections has shown that, from a societal perspective and with the stated assumptions, a program of pneumococcal vaccination for the elderly is fairly cost-effective relative to vaccination for other age groups. From this discussion, one might be led to ask: How much would a pneumococcal vaccination program for the elderly cost Medicare? What changes in Medicare expenditures, if any, might result from pneumococcal vaccination among the elderly?

To answer these questions, OTA modified the model used to develop societal costs to calculate Medicare costs and savings that would be associated with a pneumococcal vaccination program. Medicare data provided the basis for projecting that, allowing for copayments and deductibles, vaccination would save Medicare about 75 percent of the hospital costs and about 55 percent of the physician costs it incurs for the treatment of pneumococcal pneumonia (Gibson, 1978). In addition, it was projected that Medicare would pay about 45 percent of the cost of medical care in extended years of life, plus 100 percent of the vaccination cost.

Results based on these percentages and the variable values used in the base case analysis suggest that if Medicare paid $11.37 for a pneumococcal vaccination of an elderly person, the program would incur a net expenditure per vaccinee of approximately $5.13 and add .004 QALY to the person's life.

'Actually, it was assumed that a high risk individual had 1.8 times the exponential probability of dying from pneumonia as a member of the general population. If a factor of "2" had been used in the model, a non-high risk person would need to have had a negative probability y of death in order to derive the "average" probabilities used in the base case model.

On the assumption that **21.5** percent of the population age 65 and older would be vaccinated (the 1975 rate for influenza vaccination), Medicare would spend approximately $26 million over the lifetimes of those vaccinated; this expenditure would yield about 22,000 QALYs. Medicare would spend approximately $58 million to vaccinate the elderly and would incur costs of approximately $10 million for the treatment of illnesses not prevented by vaccination in extended years of life. Because Medicare would save approximately $42 million in pneumococcal pneumonia treatment costs, however, it would incur an overall net expenditure of **$26** million.

In the sensitivity analysis, the results for the Medicare program change substantially. Substituting the sensitivity analysis values one at a time for the base case values yields a range of costs per vaccinee to the Medicare program varying from a net savings of $5 to a net cost of $17.

In terms of population costs, these figures translate into a range in Medicare costs varying from $14 million in savings to a high of **$56** million in expenditures. The savings figure is based on the assumption that the vaccine is administered through a public program at a cost per vaccination of $3.45. The high figure in positive net costs is based on the assumption that the number of pneumonia deaths in 1978 was equivalent to the number of deaths in which pneumonia was mentioned anywhere on the death certificate. When this assumption is made, a vaccination program becomes more costly, apparently because, as more deaths are averted, the cost of medical care in extended years of life increases. Regardless of whether pneumococcal vaccination of the elderly would save money for Medicare, however, such vaccinations would be likely to improve the health status of Medicare vaccinees.

The more completely a financing program such as Medicare covers the medical costs affected by vaccination, the more closely the program and the societal perspectives coincide. If Medicare were to pay a higher percentage of attendant medical costs for beneficiaries 65 years and older, then according to this CEA, expenditures to the program would more closely approximate societal expenditures. In OTA's model, Medicare's net costs would exceed net societal costs. Since Medicare pays only part of treatment costs, it would realize only part of the savings in treating pneumococcal pneumonia.

DISCUSSION OF RESULTS

The differences in pneumococcal vaccination cost-effectiveness ratios for different age groups generated in OTA's analysis and the sensitivity of the results to certain variables illustrate the benefits to be gained from targeting vaccination efforts. The cost-effectiveness ratio per vaccinee for all ages combined, with base case assumptions, would be $4,800 per QALY gained. Vaccinating an additional child aged 2 to 4 would buy a QALY for $77,200, while vaccinating an additional adult 65 years or older would gain a QALY for only $1,000. Thus, to increase the cost-effectiveness of vaccination, efforts could be made to provide the vaccine to the elderly and to discourage its use by healthy children.

This analysis also shows the sensitivity of the results to key variables such as the duration of immunity. According to current information, vaccination would be more cost-effective for the elderly than for others. If immunity proves to last longer than the 8 years assumed in the base case, however, it might be efficient to expand vaccination to other age groups. Otherwise, vaccination could be targeted only to older age groups.

The variation in cost-effectiveness by age suggests the importance of considering cost-effectiveness ratios for groups at high risk of contracting pneumococcal pneumonia or suffering complications from it. Besides age, the presence of certain chronic conditions may also characterize high risk groups. Sickle-cell patients, like others with malfunctioning spleens, seem especially susceptible to pneumococcal disease (Eeckels, 1976). One clinical trial has indicated that pneumococcal vaccine is efficacious for sickle-cell patients (Ammann, 1977). Pneumococcal vaccination may or may not be cost-effective for those in high risk groups other than the elderly. Although these groups would experience benefits from vaccination in reduced treatment costs for pneumococcal pneumonia and gains in life expectancy, these benefits might be offset by high costs for treatment of other illnesses and poor general health in extended years of life. OTA's hypothetical high risk model, however, did suggest that cost-effectiveness could be improved by targeting vaccination to high risk people.

The cost-effectiveness ratios generated in OTA's analysis apply only to vaccination against pneumococcal pneumonia. If the current pneumococcal vaccine is also effective in preventing other pneumococcal diseases, then benefits of vaccination are undervalued. A pneumococcal vaccine able to prevent other pneumococcal diseases, such as meningitis and otitis media, would raise additional possibilities. Not only improved health, but also any increases in the cost of such a vaccine would have to be considered.

The importance of a number of factors whose precise value is unknown was demonstrated in the sensitivity analysis. It is striking that for only two of these uncertain variables, i.e., the discount rate and the weighings for different health states used to derive QALYs, is choosing among alternatives a matter of value judgment or subjectivity. The selection of a discount rate reflects preference for the present compared to the future and return on other uses of funds. Similarly, weighting bed- and nonbed-disability is a matter of personal preference.

Ascertaining the actual value of most of the other variables in the model is an empirical problem. Better data on pneumonia mortality and morbidity, as well as data on the percent of pneumonia that is pneumococcal, are needed to establish the magnitude of pneumococcal pneumonia as a health problem. Pneumococcal vaccine's efficacy, duration of immunity, and adverse effects are matters of probability, but subject to fact-finding research. Projecting pneumonia deaths is an estimation problem dependent on data about historical mortality trends.

Results from this analysis could substantially change if two key assumptions proved to be wrong. In the base case analysis, it was assumed that the rate of efficacy for the vaccine remained constant for all age groups. It was also assumed that the percent of pneumonia caused by the types of pneumococci represented in the vaccine did not change among different age-specific and high risk populations. Neither of these assumptions can be supported empirically. Acceptable data that would either refute or validate either of these assumptions do not exist. Data generated from current NIAID-assisted clinical studies will help to answer questions about the vaccine's efficacy and usefulness in high risk populations.

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[10]It is estimated that the incidence of sickle-cell disease among black births in the United States is 2.5 per 1,000 and that 98 percent of those with the disease in the United States are black. The age distribution of these people, however, is unclear (Gaston, 1978). Research by Powars indicates that sickle-cell patients are most at risk of pneumococcal disease during the first 5 years of life (Powars, 1975; Amman, 1977), One theory is that sickle-cell children, like other children, lack circulating anti bodies during their first 5 years and develop them gradually to the adult antibod, level by about age 10. Unlike other children however, sickle-cell pat i en ts and others with impaired spleens do not have splenic function as a second 1 ine of defense against infection. Sickle-cell children are thus more susceptible to pneumococcal disease and its complications u n t i I about age 10, by which t ı me their level of circulating antibodies has risen (Pearson, 1978). Clinical observations support this theory, because pneumococcal infection in sickle-cell patients declines markedly by age 9 (Powars, 1975).

The results of the sensitivity analysis could be used to help set priorities for research. One finding, for example, was that changes in the duration of immunity provided by vaccination produce substantial variations in the cost-effectiveness of pneumococcal vaccine. Unfortunately, no clinical data are available to permit accurate estimates of duration of immunity to be made. Furthermore, there is little, if any, research being conducted to assess this aspect of the vaccine. Because duration of immunity substantially affects the cost-effectiveness of the vaccine, persons deciding whether or not to fund pneumococcal vaccination programs could insist that clinical researchers place a high priority on answering this question. Another important challenge for future research is the assessment of the vaccine's efficacy among age-specific and high risk populations.

The per dose cost of pneumococcal vaccination had a substantial influence on the cost-effectiveness ratios. Although estimates for a public program formed the basis of the lower boundary on vaccination costs, the lower cost per dose, rather than the public program per se, affected the cost-effectiveness ratios, With a lower injection fee or vaccine price, privately provided vaccination could result in lower costs and more favorable cost-effectiveness ratios.

The general finding that cost-effectiveness ratios for pneumococcal vaccination improve with the age of the vaccinees results from a combination of factors: the incidence of pneumonia by age, the assumed duration of immunity, and the discounting procedure. From early middle age, pneumonia (and pneumococcal pneumonia) mortality and morbidity rates begin to climb. If immunity lasts 8 years, a vaccinee 65 years or older immediately benefits from reduced probability of contracting pneumococcal pneumonia. Vaccination also would render those 45 to 64 years less likely to contract pneumococcal pneumonia, but the limited immunity and discounting of future events reduce the benefits relative to costs for people 45 to 64 years. Younger vaccinees would have little immunity remaining when they reached the ages of greater pneumonia incidence and severity. Discounting has no effect on vaccination costs, which would occur in 1978, but reduces, from an economic perspective, the relative importance of improved health decades later.

5.

A REVIEW: LEGAL LIABILITY AND COMPENSATION FOR VACCINE-RELATED INJURIES

5.

A REVIEW: LEGAL LIABILITY AND COMPENSATION FOR VACCINE-RELATED INJURIES

. . . HEW carries out its contractual obligation to the manufacturers by developing an adequate informed consent statement, by requiring the State and local health agencies to use that statement, and by providing guidelines to the health agencies for obtaining informed consent from persons who are to be vaccinated. The underlying responsibility, however, to warn persons of the risks and benefits of vaccination remains upon the manufacturers.

Bernard Feiner
Office of General Counsel
U.S. Department of Health, Education, and Welfare
May *1979*

the vaccine manufacturers have now contractually shifted this [duty to warn] responsibility to the Federal Government in the vaccine supply contracts.

Clarence A. Abramson
Senior Counsel
Merck and Co., Inc.
May 1979

BACKGROUND AND INTRODUCTION

All vaccines, even when properly manufactured and administered, can produce adverse reactions. In general, adverse reactions are mild and self-limiting, including, for example, pain, redness, or swelling at the injection site. For the vast majority of individual vaccinees, therefore, as well as for society as a whole, the benefits of vaccination greatly outweigh the risks.

For an exceedingly small number of vaccinees, however, the risks of a particular type of vaccination prove to exceed the benefits. A few vaccinees do experience severe adverse reactions that result in permanent disability or death. (See table 16.) While such reactions are rare, many are unavoidable, i.e., they are caused, not by a defective vaccine product or negligence on the part of the vaccinator, but by the inherent properties of a particular vaccine.

In order to receive compensation for vaccine-related injury, injured vaccinees must establish legal liability for their injury. In addition to proving that vaccine-related injury

Table 16.—Vaccine Risks and Adverse Reactions

Vaccine	Rate of minor side effects	Rate of serious adverse reactions	Types of serious reactions
DPT	1/5 to 1/2	1/5,000 1/12,000	Convulsions Abnormal screaming
Measles	1/4	1/1 ,000,000	Encephalitis (inflammation of the brain)
Rubella	Rare	1/10 1/10,000 1/1 ,000,000	Temporary arthritis Nerve damage Brain damage
Polio (killed virus)	0	0	
Polio (oral) (live virus)	0	1/4,000,000	Paralytic polio

SOURCE: "Fact Sheet on Immunization Initiative," Center for Disease Control, 1978. (U.S. Ex. Br., CDC. Fact, 1978.)

has occurred, a plaintiff must establish in court that the defendant (e.g., vaccine manufacturer, vaccine administrator, or both): 1) knew or should have known of the possibility of injury, and 2) had the duty either to prevent the injury or to warn the vaccinee of inherent risks.

Who receives compensation for vaccine-related injuries and who is responsible for providing it at present depend on legal theories of liability. To encourage the development of appropriate safeguards against harm, the litigation process lays fault on those in the best position to develop such safeguards. Harm by itself does not necessarily give rise to liability. One of the cornerstones of the attachment of liability is foreseeability: i.e., those in a position to prevent harm know of the dangers and know what their duty is in order to avoid liability. Some courts have explicitly forewarned that they may be basing their future reasoning on considerations, not of who is best able to avoid the risk of loss, but of who is best able to bear the risk.

Most liability issues at present revolve around the legal responsibilities for the duty to warn potential vaccine recipients about inherent vaccine risks, i.e., unavoidable risks associated with nondefective and properly administered vaccines, To date, the courts have assigned legal responsibility for the "duty to warn" to the vaccine manufacturer. In three major court cases during the past 11 years, plaintiffs have successfully sued vaccine manufacturers, because the courts decided that the manufacturer had not adequately discharged its "duty to warn" injured vaccinees about the less than 1 in 1 million to 4 million chance of developing polio from live poliovirus vaccine.

Successful discharge of the duty to warn potential vaccinees about the inherent risks of vaccination would not prevent injury, but would foreclose injured vaccinees' only avenue to compensation for injury. Following the three precedent-setting **cases of** *Davis v. Wyeth Laboratories, Reyes v. Wyeth Laboratories,* and *Givens v. Lederle,* however, it is not clear how the manufacturer's duty to warn can be discharged. The direction in which these cases seem to be leading is for the courts to hold manufacturers "strictly liable" for all unavoidable injuries resulting from use of their products. It appears, in other words, that the courts **may not** allow manufacturers and other potential defendants to escape liability for injuries associated with the unavoidable risks of vaccines.

In 1976, because of their concern over liability, vaccine manufacturers, under pressure from their insurers, refused to supply vaccines for the massive federally sponsored swine flu immunization program unless the Federal Government assumed liability for the duty to warn. To obtain the manufacturers' cooperation in producing vaccines for the program, Congress enacted legislation (Public Law 94-380), under which the Federal

Government did assume the manufacturers' liability for the duty to warn. Unexpectedly, about 1 in every 100,000 vaccinees developed Guillain-Barre Syndrome (GBS) as a serious adverse reaction to nondefective and properly administered swine flu vaccines. (See appendix 5.1.) The Federal Government (HEW) is still in the process of settling some swine flu GBS claims and lawsuits.

Experience with the 1976 swine flu immunization program has heightened general concern with vaccine liability issues among manufacturers and policy makers in the Federal Government. In part because of what happened under the swine flu program, vaccine manufacturers now require as a condition of supplying vaccines for use in public immunization programs that the Federal Government assume responsibility for the duty to warn.

Currently, therefore, the Department of Health, Education, and Welfare (HEW) is assuming the duty to warn obligation from vaccine manufacturers in Government vaccine purchase contracts. In addition, HEW is requiring, in its vaccine supply contracts, that State and local health agencies that administer federally purchased vaccines in their immunization programs use HEW-developed informed consent statements and guidelines to obtain consent from persons who are to be vaccinated.

Whether the courts will uphold the contractual transfer of the vaccine manufacturer's duty to warn remains to be seen, Will the courts uphold the legality of the transfer of duty to warn obligation from the manufacturer to the Federal Government, making the Federal Government liable for injuries associated with inherent risks? Will they uphold HEW's contract with State and local health agencies, possibly making the person administering the vaccine liable? Or instead, will the courts—under theories of strict liability—hold the manufacturer ultimately responsible for harm produced by its products? Another question that may arise is this: Will the courts judge HEW's informed consent statement and guidelines to be an adequate warning?

The uncertainties surrounding vaccine liability issues appear to be undermining support for large-scale public immunization programs both in Congress and among vaccine manufacturers. Recently, for example, Congress refused to authorize HEW to establish a large continuing influenza immunization program, basing its refusal, at least in part, on concern with liability. Some major vaccine manufacturers and their insurance companies, furthermore, have indicated that unresolved liability issues threaten their continued willingness to produce and supply vaccines for public immunization programs. In addition, heightened visibility and awareness of the risks of vaccination may be diminishing the public's willingness to participate in such programs.

From the standpoint of the injured vaccinee, whether the courts uphold the contractual transfer of the duty to warn responsibility is of less vital concern than the fact that, if the courts rule that the responsible party has adequately discharged its duty to warn, no compensation for vaccine-induced injury will be provided. Legal discharge of the duty to warn would not provide any compensation to those few vaccinees who experience severe adverse reactions or who die; in fact, it would mean that compensation would be expressly denied. Furthermore, for the childhood vaccines, mandatory State vaccination laws make the duty to warn moot. Forty-seven States, the District of Columbia, and three territories mandate certain childhood immunizations upon a child's entry into a public school. (See table 17.) Warning of the possible adverse effects of vaccines implies or is based on the assumption that the vaccinee has the choice to refuse vaccination. Mandatory State vaccination laws, however, preclude this choice.

Table 17.- immunization Requirements Prior to School Entry (September 1976)

State	Type of legislation			If no State law, are there plans pending for proposing such a law?		If yes, before September 1977?	Immunizations required for specific diseases							
	Mandatory	Permissive	None	Yes	No		Diphtheria	Pertussis	Tetanus	Measles	Mumps	Polio	Rubella	Smallpox
Alabama	X						X	X	X	X		X	X	
Alaska		X					X	X	X	X		X		
Arizona [a]			X[a]		X									
Arkansas	X						X	X	X	X		X	X	
California	X						X	X	X	X		X		
Colorado	X						X	X	X	X		X	X	
Connecticut	X	X								X		X	X	
Delaware	X						X	X	X	X		X	X	
District of Columbia,	X						X	X	X	X		X	X	
Florida	X						X	X	X	X		X	X	
Georgia	X						X	X	X	X		X	X	
Hawaii	X						X	X	X	X		X	X	
Idaho			X		X									
Illinois	X						X	X	X	X		X	X	
Indiana	X						X	X	X	X		X	X	
Iowa			X	X										
Kansas	X						X	X	X	X		X	X	
Kentucky	X						X		X	X		X		
Louisiana	X						X	X	X	X		X		
Maine		X					X	X	X	X	X	X	X	X
Maryland	X						X	X	X	X		X	X	
Massachusetts	X						X	X	X	X		X		
Michigan	X						X	X	X	X		X	X	
Minnesota	X									X			X	
Mississippi		X					X	X	X	X		X	X	
Missouri	X						X			X		X	X	
Montana		X					X	X	X	X		X	X	
Nebraska	X						X	X	X	X		X	X	
Nevada	X						X	X	X	X		X	X	
New Hampshire	X						X	X	X	X		X	X	
New Jersey	X						X	X	X	X		X	X	
New Mexico	X						X	X	X	X		X	X	
New York	X						X			X		X	X	
North Carolina	X						X	X	X	X		X		
North Dakota	X						X	X	X	X	X	X	X	
Ohio	X						X	X	X	X		X	X	
Oklahoma	X						X	X	X	X		X	X	
Oregon	X						X	X	X	X		X		
Pennsylvania	X						X		X	X		X	X	
Rhode Island	X						X		X	X		X	X	
South Carolina	X						X	X	X	X		X	X	
South Dakota	X						X		X	X		X	X	
Tennessee	X						X	X	X	X		X	X	
Texas	X						X		X	X		X	X	
Utah	X						X	X	X	X		X	X	
Vermont			X[c]		X									
Virginia	X						X	X	X	X		X	X	
Washington[a]			X[a]	X		Yes								
West Virginia	X						X	X	X	X		X	X	
Wisconsin	X						X	X	X	X		X	X	
Wyoming			X		X									
Guam			X[a]		X									
PuertoRico	X													X
Virgin Islands	X			2		1	X	X	X	X	2	X	X	X
Total	47[b]		7		5		44	37	42	46		45	39	3

[a]Arizona, Washington, and Gua[illegible] have [illegible] requirements.
[b]Connecticut: rubella and measles are mandatory; polio is permissive.
[c]Vermont has local option regulations at the school district level, establishing school entry immunization requirements.

SOURCE: "Fact Sheet on Immunization initiative:' CenterforDisease Control 1978. (U.S. Ex. Br., CDC, Fact, 1978)

In this chapter, the nature and dimensions of current vaccine liability and compensation problems are discussed in relationship to three pertinent topics: 1) developments in case law on vaccine-related injuries; 2) principles underlying insurance companies' pricing of liability insurance; and 3) recent experience with vaccine risks, adverse reactions, and liability claims arising out of federally sponsored immunization programs, including the 1976 swine flu immunization program.

Issues related to vaccine liability and compensation are discussed further in chapter 6, and possible options for congressional actions to resolve some of these issues are presented in chapter 7.

CASE LAW ON VACCINE-RELATED INJURIES[1]

Developing specific policies for liability associated with the use of vaccines is complicated by the fact that vaccine-related injuries are part of two even larger issues: 1) the availability of socially useful, but unavoidably dangerous, products that inevitably cause some harm no matter what precautions are taken (i. e., product liability), and 2) compensation for injury when the person harmed was not in control of the circumstances under which the injury occurred.

At the same time that the courts are turning toward the insurance concept of spreading the risk, they must continue to work within the legal framework of an adversary, faultfinding process. The limitations of a judicial approach to insurance for injuries can be seen in the summaries of emerging case law on vaccine-related injuries presented below.

Legal Determination of Liability by Courts of Different Jurisdictions

The jurisdiction of the legal determination of liability is as important as specific legal theories embodied in the case law. The outcome of a lawsuit for a given factual situation may not be identical across the country. There is no requirement that the common or statutory law be consistent across the United States, as our Federal/State form of government results in applicable laws being those of a particular jurisdiction. [2] In cases of conflict between different Federal jurisdictions, the U.S. Supreme Court may eventually resolve the difference, but the concept of State sovereignty means that some areas and some State laws are outside the jurisdiction of even the U.S. Supreme Court.

On the other hand, courts of highest jurisdiction (i.e., the U.S. supreme Court and State Supreme Courts) may adopt legal doctrines from other jurisdictions, and the influence of case law can continue even though it may have been legislatively repudiated in the jurisdiction where it originated. [3]

[1] This topic and the broader issue of product liability recently have been the subject of several analyses. For product liability, see *Interagency Task Force on Product Liability: Final Report (Interagency, 1977)*, described as "the most thorough analysis of problems in the product liability area that has been published in the United States." For liability in immunization programs, see *Liability Arising Out of Immunization Programs: Final Report to Congress* (U.S. Ex. Br., DHEW, May 1978); T. E. Baynes, Jr., "Liability for Vaccine-Related Injuries: Public Health Considerations" (Baynes, 1976); and G. R. Smith, "Liability in Preventive Medicine: A Review and Analysis of Trends, Primarily Those Related to Vaccination Practices" (Smith, 1976).

[2] This is a simple representation of the area of conflict of laws.

[3] The most prominent recent example is *Helling* v. *Carey*, 83 Wash. 2d 514, 519 P. 2d 981 (1974), in which the court replaced a medical standard for testing of glaucoma with a legal standard. The court was overruled legislatively by Wash. Revised Code Section 4.24.290 (1976).

It is hard to predict when a court will confine case precedents to similar factual situations or when it will extend it to other situations. Three cases arising out of the use of live, attenuated polio vaccines have received the most attention in this respect: *Davis v. Wyeth Laboratories, 399* F. 2d 121 (9th Circuit 1968), *Reyes v. Wyeth Laboratories, 498* F. 2d 1264 (5th Circuit 1974), and *Givens v. Lederle,* 556 F. 2d 1341 (5th Circuit 1977). A question that arises from these three court cases is this: Will the courts limit precedents established in these cases to future situations involving injuries from live vaccines, or will they promote social policy goals?

Causes of Action for Vaccine-Related Injuries

A cause of action for vaccine-related injuries may arise in product or personal (medical malpractice) liability and may fall on any of the actors in the chain of events from manufacture of the vaccine to dispensation to vaccination.[4] Liability may arise from the intrinsic properties of a particular vaccine coupled with the failure to warn of these potential side effects, or from conduct associated with a vaccine (e. g., faulty manufacturing, nerve damage from the injection of the vaccine), in which case, liability does not depend on the vaccine's intrinsic properties.

Vaccine manufacturers' liability includes negligence in manufacturing and disseminating of the vaccine, for breach of express or implied warranty, and strict liability in tort:

1. Negligence applies to situations in which, for example, there was a reasonably correctable defect in the vaccine (e. g., contamination with bacteria or wrong labeling on the bottle) that caused an injury.
2. Breach of warranty is a claim that a contractual relationship existed between the manufacturer and the person injured. This relationship may be based on an actual contract (i.e., express warranty, although a court may read an implied warranty in the contract) or on an unwritten contract (i. e., implied warranty, where the court interprets the facts to be a contractual relationship). These "contracts" are often legal fictions to allow the plaintiff a cause of action against the manufacturer instead of against the party from which the product was actually purchased.
3. In strict liability in tort, the seller may be liable if a product leaves the seller's control in a condition unreasonably dangerous to the user. Some products are unavoidably unsafe no matter what precautions are taken, e.g., the Pasteur rabies vaccine, dynamite. If these products are socially useful, however, they are not considered "unreasonably dangerous, " providing that they are properly manufactured and accompanied by appropriate warnings regarding their inherent dangers.

Those who administer a vaccine are liable for professional malpractice associated with the vaccination procedure. Under certain circumstances, vaccinators assume the duty to inform vaccinees of the particular vaccine's inherent foreseeable risks. In this case, theoretically, the manufacturer's duty to warn legally can be transferred to the purchaser, individual, or organization actually performing the vaccination. The latter party, in turn, must gain the informed consent of the vaccinee. How the duty to warn can be transferred to the satisfaction of a court, however, is not clear.

'The differences and convergence of these theories of legal liability, especially as the, relate to manufacturers' liability, are outgrowths of very complicated historical developments of the law. (See note 1.)

In a suit against a particular party, any or all causes of action may be alleged, although one cause of action is usually decided upon by the plaintiff or court at trial or on appeal. A particular set of facts, therefore, does not necessarily indicate what the relevant cause of action is or will be. In the 1968 case of *Davis v. Wyeth Laboratories,* for example, the plaintiff brought a claim founded on 1) negligent manufacture, 2) failure to warn of known dangers, 3) strict liability in tort, and 4) breach of an implied warranty of fitness. The trial court dismissed all save that of breach of warranty. The U.S. Court of Appeals for the Ninth Circuit found that it was error to fail to instruct the jury, either in warranty or tort, that the manufacturer was strictly liable if its vaccine product caused the plaintiff to contract polio and if plaintiff's taking of the vaccine was without knowledge of risk.

Legal Liability Theories Embodied in Recent Case Law

The liability theory that has received the most attention is that of strict liability in torts Prior to the three live polio cases discussed below, the manufacturer's duty to warn the vaccine recipient about potential adverse reactions was discharged by warning the person administering the vaccine, who in turn had to warn the vaccinee. Following these cases, however, it is not clear whether a distinction can be made between factual situations in which the manufacturer's duty to warn is discharged and assumed by the vaccinator and situations in which the manufacturer's duty to warn is retained. Manufacturers may be held "strictly liable" for all vaccine-induced injuries associated with the inherent risks of their vaccine products.

1) Davis v. Wyeth Laboratories, 399 F. 2d 121 (9th Circuit 1968)—in Davis v. Wyeth *Laboratories,* the U.S. Court of Appeals for the Ninth Circuit found that the facts of the case imposed on the manufacturer a duty to warn the consumer (or make adequate provisions for the consumer's being warned) as to the risks involved, and that strict liability attached to the sale of the vaccine in the absence of such a warning.

Plaintiff Davis had contracted polio after taking live polio vaccine in a mass immunization clinic run by a pharmacist. A salesman for Wyeth Laboratories managed the vaccination campaign for the local medical society. He arranged for delivery of the vaccine and the promotional campaign, set forth the schedules and procedures to be followed, and was reimbursed for his expenses by the medical society. Vaccination fees were used to pay the medical society's bill from Wyeth, with the remainder kept by the society.

The Association of State and Territorial Health Officers, citing the U.S. Surgeon General's report, had published information that a small but definite risk of adult vaccinee's contracting polio from the vaccine did exist, and that because of this risk, the Surgeon General's report had recommended that the vaccine be given to children and high risk adults. (Mr. Davis fell into the class of high risk adults, because the parents of young children were included). The package insert accompanying the vaccine contained

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[5]Different interpretations exist on the content of this legal duty, which in part are related to legal distinctions between products that are "unreasonably dangerous" and products that are "unavoidably dangerous." The label "unreasonably dangerous" implies a traditional negligence test, where the defect is correctable under legal standards of reasonableness. "Unavoidably dangerous" implies the possibility of harm no matter what precautions are taken. For example, in *Davis v. Wyeth* ***Laboratories (Davis, 1968),*** one of the three live polio cases, the court stated:

> We conclude that the facts of this case imposed on the manufacturer a duty to warn the consumer (or make adequate provision of his being warned) as to the risks involved, and that *failure to meet this duty rendered the drug unfit in the sense that it was thereby rendered unreasonably dangerous.* (emphasis added) 399 F. 2d at 130.

Obviously, the court was not referring to the intrinsic properties of the vaccine, which would be unchanged whether or not the warning was given. Rather, it was determining who would bear the cost of injury—the manufacturer, the vaccinator, or the vaccinee—once the risk of injury was realized.

pertinent excerpts of indications and risks, but neither the pharmacist nor Mr. Davis read it. A fact sheet put out by Wyeth, contained in a book it supplied to the clinic, was published prior to the Surgeon General's report and represented the vaccine as completely safe for all ages. No effort was made by Wyeth or the medical society to inform the c1inic pharmacist of the risk.

Finally, the Ninth Circuit Appellate Court rejected the statistical argument that a risk of less than one in a million was not unreasonable, stating that the risk of contracting polio without immunization was about the same as contracting it from the vaccine.

2) Reyes v. Wyeth Laboratories, 498 F. Zd 1264 (Sth circuit 1974)—In the 1974 case of Keyes v. Wyeth *Laboratories,* the U.S. Court of Appeals for the Fifth Circuit affirmed the lower court judgment that Wyeth was liable for polio contracted by a vaccinee, because it marketed an unavoidably unsafe vaccine and failed to provide the parents of the vaccinated infant with either a warning of risk or individualized medical judgment that the vaccination was necessary and desirable for the infant.

One issue at the trial level was whether the vaccine or a wild polio virus known to be present in the community at the time of vaccination caused the polio. This was approached as a question of fact for the jury to decide, and the appellate court would not reopen the question.

Wyeth contended that, if it had a duty to warn, this duty was discharged by the warning contained on the package insert which accompanied the vials of vaccines it sold to the Texas State Department of Health, i.e., its duty to warn was the same as that for prescription drugs. It also distinguished the facts of the case from Davis for the following reasons: 1) the infant Reyes took the vaccine at her parents' request, not as a result of a mass immunization program; 2) the vaccine was administered by a public health nurse, not a pharmacist; 3) Wyeth's role was passive, not like that of its salesman in *Davis;* and 4) it claimed no knowledge that the vaccine would not be administered as a prescription drug (and thus be accompanied by an individualized medical judgment as to its use).

The appellate court dispensed of the first two arguments by finding that the prescription drug exception required an individualized medical balancing of the risks to the vaccinee. The public health nurse had testified that she had read the package insert, but that it was not the practice of the nurses at the clinic to pass on warnings to the vaccinees or their guardians, and that she had given no warning.

As for the latter two arguments, the court found that Wyeth had ample reason to foresee the manner in which its vaccine would be distributed. Since Wyeth knew or had reason to know that the vaccine would not be administered as a prescription drug, it was required to warn foreseeable users, or to see that the vaccine purchaser, the Texas Department of Health, warned them.

3) Givens v. Lederle, 556 F. 2d 1341 (5th Circuit 1977)—In the 1977 case of *Givens v. Lederle,* the U.S. Court of Appeals for the Fifth Circuit (the same court as that in Reyes) found that a rational basis existed for the jury's verdict against Lederle on the issues of failure to give adequate warning and of such failure being the proximate cause of the vaccinee's mother contracting polio.

The proximate cause issue had arisen because the trial judge had excluded testimony that the vaccine could cause polio. The original jury had found for the manufacturer, Lederle, but the trial judge had reversed himself after the Reyes decision, in which the appellate court had expressly accepted as fact that oral polio vaccine can induce an active polio case. At the second trial, the verdict went against Lederle.

The plaintiff Givens developed polio soon after having taken her daughter to her pediatrician for oral polio vaccinations. Lederle argued that, in Reyes, a county health clinic administered the vaccine, whereas in this case a private physician did. The court's rebuttal, as extracted below, was as follows (Givens, 1977):

> [T]he difference is not nearly so great as appellant indicates. The "county health clinic" in Reyes was not involved in the same sort of "mass inoculation" as was taking place in Davis v. Wyeth *Laboratories, inc.,* the case which established the duty to warn in these "unavoidably dangerous" drug cases, like Reyes and the instant one. The administration of the vaccine by a public health nurse in Reyes is as close to the instant situation as it is to the *Davis* mass inoculation . . , There is solid evidence that the vaccine was administered here in a manner more like that at a small county health clinic, as in Reyes, than by prescription. For example, Dr. LaRue, the private pediatrician, testified that the administration in his office "really didn't differ" from that of the Public Health Center, "not in the administration at all. " If so, then Lederle is responsible for taking definite steps to get the warning directly to the consumer . . . Dr. LaRue claims that "the wording on the insert states that it is a safe and affective (sic) means of immunizing the population and that the risk, if it exists, is no more than one in three million. I felt that was a very nebulous way of putting it . . , and I did not feel there was sufficient evidence or warning to warn Mrs. Givens about them." (Citations omitted.)

Following the Givens case, a manufacturer must assume that vaccines will always be administered without individual medical attention, no matter where or how they are administered. [b]

Finally, if the duty to warn is transferred to the vaccinator, that duty becomes a part of the informed consent that must be obtained from the patient for treatment.[7]

> A claim based on lack of informed consent is essentially a claim that the physician did not disclose to a patient what the nature and risk of treatment would be, that the subsequent treatment, therefore, was, in effect, without the patient's consent, and that the plaintiff is consequently entitled to seek damages for any resulting injury. The theory is that, had the physician made a full disclosure, the patient could have refused treatment, thus avoiding the adverse outcome. Lack of informed consent is an independent theory, and thus an action based on it does not require a showing of negligent conduct butmerely a failure of disclosure.[8]

It is difficult to see, though, how the *Givens* court would approach a suit in a failure to warn case against the vaccinator, and not the manufacturer. In the *Givens* case, the court chose to use testimony by the vaccinating physician as one basis for concluding that the manufacturer's duty to warn had not been discharged. [g]The court relied on the very kinds of conclusions by the physician on the statistical risk that it would not allow

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'See pp. **27-34** in *Liability Arising out* of *Immunization Programs: Final Report To Congress* (U.S. Ex. Br., DHEW, May **1978).** Baynes, on p. 168 in "Liability for Vaccine-Related Injuries: Public Health Considerations'' (Baynes, **197** makes a distinction between private and public immunization programs, but the *Givens case* had not been decided at the time of his analysis.

'Informed consent originated in the theory of battery, where harm resulted from unconsented touching. *Mohr v. Williams, 95* Minn. **261, 104** N.W. 12 (1905). It thus has a doctrinal basis that is different from that for the duty to warn. The implications of the two, however, are the same.

'See p. **37** in *Report* of *the Special Advisory Panel on Medical Malpractice, State of* New *York (Report,* 1976). There is a difference between jurisdictions in determining the adequacy of the information given to satisfy informed consent. Some courts require expert medical testimony to show what the standard of disclosure is, the plaintiff having to provide the expert testimony in order to show that the defendant deviated from it. *Natanson v. Kline,* 187 Kan. 186, 354P. 2d 670 (1960). (Other courts, emphasizing the patient's right to know, have held that expert testimony is not needed to show inadequacy of disclosure. *Canterbury v. Spence,* 464 F. 2d 772 (D. C. Circuit 1972), *Cobbs v. Grant, 8* Cal. 3d **229, 502** P. 2d 1 (1972). This is still the minority doctrine.)

'Its other reason, that the administration of the vaccine by public health nurse in *Reyes* was as close to the private pediatrician situation as it was to the *Davis* mass inoculation, is not a particularly lucid rationale and comes close to being a non sequitur.

the manufacturer to make. It is not clear that the same legal principles govern whether a manufacturer must provide a warning (to a physician or a patient) to avoid strict liability and whether a physician must warn his patient to avoid liability under the informed consent cases. The manufacturer must warn of the risks that make its products unavoidably unsafe. The physician, however, might be permitted to omit a warning if his evaluation of the patient indicates that it would cause the patient unreasonably to forego medical treatment. The outcome would be further complicated in mandatory vaccination programs.

Finally, the Givens court, the U.S. Court of Appeals, Fifth Circuit, is the same court that decided Reyes. The Reyes decision provided manufacturers two avenues for avoiding liability: 1) a warning of risk, or 2) individualized medical judgment that the vaccination was necessary for the vaccinee. With the ruling in *Givens,* the second avenue would be effectively closed. The closing of this avenue, coupled with the continuing uncertainty as to when the warning requirement has been satisfied, may mean that the only way the manufacturer can avoid liability is to expressly transfer the duty to warn to the vaccinator in the written contract of purchase of the vaccine.

When it cited a "policy factor" at work in the Reyes case, the Fifth Circuit Court of Appeals may have been forecasting its *Givens* decision (Reyes, 1974):

> Until Americans have a comprehensive scheme of social insurance, courts must resolve by a balancing process the head-on collision between the need for adequate recovery and viable enterprises. This balancing task should be approached with a realization that the basic consideration involves a determination of the most just ***allocation of the risk of loss*** between the members of the marketing chain. Statistically predictable as are these rare cases of vaccine-induced polio, a strong argument can be advanced that the loss ought not lie where it falls (on the victim), but should be borne by the manufacturer as a foreseeable cost of doing business, and passed on to the public in the form of price increases to his customers.

PRINCIPLES UNDERLYING PRICING OF LIABILITY INSURANCE[10]

As noted in the preceding section on case law, a cause of action for vaccine-related injuries may arise in product or personal liability, and liability may fall on any of the actors in the chain of events from manufacturing to dispensation to vaccination.

Vaccine-related injuries are covered by the product and medical malpractice liability insurance policies of manufacturers and health care providers (individual physicians and other independent practitioners as well as organizations such as hospitals).[11] Premiums usually are set for groups of manufacturers or categories of products. Premiums are calculated for groups of health care providers, not for individual providers. For products liability, premium calculations may be class-rated or judgment-rated, the latter being subject to negotiations between the manufacturer and the insurance company.

The logistics of underwriting liability insurance for multiple products and multiple types of providers mean that the liability experience for any particular product (e.g., vaccines) or cause of action (e. g., informed consent) will command only cursory analysis by

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[10] For more detailed discussion of th, field and of ratemaking practices, see ch. V of *Interagency Task Force on Product* Liability; *Final Report (Interagency,* 1977), "Pricing Medical Malpractice Insurance: A Technical Discussion of Rate-Making, " in *Report of the Special Advisory Panel on Medical Malpractice, State of New York (Report, 1976),* R. S. L. Roddis and R. E. Stewart, "The Insurance of Medical Losses, " 1975 *Duke L. J.* 1281 (January 1976).

[11] ' 'The recent swine flu program was an exception because of its enormous size and lack of historic data on which to base premiums.

underwriters charged with setting premium levels. When a manufacturer has one product with large liability losses, however, either this product may be excluded or two insurance contracts may be written. Until recent events spotlighted product and medical professional liability, insurance companies usually kept no separate data on these two fields and reported only the overall results for property-casualty insurance and miscellaneous liability insurance. Thus, whenever any particular area of liability was scrutinized, the insurance data were found to be inadequate.

Coverage

The typical liability insurance policy is issued on an "occurrence" basis. Under an occurrence policy, the insured is covered for injuries that occur during the policy period, usually 1 year, regardless of when a claim is filed or a suit settled. Issuing policies on an occurrence basis has caused problems in pricing medical malpractice premiums, because as courts have extended the rule of discovery, [12] leading to the "long tail" in medical malpractice suits, insurers have had difficulty in estimating payments for claims which may be brought many years in the future.

Liability insurance policies also may be issued on a claims-made basis. In claims-made policies, the insurer is liable only for claims made during the policy period. [14] The uncertainties inherent in occurrence policies are somewhat reduced by claims-made policies, because the insurer is able to know after the end of the policy period exactly how many claims are covered by a particular claims-made policy. For retiring physicians or those who switch back to occurrence policies, coverage for future claims rising out of occurrences in the claims-made policy year can be provided by a single premium, perhaps calculated as a fixed percentage or multiple of the last annual premium on the claims-made policy .15

For product liability, the occurrence is at the time of injury, not at the time of manufacture. Uncertainties in pricing occurrence insurance policies arise in two situations:

1. Situations involving liability for old products, in which a long time may have elapsed between the time of manufacturing and sale of the product to the time of injury; and
2. Situations in which adverse results may not be known and/or may not occur for many years (e. g., cases involving 'hormonal treatment and gynecological cancers, or asbestos and cancer).

Insurance is provided in several layers of coverage. First, there may be a deductible amount assumed by the insured that has to be exceeded before insurance policies pay claims losses. Second, there is a basic insurance policy that covers a specified amount, usually stated in annual amounts per occurrence and in the aggregate. (For example, the limit may be $1 million per occurrence, $3 million in the aggregate. The insurer will not pay more than $1 million for losses arising out of an incident and no more than $3 million

[12] The prototypical case is the discovery of a sponge at the operating site in the body many years after the operation occurred. Courts have ruled that the statute of limitations did not toll from the time of operation but from the time of discovery.

[13] A recent Illinois Supreme Court decision portends additional problems in calculating future payments for acts of malpractice. In *Renslow v. Mennonite Hospital, 67* Ill.2d *348, 367* N.E.2d 1250, rehearing denied (1977), the court ruled that a child may recover damages for personal injuries sustained as a result of the negligent conduct of a physician and a hospital in giving her mother a blood transfusion 8 years before the plaintiff's birth.

[14] Claims-made policies were used by some captive insurance companies termed by physician organizations during the recent medical malpractice insurance availability crisis of the mid-1970's.

[15] This also could be overcome by a surcharge on active physicians to cover possible claims against retired physicians. Also, gaps in coverage could be a problem if physicians switched back and forth between occurrence and claims-made policies.

for all incidents occurring in the policy year.) Third, the insured may purchase excess insurance covering, up to a specified limit, losses above the basic policy. Any losses above the excess insurance limit are the liability of the insured.

Insurers providing either the basic or excess insurance policies may reinsure part of the risk themselves or may spread the policy among several companies; that is, a given insurer may itself purchase insurance from an excess insurer, or it may share the coverage (and premiums) with other insurance companies. Excess insurance usually is provided by special excess or "umbrella" insurance companies. By its very nature, excess insurance is among the most speculative types of insurance. This is the primary reason that companies providing the basic policies stay out of the market. As historic data are accumulated and ratesetting becomes more reliable, basic insurers may enter this market by raising the limits of the basic policies.

Servicing of claims usually is provided by the basic insurers. The dollar figures for the deductible and basic and excess insurance policies refer to claims paid and do not include administrative costs. In calculating premiums, the basic insurers take these servicing costs into account. Some insureds, such as large drug companies, may service their own claims, in which case their premiums would reflect this by being lowered.

The insurance arrangements that were worked out for the swine flu immunization program illustrate this layering of coverage and spreading of the risks.*' The Federal Tort Claims Act was modified to require all vaccine-related claims to be brought against the Federal Government, which in turn could recover from negligent manufacturers or vaccinators. Vaccine manufacturers and insurers providing their basic policies thus were relieved of the expense of handling swine flu liability claims, although they still incur expenses in assisting the Federal Government to process these claims.

Each of the four manufacturers of swine flu vaccine self-insured for **$2.5** million, for a total of $10 million. Each manufacturer also received a basic policy of $5 million[17] and an excess policy of **$50** million, for a total of $20 million for the basic policy and $200 million for the excess coverage. Total premiums on the $20 million basic policies were $2.4 million; the premium on the $200 **million excess** policies was **$6.25** million.

Sixteen companies insured the basic policies, with each company's share ranging from **0.5** to 10 percent of the total. Thirty-seven companies issued the excess policies, with each company's share ranging from 0.05 to 17.035 percent of the total. Twelve companies participated in underwriting both types of policies,

If the Federal Government had not assumed responsibility for defending against claims, in addition to adjusting the premium upwards, the companies would have had to agree on who would be handling claims. The most likely arrangement would have been to limit the insurers underwriting basic policies to a few (perhaps one per manufacturer), with other companies reinsuring the risk, or for manufacturers to handle the claims themselves.

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[16] See p. 39 i„ *Review and Evaluation of the Swine Flu* Immunization Program (U.S. Cong., HCIFC, 1977).

[17] This amount is the aggregate limit, apparently the same as the occurrence limit.

Ratemaking[18]

Medical malpractice and product liability ratemaking practices differ somewhat in methodology, but the basic concepts and terminology are the same.[19] The following discussion is based on the specific practices followed by the Insurance Services Office (ISO), a servicing agency for the insurance industry.

Premiums are calculated on the basis of all of the following:

1. Loss and expense data,
2. Loss development factors, and
3. Trend factors.

Loss and expense data consist of paid plus incurred (but not paid) losses and expenses. Losses are the amounts paid out in claims plus loss adjustment expenses (e.g., lawyer and court fees, etc.). Expenses equal all other items such as agents' commissions, taxes, fees, overhead, profit, etc. The reliability of the loss and expense data is a function of size. In vaccine liability, for example, the data that insurers have are inadequate to be reliable for setting premiums, because: 1) there are too few claims, and 2) most large drug companies have sizable self-insured deductibles before the insurance policy goes into effect.

Loss development factors produce estimates of what incurred losses will be when finally paid. The trend factor relates largely to expenses, not losses, and is an index that measures changes in the past with the expectation that these changes will continue at the same rate in the immediate future *(Problems, 1975).* Brief descriptions of the loss development and trend factors follow.

A loss development factor is calculated to compare premiums (and relevant income derived from premiums) for any policy year against total losses. Losses include paid claims, estimated costs of known claims, and estimated costs of potential claims (commonly known as incurred-but-not-reported, or IBNR). Insurers submit loss (and expense) reports to ISO at 15 months, then every 12 months, after the beginning of the policy year. For product liability, four subsequent annual reports **are** made. **For medical** malpractice, ISO estimates that incurred losses will not be known until 10 years after the beginning of the policy year, or after nine reports. The report does not include IBNR losses *(Problems,* 1975):

> Since the first report on a policy year basis will be quite immature, reflecting as it does only a very small portion of paid claims and no estimate at all of unknown claims, those losses must be adjusted to approximate the amount that ultimately will be paid in claims and related expenses arising from incidents which occurred in that year. This adjustment is accomplished by the use of a loss development factor which is determined by comparing the more mature loss reports for prior years with the less mature reports for those same years. By means of this calculation the actual historical development which took place in the most recent past is measured and then applied to the latest policy year's incurred losses . . .

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[18] This is a very technical subject, and the reader should refer to the references in note 10 for further discussion. Also not discussed here are the effect of insurance company investment practices on premium rates and the controversy *over* how much profits or losses from these practices should be considered by State insurance commissioners in approving or denying changes in premium rates. For some State examinations of ratemaking in the medical malpractice area, see T. A. Harnett (Commissioner of Insurance, State of New York), "Opinion and Decision in the Matter of the Medical Malpractice insurance Association and insurance Services Off ice," November 1975, and Joint Legislative Audit Committee, Office of the Auditor General, California Legislature, *Doctors' Malpractice Insurance: An Interim* ***Report,*** Sept. **10,** 1975.

[19] See ch. v of *Interagency* Task *Force on Product Liability (interagency,* 1977) and *The* ***Problems Of*** *Insuring Medical* ***Malpractice (Problems,*** 1975).

Thus, for example, if the losses in the first report were $1 million and the loss development factor to the final report were 1.5, losses would be estimated at $1.5 million for the relevant policy year.

The methodology is sound, but is limited by the reliability of the data base. The data base includes estimated costs of known claims and potential claims (IBNR), and the latter especially depend on how good early-warning reporting systems are. An almost uniform finding of the various State commissions that studied the medical malpractice problem was that these reporting systems are nonexistent .20

Other factors affecting the reliability of the data comes down to the "informed best guess" of the individual underwriter trying to price a line of insurance and are affected by such things as the competitive environment of the field, the insurer's overall capacity to provide insurance of different types, management's willingness to do business in **a par**ticular line of insurance, potential defense and claims processing costs, and many other factors including the complex legal milieu described earlier. For particular lines, there may be so little claims experience or experience of such variability that it is impossible to calculate statistically valid rates. For products such as vaccines, there may not be very many claims, but claims that are made may be very high.

Early estimates of losses for any policy year may be dramatically different from eventual actual losses, as seen in the following example:

Losses for the Policy Year Ending December 31, 1966[21]

Undeveloped losses (paid claims and case reserves) as known on 3/31/67	*Actuarial estimate of what* losses will *be* on .3/.31 /71	*Paid* claims *and case reserves as* known on **3/31/71**
$5,559,547	**$12,263,892**	**$18,185,503**

SOURCE: *The Problems of insuring Medical Malpractice, 1975,* p. **17.** *(Problems, 1975.)*

Upwards adjustments of loss estimates, as would be necessary in the example above, would have the effect of increasing the loss development factor (and vice-versa) for subsequent years. Loss development factors are used as one part of the formula for calculating future premiums. The experience of previous policy years that go into the calculation also includes that of the most recent years, for which, as noted earlier, estimates of eventual losses are most tentative.

The trend factor used by ISO is derived by multiplying the average annual percent increase in claims costs by the percent increase in claims frequency from previous years' experience. It is determined separately for each policy year.

This trend factor is then applied to incurred losses as adjusted for the loss development factor. This estimate of losses is what is expected to occur under policies written after the proposed effective date. In effect, the calculation estimates what claims would cost if the underlying occurrences were to take place in the policy year for which rates are being set and were closed sometime in the future.

These losses (which include loss development and trend factors) are then divided by the premiums at current rate levels. The quotient is the "loss ratio" and represents the percentage of premiums at present rates that would be required to pay claims and related

[20] For example, see pp. 236-237 in *Report of the* Special *Advisory Panel* on Medical Malpractice *(Report,* 1976).

[21] The first policy issued would be on Jan. 1, 1965, and the last, on Dec. 31, 1965, so that coverage on the last policy issued would end on Dec. 31, 1966. The reporting date of Mar. 31, 1967, would be 27 months after issuance of the first policy. See p. 17 in The Problems of *Insuring* Medical Malpractice *(Problems, 1975).*

expenses. In order to set a figure for premiums in the next policy year, the "loss ratio" is compared to a standard, the "expected loss ratio, " which is calculated by subtracting from 100 percent the necessary business expenses plus underwriting profits and contingencies, expressed as a percent of premium. The loss ratio divided by the expected loss ratio indicates what the premium level will be. For example, if losses are 90 percent of premiums, the loss ratio will be 0.900. If the standard for the expected loss ratio assumes 25-percent business expenses and 5 percent for underwriting profit and contingencies, the expected loss ratio will be 0.700. Dividing the loss ratio by the expected loss ratio would indicate that current premiums would have to be increased by 28.6 percent (0.900 divided by 0.700 equals 1.286).

To summarize the ratemaking process:

1. The reliability of the data base may be limited. Even if resources were applied to obtain reliable data, the diversity of the risks covered and the complexity of legal liability issues would still limit the reliability of the collected data.
2. A basic requirement of ratemaking is that events must be predictable within relatively narrow boundaries of uncertainty. Fluctuations in, or changing patterns of, claims costs and frequencies raise questions about the predictive value of historic data. If predictions begin to result consistently in losses, insurers will become more conservative and price the risks at even higher levels or withdraw from unprofitable markets.
3. "Incurred" losses necessarily include estimates of losses from known and potential claims and their associated administrative costs. Loss development and trend factors then are used to further quantify these estimated losses. Estimated losses can turn out to differ significantly from actual losses. The long lag time between policy years for which total losses are finally known and policy years about to be underwritten make even known losses for past policy years of limited usefulness in the ratemaking process.

VACCINE RISKS, ADVERSE REACTIONS, AND LIABILITY CLAIMS

The previous sections have presented developments in case law on vaccine-related injuries and insurance methods for pricing liability insurance. In this section: 1) the degree of risks from vaccines is summarized, 2) data on claims for injuries are presented, and 3) the liability experience of the recent swine flu mass immunization program is discussed in terms of compensation for injury within the present tort liability system.

Degree of Vaccine Risks and Adverse Reactions

Minor side effects such as fever, sore throat, rash, malaise, etc. maybe frequent for some vaccines, but the rate of serious adverse reactions is usually low. The rates of adverse reactions to the childhood vaccines is shown in table 16. (For rubella vaccine, temporary arthritis and perhaps transient nerve damage might be classified as minor reactions by some medical authorities.)

The now familiar Guillain-Barre Syndrome (GBS) found to be associated with the swine flu (A/New Jersey/76) vaccine is an "ascending paralysis" which begins in the legs and later involves the trunk, arms, and neck. It is a transient condition in about 90 percent of the cases, leaves a residual paralysis in about 10 percent, and is fatal in about another 5 percent. In the swine flu program, one extra case of GBS above the expected incidence was observed for each 100,000 influenza immunizations (U.S. Cong., HCIFC,

1977). Cases of GBS in the vaccinated and unvaccinated populations appear in table **18.** The risk is higher in the vaccinated than in the unvaccinated population for persons **25** years and older. Preliminary data from the Center for Disease Control's (CDC) GBS surveillance program for the 1978 flu program (which was targeted at Russian flu, not swine flu) indicate that there is no significant difference in GBS rates between the vaccinated and unvaccinated populations (Hamilton, **1979). (See** appendix 5.1.)

Table 18.—Reported Fatal and Non-Fatal Cases of Guillain-Barre Syndrome in the United States October 1, 1976–January 31,1977 (by age group and A/New Jersey vaccination status)

	Vaccinated			Unvaccinated**			Total		
Age group	Cases	Deaths	Ratio	Cases	Deaths	Ratio	Cases	Deaths	Ratio
0-17 years	2	0	00/0	120	1	0.8%	122	1	0.8%
18.24 years	36	1	2.8%	76	3	3.9%	114*	4	3.5%
25-44 years	202	4	2.0%	131	4	3.1%	333	8	2.4%
45-64 years	173	12	6.9%	137	6	4.4%	313*	18	5.8%
65+ years	118	15	12.7°10	91	12	13.2%	212*	27	12.7%
Unknown	1	0	0%	3	0	0%	4	0	0%
Total	532	32	6.0%	558	26	4.7%	1,098*	58	5.3%
18 + years	530	32	6.0%	438	25	5.7%	972	57	5.9%

*Includes one or more cases with unknown vaccination status.
**Includes cases with onset of Guillain-Barre Syndrome before vaccination.

SOURCE: *Federal High-Risk Influenza Immunization Initiative—Oversight.* Hearings before the Subcommittee on Health and Environment of the Committee on Interstate and Foreign Commerce, U.S. House of Representatives, p. 52, 1978. (U.S. Cong., HCIFC, 1978.)

Claims and Lawsuits From Vaccine-Related Injuries

Existing information on the numbers of vaccine-related injury claims and lawsuits prior to those arising out of the swine flu program is conflicting, but the numbers are very small both in absolute terms and compared to those from the swine flu program. The number of claims is larger than the number of lawsuits, because filing for a claim is preliminary to filing for an actual lawsuit, and many claims may never progress to the lawsuit stage.

General Counsel for HEW stated that as of March **23, 1979, 3,694** claims had been filed under the swine flu immunization program; as of April **2, 1979, 464** of these claims had been filed as lawsuits (Hamilton, 1979). The U.S. General Accounting Office (GAO) cites Public Health Service (PHS) records showing total number of claims since **1963** to be **3,721.** The **27** claims other than the **3,694** arising from the swine flu program were listed by type of vaccine as follows (Bernstein, 1979):

Polio	19
Flu	3
Smallpox	3
Typhus/typhoid	1
Measles	1
Total	27

In its **1978** report to Congress, Liability Arising Out of Immunization *Programs (U.S.* Ex. Br., DHEW, May 1978), HEW provided the data in table 19 on the number of vaccine-related lawsuits filed against manufacturers of vaccines between **1967** and **1977.** Altogether there were a total of **89** lawsuits filed in this period. In comparison to the numbers of claims and lawsuits currently pending from the single swine flu program, the total numbers of claims and lawsuits filed against manufacturers between 1967 and 1977 for other alleged vaccine-related injuries are small.

Table 19.—Vaccine-Related Lawsuits (1967-77)'

By status of lawsuit

Status	Number of suits
Pending	41
Settled	33
Dismissed or discounted	14
Jury verdicts for plaintiff	1
Total	89

By year of fifing

Year	Number of suits
1967	3
1968	2
1969	11
1970	11
1971	4
1972	5
1973	9
1974	**10**
1975	**12**
1976	**9**
1977	**13**
Total	89

[a]This table indicates lawsuits, not claims. Numbers are based on data supplied by five manufacturers who now produce or in the past produced measles, mumps, rubella, DPT, polio, and flu vaccines, and reflect liability experience with respect to these vaccines. The table does not show cases filed against Lederle Laboratories, the sole present manufacturer of oral polio vaccine, which did not provide data.

SOURCE: *Liability Arising Out of Immunization Programs: Final Report to Congress,* U.S. Department of Health, Education, and Welfare, 1978. (U.S Ex. Br., DHEW, 1978.)

Liability Experience of the Swine Flu Immunization Program

Because vaccine manufacturers were initially denied liability insurance by the insurance industry, the swine flu immunization program was delayed until Congress enacted legislation providing that all tort suits had to be brought against the Federal Government through a modification of the Federal Tort Claims Act. Under the legislation enacted, the National Swine Flu Immunization Program of 1976 (Public Law 94-380), the Government has a right of subrogation only against manufacturers and program participants who were negligent.

As described earlier, each of the four manufacturers of swine flu vaccine self-insured for $2.5 million, for a total of $l0 million. Each manufacturer also received a basic policy of $5 million and an excess policy of $50 million, for a total of $20 million for the basic policy and $200 million for the excess coverage. Total premiums on the $20 million basic policies were $2.4 million; on the $200 million excess policies, the premium was $6.25 million. Sixteen companies issued the basic policies, each insurance company's share ranging from 0.5 to l0 percent of the total. Thirty-seven companies issued the excess policies, each company's share ranging from 0.05 to 17.035 percent of teetotal.

Both the self-insurance costs and the premiums are considered business expenses of producing the vaccines, so the Federal Goverment funded both for a total of $l8.65 million. The premiums cannot be recovered, because they were the cost of providing the insurance. The $l0 million self-insurance or remaining portions of it will be returned to the Government with interest, providing either that the money is not used to pay claims costs, or that the manufacturers are shown to have been negligent in causing injury. This does not include the duty to arn, which had been assumedly the Federal Government.

Since the Government would be recovering up to the first $10 million in negligently proven cases from funds that it would recover from the manufacturers anyway, even if no subrogation suits were brought, there seems little incentive to bring such suits. While the insurance companies are theoretically responsible for $220 million-of paid-out claims (at a premium price of $8.65 million), none of this money will be paid out unless the injuries to be covered by these funds were negligently caused and the $10 million self-insurance fund is exhausted.

Of the 3,694 claims filed as of March 23, 1979, 1,045 allege Guillain-Barre Syndrome (GBS). Of the $3.351 billion in damages sought, **$952.5** million arises from GBS (Hamilton, 1979). In fact, both these sets of figures greatly overstate the actual situation because, first, some allegations of GBS are not credible, and second, in a lawsuit, just about any dollar figure can be alleged. The numbers cited include: 1) claims alleging vaccine-induced GBS by individuals in whom the syndrome began long after there would have been any relationship to the vaccine; 2) claims by individuals in whom GBS occurred, but who had not received the vaccine; and 3) frivolous claims such as an **$80,000** claim by a truck driver who alleges having contracted GBS as a result of transporting the vaccine, and a $1 million claim for "hives, etc.;" and 4) claims filed because the statute of limitations was approaching by individuals who suffered no injuries.

The 464 lawsuits that have been filed seek damages totaling **$504.3** million. The kinds of vaccine-related injuries alleged by persons bringing suits are shown in table **20.** Between **40** and **50** claims and suits have been settled to date, with payments of approximately $1 million. This amount does not include expenses related to handling these claims. Through fiscal year 1977, the Department of Justice estimated costs of processing and defending these claims at **$170,000** (Staats, 1979).

Table 20.—Alleged Injuries in Filed Lawsuits Arising From the Swine Flu Immunization Program

Type of injury alleged	Number of suits
Personal injury related to GBS	251
Death from GBS	25
Personal injury from other neurological injuries	67
Death from other neurological injuries	3
Personal injury from non-neurological injuries	95
Death from non-neurological injuries	23
Total	464

SOURCE Statement of Peter B Hamilton, Deputy ic Research, 1979 (Hamilton, 1979)

Finally, two observations should be noted. First, the swine flu program essentially was in effect from October to mid-December 1976. Two and one-half years later—out of total filed claims (including frivolous ones) of 3,694 and total filed suits of 464—only 40 to 50 claims have been settled. For vaccinees suffering real harm or death, therefore, compensation was not timely, has yet to be provided, or may not be provided. Second, the most significant injury and the one for which most compensation probably will be paid, i.e., Guillain-Barre Syndrome (GBS), resulted without apparent negligence in the manufacturing of the vaccine. Thus, when viewed as a compensation approach, the $8.65 million premium costs for liability insurance in all likelihood will provide no return.

6.

FINDINGS AND ISSUES

6.

FINDINGS AND ISSUES

VACCINE RESEARCH, DEVELOPMENT, AND PRODUCTION

FINDINGS (See chapter 2.)

- By financing a $6 million pneumococcal vaccine research and development program, the Federal Government successfully stimulated at least one U.S. pharmaceutical company to spend an equal amount of its own money to develop, obtain licensure for, and market a pneumococcal vaccine.
- In 1976, in spite of receiving Federal funds, another pharmaceutical company, which had been an active vaccine developer and producer since 1915, abandoned its pneumococcal and most of its other vaccine research, development, and production programs; this company cited the cost of complying with certain Government regulations as one reason for its withdrawal.

ISSUE A:

The extent and nature of Federal Government intervention needed to ensure sufficient levels of vaccine research, development, and production

Vaccines are an important cornerstone to the prevention of certain infectious diseases in this country. Therefore, maintenance of the capacity of the U.S. pharmaceutical industry to research, develop, and produce vaccines is of vital concern to the Federal Government. To date, in spite of a continuing decline in the number of vaccine manufacturers and products since around 1950, the industry has continued to supply this country with most of the important vaccines for which there is public demand. In recent years, however, the capacity and willingness of the industry to continue innovative vaccine development and production has been seriously questioned.

Federal policies may be affecting manufacturers' decisions to withdraw from the vaccine business. The major unanswered question, however, is this: When viewed in combination with general economic factors, what impact do selected Federal Government policies have on the overall commitment of U.S. pharmaceutical manufacturers to vaccine research, development, and production? Specific areas of concern are described below. Policy options related to these areas of concern are presented in chapter 7.

Federal Financing of Vaccine Research and Development

The appropriateness of the Federal Government's role in financing basic and epidemiologic research on infectious diseases is generally not in dispute (Hilleman, 1976; Jordan, 1977). Most federally supported research is conducted outside the pharmaceutical industry in academic and governmental research settings. Some companies undertake federally financed research, as did Lilly in the case of pneumococcal vaccine, and a few companies, such as Merck and Lederle, fund basic research themselves. For the most part, though, basic and epidemiologic research is conducted outside the industry.

The appropriateness of Federal financing of vaccine product development is a matter of considerable controversy. Traditionally, the primary source of financing for actual vaccine product development has been individual pharmaceutical companies hoping to develop a marketable product. In the case of pneumococcal vaccine, however, funding for product development also was provided by the National Institute of Allergy and Infectious Diseases (NIAID), a Federal agency.

Federal financing for vaccine product development provides a classic illustration of the more general controversy regarding the Federal Government's role vis-a-vis private industry in financing product development. One view is that Government has a public responsibility to finance the development of vaccines with documented or potential value for the public, especially in the absence of private sector initiative to do so. From this perspective, the Federal Government's provision of funds to industry for vaccine product development is analogous to its purchases from industry of vaccines to be used in public immunization programs. Further, Federal provision of funding to private industry for vaccine product development may be more efficient than either of the two infrequently used alternatives of: 1) establishing Government facilities to develop vaccines, or 2) using non-governmental vaccine development facilities in academic institutions or other not-for-profit settings.

An opposing view of Federal Government financing of vaccine product development, is that it not only is unnecessary, but actually may impede privatd sector research efforts. Some pharmaceutical companies do not want to accept Federal research funds, because once they do, their research findings become public record and can be used by competing firms to develop similar products. Other firms believe that by accepting Government contracts, they lose flexibility in their ability to allocate company resources —both facilities and personnel.

Federal Vaccine Safety and Efficacy Requirements

A vaccine manufacturer's ability and willingness to comply with Government regulations concerning vaccine safety and efficacy are other factors that may influence a company's decision either to bring a new vaccine to the market or to continue producing a licensed product.

The standards and procedures used by the Food and Drug Administration's (FDA) Bureau of Biologics (BOB) to assess the safety and efficacy of vaccines are discussed in chapter 3 and in appendixes 3.1 through 3.4. Because vaccines contain either attenuated (weakened) live organisms, or materials extracted from micro-organisms such as viruses or bacteria, BOB requires manufacturers' products to meet certain standards for purity, sterility, safety, and effectiveness. To assess the safety and efficacy of new vaccines, for example, BOB requires manufacturers to generate data from premarketing clinical trials. Further, once a product is marketed, not only must manufacturers test their vaccine products themselves, but they must submit to BOB samples of vaccines for verification of the results.

The pharmaceutical industry often complains that the costs of complying with existing premarketing safety and efficacy regulations have become so exorbitant, and the process so time-consuming, that the marginal value of developing or producing a new product is often too low to warrant manufacturers' efforts (Johnson, 1978). Some researchers believe that Federal regulations, promulgated by FDA for all prescription drug products, both increase the cost and delay the introduction of new products, and that the latter effect may be more detrimental to people's health than potential adverse reactions to less thoroughly tested drugs (Warden, 1978). FDA contends that current Federal reg-

ulations have not kept any new important therapeutic or biological products off the U.S. market (Kennedy, 1978).

FDA at present has little ability to monitor the use of drugs or collect comprehensive data about adverse reactions to marketed products. Currently, it is attempting to obtain statutory authority to conduct postmarketing surveillance of selected prescription drugs. As discussed further in this chapter beginning on page 107 and in chapter 7, such authority could include surveillance of vaccines.

Federal Government Vaccine Purchasing Policies

The Federal Government is the largest single purchaser of vaccines produced in this country. Federal vaccine purchasing policies, therefore, can affect pharmaceutical manufacturers' profits from vaccine sales. Some pharmaceutical manufacturers cite inadequate profits from vaccine sales as a deterrent to vaccine research, development, and production (Schmeck, 1978). Some companies, though, apparently do earn profits on the vaccines they produce and also reinvest a portion of these profits in vaccine research and development (Schmeck, **1978).**

Government purchasing policies can influence two factors that determine a vaccine manufacturer's profits from a particular vaccine product: 1) size of the market for the product, and 2) the product's selling price. Federal Government purchasing of measles vaccines for its childhood immunization programs, for example, has been a major determinant of the size of the measles vaccine market. In 1965, Congress included measles vaccine in the Community Health Service Extension amendments, which authorized provision of this vaccine through community immunization programs; as a result, in 1966, about 7.9 million doses of measles vaccine were distributed throughout the country (Sencer, 1973). In 1969 and 1970, Congress authorized no funds for community immunization programs, and in those years, the total number of doses of measles vaccine distributed dropped to 4.9 million and 4.5 million, respectively. When funding was resumed in 1971, about 8.1 million doses of measles vaccine were distributed. (See appendix 4.2.)

The Federal Government also dramatically altered the market for swine flu vaccine. In essence, by enacting the swine flu program of 1976, under which almost the entire U.S. adult population was to be immunized, Congress created a huge temporary market for swine flu vaccine. Actual production of this vaccine totaled about 157 million doses; by the time the program was terminated, about 45 million doses had been administered (U.S. Cong., GAO, 1977).

The size of the market for pneumococcal vaccine has not yet been affected by Government purchasing policies, because the Government does not directly purchase this vaccine. On the basis of the examples cited above, however, it is reasonable to expect that should the Federal Government purchase this vaccine for its public immunization programs, it would thereby increase the size of the pneumococcal vaccine market.

In addition to market size, Government purchasing policies can affect the selling price of vaccines. Manufacturers charge vaccine purchasers in the private sector generally higher prices than they charge the Federal Government. (See appendix 4.5.) In general, however, the cost of vaccines to the private sector has remained fairly low. For reasons that are *not* entirely clear, this apparently continues to be the case. In fact, for some vaccines, such **as** measles, the price has actually dropped (Risky, 1978).

Several factors may be contributing to low vaccine prices. First, it may be that American consumers are unwilling to pay higher prices. Often neither the societal value of an item nor the cost of producing it has much bearing on consumer perception of the

item's value. This may be true with regard to vaccines. Second, it might be that vaccine manufacturers are selling their products at low prices to maintain goodwill with the Government and to forestall further Government regulation. Various companies may produce vaccines for Government immunization programs as a public service. In the swine flu program, for example, manufacturers agreed to participate on a nonprofit basis. A third possibility is that low vaccine prices are affected by Government purchasing policies. These policies may allow certain manufacturers to minimize their risks by obtaining secure shares of the vaccine market. Large volume contracts also permit manufacturers to reduce product packaging costs, and eliminate or reduce their advertising costs.

To contain the cost of its immunization programs, the Federal Government purchases vaccines on a low-bid contractual basis. In theory, at least, Government contracts are awarded to those manufacturers best able to cut costs and expand vaccine production volume. In some cases, vaccines purchased by the Federal Government are produced by only one manufacturer. Theoretically, a manufacturer who essentially has a monopoly on the market for a particular vaccine product, such as poliovirus vaccine, is in a good position to negotiate a selling price to the Federal Government that will yield the company a reasonable profit. In general, however, this does not appear to be the case.

In comparison to the price of some similar products, such as influenza vaccine, the manufacturer's selling price for pneumococcal vaccine is relatively high—between $4 and $5 per dose. This price may reflect, in part, the high production costs associated with the manufacture of a product that is actually a combination of 14 different vaccines; it also may reflect an effort by Merck, the manufacturer, to recoup its investment in research and development of this vaccine, or to increase its rate of return on vaccines in general.

Unresolved Vaccine Liability Issues

To get the pharmaceutical industry's cooperation in producing swine flu vaccines for its public immunization program, in 1976, Congress enacted unprecedented legislation mandating Federal Government assumption of swine flu vaccine manufacturers' "duty to warn" liability. Unexpectedly, about **soo** of the approximately **40** million recipients of swine flu vaccine reportedly contracted Guillain-Barre Syndrome (GBS), a rarely reported paralytic syndrome. In the wake of many legal debates, the Department of Health, Education, and Welfare (HEW) is slowly settling some GBS liability claims.

The liability problems encountered with the swine flu program have heightened vaccine manufacturers' concern with vaccine liability issues. Citing liability as a major reason, one manufacturer, Merrell-National, has terminated its vaccine production by selling its vaccine business to another company, Connaught Laboratories, Inc. The effect of unresolved vaccine liability and compensation issues on the willingness of U.S. pharmaceutical companies to engage in vaccine research, development, and production, at the very least, would seem to warrant further investigation.

An analysis of vaccine liability and compensation problems was presented in chapter 5 of this report. General issues are discussed further in this chapter beginning on page 119, and possible options for congressional action are presented in chapter 7.

Federal Government Vaccine Production

No Federal agency produces vaccines for commercial use. So far, the American pharmaceutical industry has been able and willing to supply most vaccines needed by the American public. Some authorities, however, apparently believe that, because of industry's diminishing capacity or commitment to produce or supply certain vaccines, greater

Federal Government involvement in vaccine production may become necessary (Krugman, 1977).

An option for the Federal Government to undertake vaccine production and an option for it to subsidize production by private industry are presented in chapter 7.

VACCINE SAFETY AND EFFICACY

FINDINGS (See chapter 3.)

- The procedures used to evaluate the safety and efficacy of pneumococcal vaccine prior to licensure did not allow investigators to predict the incidence of rare or insidious-onset adverse reactions and included only limited testing of this vaccine in persons at high risk of dying from pneumococcal disease.
- The Food and Drug Administration's (FDA) Bureau of Biologics (BOB) has statutory authority to remove from the U.S. market licensed vaccines that it deems to be unsafe or inefficacious; however, neither BOB nor any other Federal agency currently collects data needed to conduct comprehensive postmarketing evaluations of the safety, efficacy, or conditions of use of licensed vaccines.

ISSUE B:

The value and potential implications of establishing an active, possibly mandatory, postmarketing surveillance (PMS) system to assess the safety, conditions of use, and possibly efficacy, of licensed vaccines

Perceptions of the need for strengthening postmarketing surveillance of adverse reactions to licensed vaccines depend, first, on one's perception of the adequacy of the current premarketing safety requirements, and second, on one's confidence in the Government's ability to develop an effective PMS system.

BOB is publicly responsible for evaluating the safety and efficacy of all vaccine products sold in the United States. Before BOB (technically, FDA) issues a manufacturer a license to market a new vaccine product, it requires the manufacturer to provide clinical documentation of the product's safety and efficacy. In terms of evaluating vaccine safety, premarketing clinical trials and studies probably do allow detection of most types of acute local and systemic adverse reactions. The limitations of basing evaluations of vaccine safety exclusively on data from premarketing clinical trials, however, appear to be these:

1. Premarketing clinical trials involve small numbers of people and short periods of observation, so investigators frequently are unable to detect rare or delayed-onset adverse reactions.
2. Because some preventable diseases have such a low incidence rate in the United States, premarketing clinical trials to evaluate vaccine efficacy and safety may have to be conducted in foreign countries; the data generated by foreign trials, however, may or may not be applicable to the U.S. population.
3. For reasons of bioethics and economics, clinical trials of new vaccines most often are conducted among healthy persons; hence, the safety and efficacy of certain vaccines may not be evaluated in clinical trials involving primarily high risk persons for whom vaccination may be most beneficial.

As demonstrated in the swine flu immunization program, the limitations of premarketing evaluations of the safety of certain vaccines may lead to problems both for vaccinees and for Federal policy makers. In 1976, before the swine flu program was underway, there was a great deal of uncertainty regarding the extent, if any, to which neurological problems would occur as adverse reactions to swine flu vaccine. To avert what was believed by some at the time to be a potential swine flu pandemic, however, Congress approved a large-scale public immunization program. Subsequently, and quite unexpectedly, about 1 of every 100,000 swine flu vaccinees developed the neurological disorder, Guillain-Barre Syndrome (GBS). (See appendix 5.l.) A multitude of GBS-related health and legal problems from the swine flu immunization program consequently arose. Uncertainty regarding the types and expected incidence of rare adverse reactions to swine flu vaccine ultimately proved expensive—in terms of lives and money.

BOB appears to have substantial authority to ensure that a vaccine manufacturer complies with current regulatory standards for product quality. This Bureau also has authority to remove a product from commerce if: 1) a manufacturer fails to comply with standards, or 2) upon BOB's review, a product is found to be unsafe, ineffective, or misbranded. Mechanisms by which BOB (technically, FDA) can take products off the U.S. market include product recalls, injunctions, and seizures, as well as license suspension or revocation procedures. (See appendix 3.3.)

While BOB may have adequate authority to remove unsafe or ineffective products from commerce, however, it may not have adequate authority to collect comprehensive data on which to base its postmarketing evaluations. BOB has proposed regulations that would establish its authority to require vaccine manufacturers to submit to FDA all reports they receive regarding adverse reactions to their vaccine products. Some manufacturers, although they are not required by law or regulation to do so, do submit reports of adverse reactions to BOB voluntarily. Under current regulations, though, manufacturers are required only to maintain 5-year records of reports of adverse reactions and to provide access to these records to BOB inspectors. (See appendix 3.3.) BOB's evaluations of licensed vaccines, therefore, have to be based largely on voluntarily submitted case reports from physicians who administer these vaccines. Isolated case reports submitted to manufacturers, medical journals, or Federal agencies such as the Center for Disease Control (CDC) or FDA cannot be used to determine statistically significant incidence rates of adverse reactions to specific products.

To permit the collection of more comprehensive data regarding the safety of licensed vaccine products, at the end of last year, CDC established a passive vaccine surveillance system to collect—primarily from State and local health departments—voluntarily submitted case reports regarding adverse reactions to vaccines administered under public immunization programs. (See appendix 3.7.) CDC's system is very new, so its effectiveness cannot yet be evaluated.

Because it is both passive (i. e., CDC does not actively solicit reports of vaccine reactions) and voluntary (i.e., State and local health departments are not required to submit reports of adverse reactions), however, CDC's system at best will allow case reporting of rare adverse reactions not detected in premarketing clinical trials. Data collected under CDC's new system will not permit correlation of the number of reported adverse reactions with the total number of vaccine doses administered in a given period of time in a defined population. As currently planned, in other words, CDC's system will not generate the data needed to calculate statistically significant incidence rates of vaccine-induced adverse reactions.

The advisability of developing some type of active and mandatory postmarketing surveillance system to collect and analyze data regarding patients' reactions to drugs that have been released for marketing currently is being studied by the Joint Commission of Prescription Drug Use, as well as by groups within FDA. Furthermore, the proposed Drug Regulation Reform Act of 1979 (S. I075) contains a provision that would permit FDA to conduct postmarketing surveillance of selected products released for general use. Inclusion of this provision was intended, not to reduce premarketing safety evaluation requirements, but to add a postmarketing requirement for testing of new products representing important therapeutic breakthroughs, whose potential toxic capabilities could not be precisely determined in premarketing tests.

The Federal Government spends far more money on vaccine research and development than it does on evaluation of vaccine safety and efficacy. In 1976, the National Institutes of Health (NIH) spent at least $68 million on basic and applied vaccine research, while the Bureau of Biologics (BOB) spent $7. s million to assess the safety and efficacy of experimental and licensed biological products, including vaccines (Jordan, 1977). In these two agencies alone, the Federal Government spent approximately nine times as much money on the search for new vaccines as it did on assessing safety and efficacy of existing vaccines. To complete the comparison between Federal expenditures on vaccine research and development and Federal expenditures on the evaluation of vaccine safety and efficacy, one should include the amount spent for these purposes by other Federal agencies, such as CDC and the Department of Defense (DOD). Relative to annual Federal expenditures for vaccine research and development, purchases, and distribution (and possibly liability claims made under the swine flu immunization program), however, Federal expenditures for the evaluation of vaccine safety and efficacy are even less.

The potential implications of an increased Federal commitment to evaluate more comprehensively the safety and efficacy of the products it helps develop, licenses, and purchases for use in public immunization programs are discussed in chapter 7.

COST-EFFECTIVENESS ANALYSIS OF VACCINATION PROGRAMS

The findings and issues relating to the use of cost-effectiveness analysis (CEA) are categorized into three topics of concern: 1) general applications, 2) specific use in reimbursement decisions, and 3) methodological and data problems. While to some extent, concerns in these areas overlap, each area has particular issues that deserve individualized discussion.

General Applications of CEA

FINDINGS (See chapter 4.)

- OTA's cost-effectiveness analysis of vaccination against pneumococcal pneumonia could be used to assess the relative economic efficiency of vaccinating different age-specific segments of the population.
- OTA's analysis also could be used to identify factors, some of which are subject to control, that substantially influence the cost-effectiveness of vaccination against pneumococcal pneumonia.

ISSUE C:
The degree to which CEA could be useful in allocating Federal funds for vaccination and other health programs

Potential Uses

Most decisions to allocate public funds for vaccine-related programs at present are based on considerations of social values, biomedical research findings, clinical perceptions, political implications, and legalities. The potential utility of CEA in decisions regarding funding of either vaccination or other publicly financed health programs has not been thoroughly investigated. OTA is currently studying the potential uses and limitations of CEA as a tool for evaluating various types of medical technologies. (An OTA report entitled *Assessing the Cost-Effectiveness of Medical Technologies* is due to be released in the summer of 1980.)

Cost-effectiveness analysis has several potential uses. First, CEA provides a systematic framework for comparing the economic efficiency of programs that produce similar, if not the same, results and that compete for limited funds. Thus, it might be used to compare the economic efficiency of a program designed to prevent a specific disease to the efficiency of a treatment program for that disease among specified populations. In OTA's analysis in chapter 4, for example, the efficiency of preventing pneumococcal pneumonia through vaccination was compared to the efficiency of continuing to rely solely on medical treatment of that disease (primarily through the use of antibiotics).

Second, theoretically, CEA could be used to compare the efficiency of medical programs aimed at eliminating different diseases. If standard CEA methodologies were to be developed and adopted, and program effects on health status could be measured in common terms, then comparisons among programs might be possible. In OTA's nalysis, net cost per quality-adjusted life year (QALY) gained through pneumococcal vaccination ranged from $1,000 to $82,100 for individuals aged 25-44. It is conceivable that the cost-effectiveness ratios for a pneumococcal vaccination program might be compared to ratios for other types of health programs. The potential feasibility and implications of making and using comparisons among programs will be discussed in OTA's upcoming report on CEA.

Third, CEA might be used to help identify target populations among which reduction of disease would be the most cost-effective. According to OTA's analysis, for example, if public policymakers wanted to increase the cost-effectiveness of a pneumococcal vaccination program, they might do so by encouraging vaccine use among the elderly. Efforts to encourage such use could include subsidizing the cost of administering the vaccine to elderly individuals within the private sector, or having public health clinics offer the vaccine to the elderly at no charge.

Fourth, CEA might be used to help identify particular factors that influence the efficiency of a preventive or treatment program. Such factors may include variations in the cost of services provided, the efficacy and safety of the technology involved, and the degree of disability produced by the target disease(s). Factors that would influence the cost-effectiveness of a pneumococcal vaccination program, for example, are discussed in chapter 4.

Potential Users

CEA potentially could be used by both Congress and the executive branch in decisions regarding the allocation of Federal funds for vaccine-related programs. The National Institute of Allergy and Infectious Diseases (NIAID), for example, might use this

type of economic analysis to help decide which types of vaccine research programs to fund. NIAID might use CEA to help identify diseases, the prevention of which would provide the largest economic gain. It also might use this type of analysis to select a particular type of research to fund, for example, basic research on an organism versus applied research on a vaccine.

FDA's Bureau of Biologics (BOB) might use CEA to help design formulations of certain types of vaccine products. Currently, for example, there are 83 known types of pneumococci, 14 of which are represented in the recently licensed pneumococcal vaccine. If epidemiologic research demonstrates the existence of geographical variations in the prevalence of the **83** types of pneumococci, then specialized pneumococcal vaccine products could be formulated to match the variations. CEA could be used to help calculate the marginal costs, risks, and benefits of adding or removing selected types of pneumococci from the basic vaccine formula. Cost-effectiveness calculations could be used to help determine the advantages and disadvantages of developing separate vaccines for specific categories of individuals at high risk of contracting pneumococcal pneumonia.

The Center for Disease Control (CDC) possibly could use CEA to help decide how to allocate its funds for public immunization programs. CDC has informally assessed the potential economic benefits derived from immunization programs that have already been implemented (Sencer, 1973), but at the present time, it does not routinely use formal CEA to assess prospectively the potential effects of planned immunization programs.

CEA also could be used by the Health Care Financing Administration (HCFA) to help select vaccines or other types of health technologies into the Medicare and Medicaid benefit packages. As illustrated in OTA's analysis, for example, by paying for pneumococcal vaccine, Medicare would help improve the health status of its beneficiaries at a relatively low cost. (See chapter 4 and discussion of "CEA and Its Relationship to Reimbursement for Vaccinations, " page 112.)

CEA also might prove useful to the Advisory Committee on Immunization Practices (ACIP), a private body of experts that advises CDC on the need for public vaccination programs. In recommending against a mass immunization program for the pneumococcal vaccine, ACIP relied on information on the vaccine's clinical efficacy and safety, the susceptibility of high risk groups to the disease, and degree of mortality caused by pneumococcal pneumonia and bacteremia among high risk groups. In making its recommendation, ACIP did not use cost-effectiveness analysis to determine the vaccine's usefulness for different ages or groups at high risk.

Limitations

Cost-effectiveness analysis is subject to certain limitations. First, it does not necessarily or easily take into account social values, moral judgments, legal implications, or political realities. At most levels of Government decisionmaking, these factors may limit the relevance of formal economic analysis. In the aftermath of the problems encountered with Guillain-Barre Syndrome (GBS) among vaccine recipients under the publicly funded swine flu program, for example, Federal legislators (in the absence of an apparent crisis) might be reluctant to embark on another mass public immunization program for other types of influenza—no matter how cost-effective. Further, if a cutoff is used in decisions about whether to fund programs or use technologies, and if the cutoff point is based on such considerations as how much it may cost to produce each extra quality-adjusted life year (QALY), then society will be using CEA to place an explicit dollar value on human life. Whether this situation would be morally or politically acceptable is not known at this time.

A second, and related, limitation of CEA is its strong focus on economic efficency. Issues of equity and distribution are not easily or commonly addressed by cost-effectiveness analysis. In general, CEA models are not designed to assess shifts in benefits and costs such as income redistribution.

Third, although cost-effectiveness analysis may be helpful in comparing alternative methods of attaining a goal, its use may serve to narrow the range of options considered to those most easy to quantify. For example, the analysis in chapter 4 concerned the changes in medical costs and health effects expected from pneumococcal vaccination. Whether better nutrition or better housing might be a more cost-effective approach to reducing the incidence of pneumococcal pneumonia was not considered.

A fourth limitation of CEA is its investment orientation. One premise of such analysis is that moneys spent on programs today may yield benefits and savings—some now and some in the future. In an era of scarce money and possibly balanced budget, the willingness of society to sacrifice present benefits for possible future ones cannot be predicted. At a minimum, a certain level of confidence in the yield of future benefits from present investments will be needed to permit the use of CEA calculations.

The matter of confidence, however, leads to another limitation of CEA. There are a number of generic difficulties associated with the methodology of cost-effectiveness analysis. Some are minor, others more serious. These methodological problems, along with problems of availability of data, are discussed in the "CEA Methodology and Data" section on page 115.

Finally, another aspect of CEAs that needs to be taken into account are the resources required for their conduct. Just as there is a wide range of CEAs—in terms of complexity, alternatives considered, the amount of original data collection required, etc.—there is an enormous range of time and financial resources required to conduct such analysis. When existing data can be used and the analysts are familiar with the subject areas, a relatively formal CEA can be conducted for perhaps **$5,000** to $10,000. More commonly, however, a much larger effort will be needed. Hundreds of thousands of dollars can be spent, using many person-years of analyst and support personnel time. While this factor is not strictly a limitation of the technique, it could limit its use.

Potential implications of increasing the Federal Government's use of formal CEA in allocating funds for vaccination and other health programs is briefly discussed in chapter 7.

CEA and Its Relationship to Reimbursement for Vaccinations

FINDINGS (See chapter 4.)

- According to OTA's cost-effectiveness analysis, administration of pneumococcal vaccine to roughly 5 million people over the age of 65 might be expected to yield a net gain of about 22,000 quality-adjusted life years (QALYs) at a net societal cost of $23 million over the vaccinees' lifetimes.
- Several factors influence the cost-effectiveness of pneumococcal vaccination. Depending on the different assumptions made regarding these factors in OTA's analysis:
  —Vaccinating 5 million people over the age of 65 could cost society as much as $88 million and in turn yield 84,000 QALYs; or instead, it could save society as much as $18 million and yield about 22,000 QALYs.

—An additional QALY gained by a vaccinee over the age of 65 could cost society as much as $4, 000 or yield a net savings.

ISSUE D:

Whether the Medicare law should be amended to permit reimbursement for preventive vaccinations

The Medicare law specifically excludes preventive vaccinations from its list of reimbursable benefits. This exclusion may be incongruous with other major Federal policies related to vaccines. First, the Federal Government spent $6.5 million to help develop pneumococcal vaccine, and on the basis of clinical evidence, the Food and Drug Administration (FDA) approved the use of this vaccine for the high risk group of those over 65 years old. Thus, the Federal Government cannot pay for pneumococcal or other vaccinations among the elderly, even though at least one Federal agency has stated that the elderly would benefit from pneumococcal vaccination (U.S. Ex. Br., BOB, 1977).

Second, while the Medicare **law** does not permit payment for the prevention of pneumococcal pneumonia through vaccination, it does allow payment for the treatment of pneumococcal pneumonia. According to OTAs cost-effectiveness analysis in chapter 4, use of the new vaccine to help prevent pneumococcal pneumonia is a reasonably inexpensive method of saving a year of life for an elderly vaccinee. Further, this analysis shows that regardless of the size of its financial impact, the use of this vaccine would yield health benefits that cannot be derived from treatment.

The Social Security Act Amendments of 1965, which established Medicare and Medicaid, was modeled after private health insurance plans that specifically excluded payment for most preventive health services. Preventive immunizations, therefore, along with physical examinations, examinations for eyeglasses, and examinations for hearing aids, are not reimbursable under Medicare. (Note: Under Medicaid, vaccination coverage varies from State-to-State. The number of States that pay for this preventive service for adults under Medicaid was not assessed in this study.)

The regulations implementing the Medicare Act expressly forbid payment for vaccinations by Medicare unless a vaccination is used for treatment after injury or direct exposure to a disease. In addition, they specifically exclude payment for influenza vaccines, which, along with pneumococcal vaccine, are the only types of preventive vaccines available for extensive use among the elderly. The regulations read as follows;

> Immunizations.—Vaccinations or inoculations are excluded as "immunizations" unless they are directly related to the treatment of an injury or direct exposure to a disease or condition, such as antirabies treatment, tetanus antitoxin or booster vaccine, botulin antitoxin, antivenin sera, or immune globulin. In the absence of injury or direct exposure, preventive immunization (vaccination or inoculation) against such diseases as smallpox, polio, diphtheria, etc., is not covered. (Flu injections are administered as a preventive measure and are excluded from coverage without regard to a patient's particular susceptibility to influenza.) In cases where a vaccination or inoculation is excluded from coverage, the entire charge should be denied.
>
> (Medicare Carriers Manual, paragraph C, section 2050.5C, 2050 services and supplies, **205.5** drugs and biological.)

Legislation has been introduced in Congress to expand Medicare coverage to include selected preventive services, and some bills include payment for vaccinations, In March 1979, for example, Congressman Claude Pepper (D-Fla.) introduced H.R. 2560, which would provide payment for biologics under Part B of Medicare.

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The impact of reimbursement on the demand for vaccinations by Medicare beneficiaries cannot be projected on the basis of currently available data. Studies to date, however, have shown a general tendency toward increased utilization of preventive health services when the cost of such services is reduced or eliminated. (See appendix 4.1.) The results of these investigations are mixed, though, and no studies relate specifically to the demand for vaccines by older adults. On the one hand, reimbursement could have an important impact on the demand for pneumococcal vaccine. The cost of vaccination in the private sector is about $11. For many Americans 65 years and older, this cost alone might be a possible deterrent to the use of pneumococcal vaccine. On the other hand, if this cost is not a substantial determinant of use, reimbursement through Medicare would likely have little impact on demand.

How, if at all, the Federal Government's legal liability for vaccine-induced injury would be affected if it paid for a vaccine through Medicare rather than through a publicly financed immunization program is also unknown. At present, the Federal Government is not held legally liable for breach of the duty to warn beneficiaries about the inherent risk of other medical goods and services paid for through Medicare. Furthermore, harm produced through provider or manufacturer negligence is the legal responsibility of those parties, not an involved insurance carrier who serves only as a fiscal intermediary or insurance underwriter. Because of the current uncertainty surrounding the Federal Government's legal liability for vaccine-induced injury, however, projections about the impact of reimbursement on the Government's liability cannot be made. (See chapter 5.) Medicare would pay for the treatment of vaccine-related injuries among its beneficiaries.

The safety, efficacy, and cost-effectiveness of both influenza and pneumococcal vaccines may not yet have been comprehensively evaluated. The safety and efficacy of influenza vaccines are debated almost annually. In the case of pneumococcal vaccine, much of the data on which FDA's Bureau of Biologics (BOB) based its prelicensing evaluation was generated from studies in foreign populations, (See chapter 3.) Extrapolating foreign data to U.S. populations may not yield an accurate indication of the vaccine's safety and efficacy among persons residing in this country, particularly the elderly. Possibly, however, an evaluation of the safety and efficacy of pneumococcal vaccine among Medicare beneficiaries can be based on additional data that have been generated since the vaccine has been marketed. Further, this vaccine has not been widely evaluated in other types of Medicare beneficiaries, that is, those with end-stage renal disease or other chronic illnesses. NIAID has helped coordinate such research efforts, and results of some of these investigations should be available in the spring of 1980.

According to OTA's analysis in chapter 4, the cost-effectiveness of vaccinating against pneumococcal pneumonia versus continuing reliance solely on treatment varies substantially depending on the age of the vaccinee and values assigned to selected variables, e.g., duration of immunity. In terms of cost-effectiveness, with the possible exception of end-stage renal dialysis, however, most benefits currently reimbursable under Medicare probably have not been as thoroughly evaluated through statistical analysis as has pneumococcal vaccine in OTA's cost-effectiveness analysis.

Possibly because our Nation's social policymakers have not viewed the elderly as a prime target for preventive services, Medicare currently pays for almost no preventive services for its beneficiaries. According to OTA's analysis, vaccination against pneumococcal disease would benefit the elderly. Kavet has demonstrated that vaccination against influenza also yields benefits for the elderly (Kavet, 1972).

In chapter 7, the potential implications of permitting Medicare to pay for preventive vaccinations are discussed.

CEA Methodology and Data

FINDINGS (See chapter 4.)

- The methodology of CEA as applied to vaccines and other preventive technologies is in a developmental stage.
- Standardized methodologies have not been used in CEAs of preventive technologies.
- Some of the basic data required or desired for OTA's cost-effectiveness analysis of pneumococcal vaccination were lacking or difficult to secure.

ISSUE E:

Whether the Federal Government should seek to overcome methodological problems of CEA and problems related to the availability of data for CEAs

Methodology

The methodology of CEA has certain generic difficulties. The problems discussed below relate to variations in models, measures of effectiveness, treatment of time, external i ties, and equity as well as distribution.

One problem is that the models used to relate costs to outcomes vary from one study to another. Two basic types of analyses that relate costs to outcomes can be used: cost-effectiveness analysis (CEA) and benefit-cost analysis (BCA). Both have been applied to vaccines (Schoenbaum, 1976; Sencer, 1973; Weisbrod, 1961). In BCA, effects of one program across the economy are considered, while in CEA, two alternatives to achieve a given goal are compared. In BCA, costs and effects (benefits) are valued in the same—invariably monetary—units. In CEA, however, while costs are valued in monetary terms, effects (e. g., improvement in health) are not necessarily quantified in dollar terms. BCA methodology facilitates comparisons across various sectors of resource allocation, but in health care, the gain in flexibility may be more than countered by methodological difficulties and offended sensibilities.

Consistency of models is a problem even when only CEAS are considered. In the CEA models applied to medical technologies to date, there have been many variations. For example, the Klarman and Guzick study of influenza valued health effects from influenza but not death (Klarman, 1976). Further, the value assigned to morbidity averted by vaccination was based on the expected gain in productivity from increased working time. Weinstein and Stason included in their model the costs of illness in the extended years of life that would result from receiving treatment for hypertension (Weinstein, 1976), but did not include the morbidity from such illnesses. The selection of costs and effects and the assignment of values to them are decisions made by each analyst based on the model he or she follows. A lack of consistency in cost-effectiveness models used for CEAs means that the results are less likely to be comparable across studies and that evaluating the usefulness of each analysis is a complex and difficult task.

Another methodological problem centers on the measurement of effects. There is no widely agreed upon health status index that can be used to value the health effects of medical technologies. Health is a complex, multidimensional concept. Measures of health can range from mortality rates to morbidity rates, to estimates of functioning capacity, and even to "feelings of well -being." To conduct a CEA of a preventive technology that

affects both death and illness, a health status index that incorporates both these effects is needed. In OTA's analysis, the index used was one developed to mitigate this methodological difficulty through the use of a multidimensional measure of health called quality-adjusted life years (QALYs), (See appendix 4.4). Further, the values for QALYs in OTA's analysis were based on previous surveys of weights to be assigned to various levels of morbidity or reduced functioning. Although use of such surveys may represent an advance over the usual practice of the analysts' using their own weighings (based on their own preferences in regard to disability, etc.), much broader surveys are needed to assess how various populations value levels of health.

Improved health status indexes will have to incorporate the degree to which various aspects of psychological, social, and physical functioning affect well-being. This will be necessary in order to assign weights to morbidity days. Does prolonging the life of a chronically ill patient result in a net gain or loss in well being? Under what circumstances? Research on health status indexes is currently taking place at the National Center for Health Services Research (NCHSR) and the National Center for Health Statistics (NCHS) (Wan, 1978).

A third methodological problem is uncertainty and inconsistency in ways of dealing with time. As mentioned in the pneumococcal vaccination case study, future costs and benefits are usually valued less highly than those occurring in the present, and therefore are discounted. Discounting of costs is generally recognized as a necessary principle. The question of what discount rate to apply, however, is unsettled. (See appendix 4.4). The Office of Management and Budget (OMB) believes that the rate should be 10 percent for Government projects, but the appropriateness of this value is a matter of judgment, not interpretation of data. Even more serious are the inconsistencies among studies. Further questions concerning discounting are whether it is appropriate to discount health effects, and if so, at what rate. For costs, financial discounting rates can be used as proxies, but where can we find proxies for the rate to be applied to health?

Additional methodological difficulties in CEA are whether and how to incorporate externalities. Should a CEA include, for example, any of the effects on people other than the patient, if the patient's death results in other people's becoming orphans or widows? How can these effects be identified and measured? The methodology of CEA has not progressed to the point where these questions can be answered consistently. There are many other examples of externalities whose inclusion in or exclusion from CEAs is not a settled matter. Should effects on other sectors of the economy be included? To what extent? A successful pneumococca] vaccination program, for example, might affect the productivity of workers by improving their health and possibly might affect the demand for other social services and housing for the elderly by prolonging vaccinees' lives. Other externalities might relate to other effects on the health care system. A successful pneumococcal vaccination program might result in a need for more chronic care facilities relative to these for acute care. Should those potential effects be taken into account by a CEA?

Another methodological problem of CEA is the difficulty of taking into account questions of distributional equity. Like other types of economic analysis, CEA primarily evaluates the efficiency of resource allocations. Aggregate measures of cost and benefits may neglect or disguise variations that are important for specific subgroups of the population. Even though aggregate cost-effectiveness measures might show that a program would result in an improvement in societal economic welfare, program beneficiaries and payers might not be the same. If Medicaid were to pay for vaccinations for nonworking, low income individuals, for example, then these individuals would derive the benefits of

vaccination, but the program would be financed by employed taxpayers who would not benefit directly from the program. Again, issues of distribution and equity largely involve differences in judgments and personal values rather than differences in empirical findings.

The above discussion does not exhaust the list of methodological shortcomings, but rather covers the major difficulties that are common to CEAS as a class of studies. These methodological problems should be viewed in perspective: Although some of the basic concepts of CEA and BCA are several years old (see appendix 4.3), the many current aspects of its methodology have been developed a great deal in a fairly short time. It was not until 1974, for example, that a serious call was made for testing the sensitivity of CEA results to changes in certain variables (Roberts, 1974). Quality-adjusted life years (QALYs) area recent development and are in need of much refinement. Also, CEA methodology still does not routinely include efficacy rates and side effects of technologies. These and other examples may not represent problems inherent to CEA methodology but perhaps are symptoms of a technique still in the process of maturing.

Data

A major difficulty in applying cost-effectiveness analysis to a medical technology is the lack of appropriate data. The pervasiveness of data problems was illustrated in OTA's study of pneumococcal vaccine. Pneumonia is the leading infectious cause of death and the fifth overall cause of death in the United States (U.S. Ex. Br., Census,]977). pneumonia is a *major* cause of hospitalization and restricted activity, and as a cause of death is exceeded only by heart disease, cancer, stroke, and accidents. Because of its importance, one would expect data on pneumonia to be more detailed than for most illnesses.

Klarman stressed that CEA required a clear link between cause and effect (Klarman, 1967). Many of the data needs in OTA's study pertained to that link. For example, the incidence rate of pneumococcal pneumonia is not known. Does it account for 10 or 35 percent of all pneumonia? The morbidity and mortality from pneumococcal pneumonia is equally difficult to assess. Without answers to epidemiologic questions, determining the pattern of the disease and the effect of the vaccine is difficult.

For data other than clinical data used in its analysis, OTA relied mostly on the National Center for Health Statistics (NCHS) in HEW. NCHS data have major limitations, which characterize data from other statistical sources, as well. One major 1imitation is the lack of population-based data. Health data in general are oriented to describing specific medical diseases or conditions, but cannot be aggregated to describe the population. The Health Interview Survey (HIS), for example, has collected data on certain chronic conditions, but not on the number of different people involved. Since a person may have more than one chronic condition, merely summing the number of different chronic conditions would produce a gross overestimation of the number of people afflicted. Such data problems hindered OTA's calculation of the cost-effectiveness of pneumococcal vaccination for people with certain chronic conditions who are considered at high risk of contracting or dying from pneumonia.

Although existing data are disease-centered, they do not convey a total sense of a specific disease. For example, of all 1976 hospital discharges with pneumonia listed as a diagnosis, 66 percent had pneumonia listed first, and 34 percent had it listed subsequently (U.S. Ex. Br., NCHS, HDS). Restricting consideration of pneumonia to first-listed diagnoses would understate the extent of the disease. Too little is known, however, about

how pneumonia interacts with other medical conditions to make a precise statement about the (at least) 34 percent of cases in which pneumonia occurred with another condition.

The failure to specify the full effect of a disease is even more serious with mortality data. Deaths are attributed to a certain cause in NCHS data only if it is considered the underlying cause of death, i.e., the cause that initiated the sequence resulting in death. Thus, for a terminal cancer patient with pneumonia who died, cancer would be reported as the cause of death. For an otherwise healthy person who contracted pneumonia and died, pneumonia would be listed as the cause of death. Limiting consideration of pneumonia as a cause of death to cases in which pneumonia was the underlying cause would understate pneumonia's role in causing death. Including all cases in which pneumonia was listed anywhere on the death certificate (pneumonia mentions) however, would overstate its role.

Because the mortality data reported by NCHS do not reflect certain subtleties, they minimize pneumonia's role in causing death. The problem, which also applies to other health data, is that the effect that one medical condition has on another is not taken into account. Identifying interactive effects and formulating a methodology to incorporate multiple causes into mortality data are at an early stage of development. The availability of mortality data concerning multiple causes is intertwined with methodological difficulties. NCHS is developing multiple cause data at the present time.

In addition to being hindered by the lack of population-based data and methodological problems, the use of data is handicapped by incompatible definitions and categories. NCHS collects data covering a wide range of health matters, but inconsistencies among the data sets inhibit merging these sets to describe the health and resource utilization of the population. The population base for death certificates, for example, differs from that for the Health Interview Survey (HIS). Mortality statistics are based on death certificates of the entire U.S. population, including the military and institutionalized populations; HIS though, surveys only the civilian, noninstitutionalized population.

Much the same problems that characterize incidence and utilization data also pertain to expenditure and price data. The Health Care Financing Administration (HCFA) in HEW publishes an annual series of health expenditures. Data on the prices of particular services and expenditures for certain diseases, however, are less readily available. Rice and her colleagues have complied expenditures by broad diagnostic groupings, such as infective and parasitic diseases, diseases of the respiratory system, and accidents, poisonings, and violence (Cooper, 1976; Rice, 1976). Medicare carriers and intermediaries, including many Blue Cross and Blue Shield plans, collect data on the prices of particular services in order to calculate customary and reasonable charges, the basis of their payment to physicians. Neither Medicare nor any other third-party payer, however, routinely constructs national estimates from these regional data. Periodic surveys of physician prices such as that by Schieber, et al., are another data source, but an irregular one (Schieber, 1976). The dearth of national cost **data is** illustrated by the widespread use of data complied by Scitovsky and McCall from the records of one practice in California (Scitovsky, 1977). Although the drawbacks of generalizing from such limited experience are well known, in the absence of acceptable alternatives, data from this practice are used for prices, utilization, and disease expenditures.

More than a litany of deficiencies, these data problems have implications for the feasibility of performing cost-effectiveness analyses as an ongoing activity. If cost-effectiveness analyses of technologies were performed with any regularity, special tabulations, such as were required for OTA's analysis, would tax the resources of NCHS. Since the

time required to conduct an analysis and the rigor of the results depend so heavily on the data available, exploration and resolution of key data problems are prerequisites for any routine Government program of cost-effectiveness analysis.

LEGAL LIABILITY AND COMPENSATION FOR VACCINE-RELATED INJURIES

FINDINGS (See chapter 5.)

- Ž At present, persons injured as a result of being vaccinated in a publicly financed immunization program must seek compensation through the legal liability system.
- In spite of contractual transfers of the "duty to warn" from vaccine manufacturers to the Federal Government, the legal assignment of this responsibility will be determined by future court cases and cannot be predicted at this time.

ISSUE F:

The extent, if any, to which the Federal Government should assume legal responsibility for compensating vaccinees injured in public immunization programs

Developing Federal mechanisms to compensate injured vaccinees can be based on two rationales: 1) social responsibility for those harmed by preventive medicine practices that often have public health goals in addition to benefits conferred on individuals, and 2) the consequences of liability insurance problems on vaccination policy per se.

The Federal Government is an active promoter of vaccination programs, and the overwhelming majority of States and U.S. territorial jurisdictions have mandatory childhood vaccination laws. Vaccination programs often have dual purposes: 1) to protect the general or specifically targeted segments of the population against particular infectious diseases, and 2) to protect the individual. If a high percentage of the target population is vaccinated, many unvaccinated individuals may gain protection from a disease through herd immunity. From the standpoint of society as a whole, as well as from the standpoint of most vaccinated individuals, the morbidity and mortality that vaccination helps prevent greatly exceed the morbidity and mortality that vaccination causes. For the statistically small number of individuals who experience rare severe adverse reactions, including permanent disability or death, however, this is not the case.

The kind of vaccine liability that has led to major concerns has not been liability for injuries that result from faulty behavior such **as** negligence in the manufacture or administration of a vaccine, but liability for injuries that are associated with inherent, and more or less predictable, vaccine risks. In classical negligence law, the element of fault is pronounced, and negligent behavior can be corrected to diminish the problem or injury in which it results. The problem of injury resulting from nondefective and properly administered vaccines, however, is essentially unavoidable. All vaccines have certain inherent risks, and because of this, will produce severe injury to a very small percentage of vaccinated individuals no matter what precautions are taken.

In their quest for an equitable solution, the courts have shown an increased tendency to find some doctrinal basis for compensating the injured. While the courts are turning toward the insurance concept of spreading the risk, though, they must continue to work within the legal framework of an adversary, faultfinding process. As the courts adopt a

more explicit insurance rationale for their decisions on where liability should rest, the adequacy and appropriateness of a judicial approach to compensation for vaccine-induced injury comes into question.

The duty to warn raises ethical issues in public immunization programs. The basic issue is the moral obligation of the Federal Government to compensate vaccinees for injury sustained under circumstances over which they were unable to exercise any control. Especially for mandatory vaccination programs, the duty to warn is not a legal doctrine designed to avoid injury; it is a doctrine designed to avoid or assign liability for injury. Warnings are supposed to provide potential vaccinees (or their parents or guardians) with information on the risks and benefits, so that the person informed can decide whether to be vaccinated or not. Children who are not vaccinated may be prohibited from entering school. When vaccination is mandatory, potential vaccinees have no options.

Concern over liability insurance has affected and may again affect vaccination programs. In the recent swine flu immunization program, manufacturers were denied liability insurance by the insurance industry until Congress enacted legislation (Public Law 94-380) providing that all tort suits had to be brought against the Federal Government through a modification of the Federal Tort Claims Act. The Government retained the right of subrogation only against manufacturers and program participants who were negligent.

The possible implications of another insurance availability crisis include the following:

Vaccine Manufacturers.—The production of vaccines is a private enterprise. Although the cost of liability insurance is a business expense that can be passed on to the purchasers of vaccines, evolving judicial theories of liability for vaccine-related injuries cause uncertainties in pricing liability insurance. The high cost, or even possible unavailability, of such insurance could cause vaccine manufacturers to withdraw or reduce their commitment to produce and supply vaccines.

Government.—The primary use of vaccines is to promote public health. The Federal Government has assumed major responsibility for ensuring the safety and efficacy of vaccines and for promoting their use through public immunization programs. Furthermore, the great majority of States and territorial jurisdictions have passed legislation requiring certain vaccinations prior to school entry. As of September 1976, 47 out of 54 jurisdictions (the 50 States plus the District of Columbia, Guam, Puerto Rico, and the Virgin Islands) required vaccinations before entry to school, 42 being mandatory, 5 permissive. At present, vaccine liability insurance is provided largely by private enterprise, and insurance regulation is a function of the States. With another vaccine liability insurance crisis, which might lead vaccine manufacturers to refuse to supply vaccines for public immunization programs, the Federal Government might have to produce vaccines itself and also could end up as insurer or insurance regulator.

Health Care Providers.—The threat of liability may reduce the private, voluntary promotion of, and participation in, vaccination programs by physicians and other health care providers. The crucial liability issue in vaccination programs is not traditional negligence, but the duty to warn of potential side effects, The legal theory of informed consent has been particularly disturbing to providers because of the difficulty in knowing prospectively (before an injury occurs) when that duty as been discharged or not.

The Public. —The individual's right to know of the risks and benefits accompanying a particular vaccine is of little substance if the right to refuse the vaccine is not available.

Mandatory vaccination laws work against this right, but voluntary programs will suffer if the information provided has the effect of raising fears of vaccine side effects. Insurance availability difficulties raise public fears that something is wrong with the vaccine under question or draw excessive attention to rare, though serious, side effects. The occasional large awards from litigation or even providing more certain compensation through the development of alternative approaches to litigation will not mitigate the negative impact of the liability problem on public participation in vaccination programs.

Liability for the rare, severe, and unavoidable adverse health effects of vaccines has had an effect on vaccination programs way out of proportion to the magnitude of the risk. Furthermore, in addition to the negative impacts on vaccination programs of liability problems discussed above, the cost of liability insurance is becoming a matter of greater concern to those who ultimately must pay for those costs—Federal, State, and local governments, and vaccinees. By raising overall program costs, higher liability insurance costs may limit the size and scope of certain types of public immunization programs. Higher liability insurance costs do not necessarily lead to increased amounts of compensation or to the provision of compensation to a larger number of injured vaccinees; nor do they lead to more timely compensation, since the dispensation mechanism is the legal system.

Two policy options for mitigating vaccine liability problems and for improving injured vaccinees' access to compensation are presented in chapter 7.

7.

POLICY OPTIONS

7.

POLICY OPTIONS

VACCINE RESEARCH, DEVELOPMENT, AND PRODUCTION

The Federal Government to date has not investigated the causes or potential implications of the recent decline in the number of pharmaceutical manufacturers producing vaccines in this country. Nor has it fully evaluated the effects on private sector vaccine research, development, and production of Federal policies established by at least three different agencies within the Department of Health, Education, and Welfare (HEW): the National Institute of Allergy and Infectious Diseases (NIAID), the Bureau of Biologics (BOB), and the Center for Disease Control (CDC). (See chapters 2 and 6.)

Unless Congress acts, the Federal Government is not likely to conduct comprehensive investigations in either of these areas. Three potential implications of maintaining the status quo include these:

1. The commitment of the pharmaceutical industry to vaccine development and supply will remain tenuous and unpredictable.
2. HEW agencies with vaccine-related responsibilities will continue to work together informally and establish policies in accordance with their own jurisdictional interests:
   —NIAID will continue to finance vaccine research and development in accordance with its own priorities and limited funds.
   —BOB will continue to establish new criteria and interpret existing standards for vaccine safety and efficacy, emphasizing the premarketing evaluation of biological products.
   —CDC will continue to survey the incidence and prevalence of certain infectious diseases, coordinate the use of Federal funds to establish or maintain public immunization programs, and collect voluntarily submitted reports of adverse reactions to vaccines.
3. Congress will continue to receive single agencies' perspectives on vaccine-related issues. It will not develop an ongoing capability to survey both comprehensively and prospectively vaccine research, development, and production activity in either the private or the public sector. For the most part, congressional activities related to vaccine research and development will remain oriented toward specific issues or crisis situations.

If Congress believes that the impact of Federal vaccine policies on the commitment of the pharmaceutical industry to develop and supply vaccines needs to be assessed, or if it believes that the recent decline in number of vaccine manufacturers may portend a decline in the capacity of the pharmaceutical industry to develop and produce needed vaccines, then it might adopt one or more of the three options presented below.

OPTION A-1:

Establish a permanent interagency body within HEW to:

- **Develop priorities for facilitating and coordinating vaccine research, development, and evaluation in the public sector;**
- **Monitor vaccine research, development, and production in the private sector; and**
- **Report to Congress periodically.**

Federal agencies represented in this body could include HEW agencies with vaccine-related responsibilities, such as CDC, NIAID, and BOB, as well as other Government agencies (e. g., the Department of Defense) that influence vaccine research, development, and evaluation. In addition, vaccine research communities from the pharmaceutical industry and academe, as well as consumers, could be represented. This body could report either to the Secretary of HEW or to the Assistant Secretary for Health.

All Federal and private agencies represented in this body could contribute data that could be used to accomplish the following tasks:

1. Develop national priorities for basic, epidemiologic, and applied research that relates to vaccines.
2. Assess the level of public and private resource commitment to the identified priority areas of national vaccine research and development.
3. Recommend Federal funding levels and topics for vaccine research and development.
4. Monitor the capacity and willingness of the U.S. pharmaceutical industry to produce and supply vaccines.
5. Assess the capacity of the Federal Government to produce vaccines, should the need for Government production ever arise.
6. Assess the impact of all Federal laws, regulations, and policies that may affect manufacturers' commitment to vaccine research and development.
7. Report results from its continuing investigations and analyses to Congress in written documents, as well as congressional testimony, on a regular basis.

Specific questions that could be addressed by this body are identified in figure 11.

Figure 11.—Questions That a Government Interagency Body on Vaccine and Immunization Issues Could Consider

Federal Financing of Vaccine Research and Development

1. What criteria do Federal agencies such as NIAID that support vaccine research and development use to allocate research dollars? How do these agencies plan to use their resources in the future?
2. To what extent does the availability of Federal funds for vaccine research and development influence a pharmaceutical company's decision to develop a vaccine product?
   - Has NIAID or any other Federal agency influenced the willingness of a company to pursue the development of a vaccine other than pneumococcal vaccine?
   - Has Federal financing for vaccine research ever deterred a company from developing a vaccine?
3. Should public funds be given to private companies to support research that leads directly to the development of a marketable product on which a company can make a profit?
4. To what extent and in what ways can Government and private industry share the financial responsibility for researching, developing and selling new vaccines?
   - What percentage of vaccine research and development is financed by the Federal Government?

Figure 1 l.-(Questions That a Government Interagency Body on Vaccine and Immunization Issues Could Consider-cont.

- What types of vaccine research do pharmaceutical companies conduct without Federal funds, and for what types do they rely on the Federal Government?

Federal Vaccine Safety and Efficacy Requirements

1. Has any manufacturer curtailed the development, clinical testing, or production of a vaccine because of the costs related to complying with procedures and standards established by BOB? If so, did any other manufacturer overcome these obstacles and market the product involved?
2. Can the need for, and effectiveness of, BOB's procedures and standards be demonstrated?
   - How does the reported incidence of faulty Vadcine products or vaccine-induced harm compare before and after BOB intensified its activities in 1972, or before and after BOB's predecessor, the, Division of Biologics Standards, wasestablished in 1955?
   - How does the record of safety and efficacy of vaccines marketed in the United States compare to the record of vaccines sold in other countries?
3. If current Federal vaccine safety regulations and policies are found necessary to protect vaccine recipients, but are also found to be impediments to vaccine innovation and production in the private sector, what types of activities could the Federal Government undertake to help overcome these impediments and yet help protect the public?

Federal Vaccine Purchasing Policies

1. To what extent do Government vaccine purchasing policies affect the market size for, and pharmaceutical companies' profits from, vaccines, thereby possibly influencing these companies' commitment to vaccine research, development and production?
2. What effect do the low-bid prices of vaccines sold to the Government have on the prices of vaccines sold in the private sector?

Federal Liability for Vaccine-Induced Injuries

1. To what extent, if any, are unresolvedvaccine liability issues affecting American pharmaceutical companies' overall commitment to vaccine research, development, and production activities?
2. If the courts continue to broaden vaccine manufacturers' liability for unavoidable injuries caused by their products, what impact will this liability have on the willingness of manufacturers to develop and supply vaccines needed by the Ameriean public?
   - Will pharmaceutical companies continue to develop and supply vaccines to be used in public immunization programs?
   - Will they continue to develop and supply vaccinesto be used inthe private sector?
   - To what extent will this unpredictable liability lead vaccine manufacturers to increase the prices of vaccines sold to the Federal Government, to the private sector, or both.
3. What types of actions might the Federal Government take to help cvercome vaccine liablity problems?
   - To what extent, if any, should it assume liability for vaccine-related injuries produced in public immunization programs?
   - To what extent, if any, should it develop approaches for compensathing victims of vaccine= related injuries?
   - Could it develop mechanisms to allow more comprehensive evaluations of the inherent risks associated with particular vaccines to be used in mass immunization programs?

Federal Government Vaccine Production.

1. Has the pharmaceutical industry ever refused to produce a vaccine that was technically possible to produce and proven to provide safe and effective protection against a known health hazard? If so, what factors led to its refusal?

subsidize—or initiate
vaccines by the pharmaceutical

3. Does the Federal Government already have the resources necessary to produce vaccines, or would Government production require additional investment in capital and human resources? if the latter, what would the costs be? How would these costs compare to those in private industry?

If given only an advisory status, an interagency body would primarily provide a forum for discussion. An advisory body would not likely be a threat to existing powers within HEW nor a threat to the pharmaceutical industry; however, it would have limited ability to make changes in the existing system of vaccine research and development.

An interagency body could be assigned authoritative functions. It could be assigned, for example, responsibility for establishing the priorities and coordinating Federal financing for vaccine research and development. Given authoritative functions, such a body would be better able to change Federal vaccine R&D resource allocations, if deemed appropriate. It also would be more likely to gain the respect of vaccine researchers in the public and private sectors. Centralization of this type of authority might lead to more efficient uses of vaccine research resources; however, centralized authority might create an additional layer of bureaucracy between vaccine researchers and Federal research financing agencies, leading to possible delays in some research efforts.

Implementation of this option would add a formal mechanism for interagency collaboration on vaccine-related issues and situations. Establishment of an interagency body with the tasks listed above could add a prospective or foresight emphasis to the actions of participating agencies. The proposed mechanism also might help to increase the awareness of individual agencies with vaccine-related responsibilities about the potential implications of their actions on the operation and policies of other agencies.

Creation of a vaccine interagency program would give consumers and vaccine manufacturers a forum of Federal regulators and administrators to which they could present their problems and perspectives. In addition, Government regulators could explain more fully to manufacturers and consumers the reasons for their actions.

OPTION A-2:

Establish either a small- or large-scale Federal vaccine production program.

The Federal Government does not produce vaccines for commercial or public use, Supporters of Government-sponsored vaccine production, many of whom work in academe or Government, have suggested that the pharmaceutical industry might fail to market certain vaccines that are safe, effective, and technically possible to produce—but unprofitable (Krugman, 1977). Opponents of Government vaccine production, many of whom work in the pharmaceutical industry, argue that Government production would reduce the incentives for production by private industry (Stessel, 1978).

SMALL-SCALE GOVERNMENT PRODUCTION PROGRAM

A Federal vaccine production program could be designed to produce only products that are not commercially available, i.e., “orphan” and experimental vaccines. In this case, Federal vaccine production would be restricted to only a few products that are designed for limited use among specialized populations or those products used in vaccine research programs..

A recent example of an orphan vaccine is Rocky Mountain Spotted Fever (RMSF) vaccine (Rocky, 1978). A new RMSF vaccine that appears to be more effective than the old one recently was developed by the U.S. Army. The National Institutes of Health

(NIH) is planning to conduct clinical trials of this vaccine, and at least one pharmaceutical company is currently evaluating its market potential. No manufacturer to date, however, has decided to sponsor clinical trials or to apply for product licensure.

A small Government program would help ensure the availability of orphan special-purpose vaccines, such as RMSF vaccine. Because a small program would likely leave intact industry's production of commonly used vaccines, it probably would not substantially affect industry profits from large-scale vaccine production programs.

The costs transferred to U.S. taxpayers for a small vaccine production program have not been estimated in this report, but would be much less than expenses associated with a large-scale program. The costs of settling lawsuits resulting from increased Government liability for injury caused by Government-produced vaccines are unknown. By charging for its vaccine products, the Government could recoup at least some of its expenses.

LARGE-SCALE GOVERNMENT PRODUCTION PROGRAM

Alternatively, a Federal Government production program could be designed to encompass, for example, the manufacture of all vaccines used in federally sponsored immunization programs. Examples of such vaccines include measles, mumps, rubella, polio, diphtheria, tetanus, pertussis, and influenza vaccines.

By establishing a large vaccine production program, the Federal Government would substantially control the availability of most vaccines in this country. It therefore would probably be able to ensure the production of commonly used vaccines, such as poliovirus vaccine, that currently have only one commercial manufacturer.

A large Government production program, however, might erode manufacturers' profits from vaccines. This erosion of profits could reduce even further the industry's diminishing commitment to vaccines, and might lead to a situation in which the Federal Government would be the sole producer of commonly used vaccines.

The costs associated with a large Government-operated vaccine production program have not been estimated in this report.

OPTION A-3:

Subsidize vaccine production by private industry.

Instead of establishing its own production program to ensure the availability of vaccines, the Federal Government could subsidize vaccine manufacturers of produce selected products. Payment could be provided either in the form of direct contracts for production or as a condition of purchase of vaccines by the Federal Government. In the case of pneumococcal vaccine, the direct contract method was used by NIAID when it contracted with Eli Lilly and Company to produce experimental pneumococcal vaccines. (See chapter 2.)

To date, the Federal Government has not required any manufacturer to produce one vaccine as a condition for its purchase of another vaccine. Conceivably, however, the Federal Government could require this. For example, a situation could arise in which two companies were bidding for a large contract to supply the Federal Government with a vaccine, such as measles vaccine, to be used in public immunization programs. If the Federal Government wanted to ensure the production of a relatively unprofitable special-use product, such as RMSF vaccine, it could award the measles contract to the company that guaranteed, for a price, that it would produce a specified amount of the special-use product.

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VACCINE SAFETY AND EFFICACY

The Center for Disease Control's (CDC) system for monitoring adverse reactions to licensed vaccines (see appendix 3.7) may permit detection of certain types of rare adverse reactions not detected in premarketing clinical trials. (See chapters 3 and 6.) As currently planned, however, the system will not generate data that will permit calculation of incidence rates of adverse reactions among defined populations.

If Congress believes that the collection of data more comprehensive than those collected under CDC's system is unnecessary, then it could take no action and await more complete assessment of the effectiveness of this system. If Congress believes that the establishment of an active or mandatory postmarketing surveillance (PMS) system is desirable, however, it could authorize one or more agencies of the Department of Health, Education, and Welfare (HEW) to conduct active surveillance of licensed vaccines.

Potential participants in an active PMS system are vaccinees, health professionals, the Government, industry, and academe. A successful system would be one with positive incentives for these five potential participants collectively to provide, collect, and analyze data in a way that would permit comprehensive evaluations of the safety and efficacy of vaccines in general use.

The ultimate source of financing for PMS would be consumers; the two indirect sources would be vaccine manufacturers and the Federal Government. The distribution of the direct operating costs of a PMS system probably would influence the distribution of authority to operate the system. If the bulk or all of these costs were borne by the Federal Government, then the Government probably would have greater authority and control over the operation of the system than it would if these costs were incurred by vaccine manufacturers.

PMS costs could be distributed on the basis of the perceived distribution of benefits. If, for example, PMS is perceived to benefit all members of society (e.g., PMS could lead to the development of safer vaccines that produce herd immunity), then perhaps the cost of PMS should be borne by society at large. The use of Government funds would distribute the costs of PMS among all members of society who pay Federal income taxes. If, however, PMS is perceived to benefit only vaccine recipients, then perhaps the costs of PMS should be borne only by them. If this judgment were made, then PMS costs could be borne directly by vaccine manufacturers, who in turn would pass their costs on to vaccine purchasers in the form of higher prices. In the private sector, vaccine purchasers are, for the most part, vaccine recipients. In the public sector, however, the major vaccine purchaser is the Federal Government.

The two options presented below are not mutually exclusive. Congress could require HEW to implement a PMS system in the private sector which would rely on the mandatory cooperation of vaccine manufacturers and the voluntary cooperation of health professionals in private practice. In addition, or alternatively, Congress could establish a mandatory PMS system to collect and analyze data regarding adverse reactions to vaccines administered in the public sector.

OPTION B-1:

Authorize FDA to require vaccine manufacturers to conduct postmarketing surveillance (PMS) of adverse reactions to specific vaccines and intensify Federal efforts to encourage voluntary reporting of such reactions by private sector physicians and clinics.

The Food and Drug Administration's (FDA) Bureau of Drugs (BOD) uses at least three mechanisms to evaluate the safety of marketed prescription drugs. First, for selected new drugs, i t can require pharmaceutical manufacturers to conduct PMS as a condition of approval for marketing. This mechanism is usually reserved for use in situa - tions in which the efficacy of, and public need for, a new drug has been satisfactorily established, but the safety of the drug was not satisfactorily evaluated in premarketing clinical investigations. Second, FDA operates an adverse drug reaction reporting program, in which it receives, tabulates, analyzes, and makes publicly available data from adverse reaction reports voluntarily y submitted by practicing health professionals (Welsh, 1979). Third, FDA requires pharmaceutical manufacturers to submit at least annually to FDA reports they receive from health professionals concerning adverse reactions to their prescription drug products. (See appendix 3.2.)

FDA is seeking congressional approval for more substantial and expanded authority for its PMS activities. The agency is seeking stronger statutory authority on which to base its PMS regulations. It is also seeking authority to require that PMS be conducted for any approved prescription drug that, according to FDA's evaluation, represents a potential hazard to the public's health. Congressional passage of the Drug Regulation Reform Act of 1979 (S. 1045) would give FDA the postrnarketing authority that it wants.

Of the three types of FDA mechanisms cited above; only one, i e., the voluntary adverse reaction reporting system, is used by FDA's Bureau of Biologics (BOB) to evaluate the safety of marketed vaccines. (See chapter 3.) BOB also relies on CDC's voluntary adverse reaction reporting system for data regarding the safety of marketed vaccines.

BOB does have regulatory authority to evaluate licensed vaccines and remove unsafe or ineffective ones from the market. (See appendix 3.1.) This Bureau may lack the authority, however, to mandate the collection of data it needs to comprehensively evaluate the safety of 1icensed vaccines. BOB is attempting to establish its regulatory authority to require vaccine manufacturers to submit to BOB records of reports of adverse reactions to their products; at present, it has no such authority. Further, BOB has not required a vaccine manufacturer to conduct PMS of a new vaccine as a condition of licensure. (Its regulatory authority to do so is not evaluated in this report.)

By including vaccines and other biological products in the postmarketing sections of the HEW-proposed Drug Regulation Reform Act of 1979 (S. 1045), or similar legislation such as that introduced by Senator Edward M. Kennedy (S. 1075), Congress would likely ensure that BOB would have more substantial authority to evaluate the safety of marketed vaccines **than** it has at present. This legislation would give BOB the same statutory authority that it would provide for BOD.

If Congress does not include vaccines in the proposed legislation cited above, then, for its assessment of the safety of marketed vaccines, BOB will have to: 1) remain dependent on the reports of adverse reactions voluntarily submitted by health professionals

and vaccine manufacturers; 2) attempt to promulgate more postmarketing regulations using its existing statutory authority; or 3) seek congressional approval for expanded postmarketing authorities under separate legislation.

The costs of PMS to vaccine manufacturers have not been estimated in this report. Some pharmaceutical manufacturers have claimed to have spent between $500,000 and $1 million on PMS activities for a prescription drug (Kennedy, 1979). Most manufacturers' PMS-related expenses probably would be passed on to vaccine purchasers in the form of higher product prices. In the private sector, the costs of PMS would likely be incurred by vaccine recipients. Any PMS costs incurred by manufacturers for products used in the public sector would 1ikely be incurred by the Federal Government.

To encourage voluntary reporting of cases of adverse reactions to vaccines by health care practitioners in the private sector, the Federal Government could create health care provider education and participation programs. Such programs could increase practitioners' awareness of potential adverse reactions, encourage them voluntarily to submit reports of such reactions, and provide them with results generated from the nationwide surveillance system.

Implementation of this option probably would yield more data regarding the safety of licensed vaccines than are yielded at present. Because of the difficulties involved in determining the number of vaccine doses administered to defined populations in the private sector, however, it would not be likely to yield data that could be used to calculate the rate at which such reactions occur. Data generated through case reports collected through this type of system, however, could supplement data from CDC's voluntary case reporting system in the public sector.

On the negative side, implementation of this option might reduce pharmaceutical manufacturers' commitment to vaccine research, development t, and production. Some manufacturers might perceive mandated participation in postrnarketing surveillance as unnecessary and costly, and consequently, might terminate the vaccine component of their business.

Further, mechanisms which the Federal Government might employ to solicit information regarding adverse reactions to vaccines administered by physicians in the private sector, including the mechanisms described above, are likely to fail. The Federal Government at present has no effective means by which to compel private sector physicians to report the number and types of vaccinations they administer, let alone the number of adverse reactions to these vaccinations. Private sector physicians' participation in public health data reporting systems in the past, in tuberculosis and venereal disease reporting programs, for example, has been less than enthusiastic. Private sector physicians may be especially reluctant to report adverse reactions to vaccines for fear of malpractice suits alleging physician negligence in administering a vaccine as the cause of an adverse reaction.

OPTION B-2:

Convert CDC's passive, voluntary case reporting system to an active, mandatory postmarketing vaccine surveillance system to monitor reactions to vaccines used in public immunization programs.

Congress could authorize HEW to undertake active postmarketing surveillance of selected vaccines administered in public health c1inics under federal] y sponsored immunization programs. Given such authorization, CDC could require participating State and

local health departments to maintain records of the number of doses of vaccines administered and actively to solicit information regarding adverse reactions.

An active, mandatory surveillance system to monitor reactions to vaccines administered in the public sector would involve varying degrees and types of participation from the following: vaccinees, physicians or other health professionals in State and local health departments who administer vaccines, and Federal Government scientists (e. g., epidemiologists and statisticians). Tasks assigned various participants would be to:

1. Maintain vaccination records (i.e., records of who got what vaccine, where and when).
2. Solicit, verify, and tabulate the number and types of adverse reactions experienced by vaccinees over a given time period (Kramer, 1979).
3. Compile data regarding the number and types of adverse reactions to particular vaccines, analyze these data, and calculate rates for the incidence and prevalence of specific adverse reactions.
4. Publicize the results among health professionals, State and local health departments, and the public.
5. Reassess the relative benefits and risks of licensed vaccine products for which an unacceptably high incidence of serious adverse reactions is found.

Mandatory use of a PMS system for- all vaccines used in public immunization programs probably would not be warranted. A mandatory PMS system for vaccines administered in the public sector could be used to monitor selected vaccines at various stages of development. Thus, licensed products that pose reasonably well-known risks, but meet a special societal need, could be monitored along with products that appear to represent new immunizing breakthroughs, but which may also have unknown toxicities.

Congress itself could develop criteria for the use of PMS to monitor vaccine safety, to or it could assign this responsibility to the Secretary of HEW. One reason for assigning the task of developing PMS criteria to the Secretary of HEW might be to allow participation of HEW agencies with specific areas of expertise, such as CDC, FDA, and NIH. Precedent for- assigning the task of developing criteria to the Secretary of HEW is the assignment to the Secretary under the “eminent hazard” section of the Food, Drug, and Cosmetic Act (2 I USC 355E) of authority to remove from interstate commerce any drug shown to be an eminent hazard to the public’s health. In contrast, precedent for establishment of criteria by Congress is the Delany amendment contained in the 1958 Food Additive Amendments to the Food, Drug, and Cosmetic Act, under which Congress required FDA to remove from interstate commerce any carcinogenic (cancer-producing) food additive.

Under the swine flu immunization program, active postmarketing monitoring of adverse vaccine reactions led to a more thorough evaluation of the safety of swine flu vaccine than was originally intended. This program was operated by Federal, State, and local government agencies, and many people were vaccinated in public programs. CDC, in cooperation with State and local health departments, was able to collect and analyze data generated by participating health professionals. Thus, the approximate incidence of Guillain-Barre Syndrome (GBS) associated with swine flu vaccination, one case per 100,000 vaccinees, could be calculated. (See appendix 5.1.) If swine flu vaccine had not been given to as many people (40 million) over such a short period of time (about 3 months), and if more people had received the vaccine in the private sector (from community-based physicians), the association between GBS and swine flu vaccine probably would be less clear.

A PMS system that accomplishes all of the tasks described above would allow for more comprehensive evaluations of the safety of vaccines used in public immunization programs than are possible at the present time. Such a system, however, would require more resources than CDC's voluntary, case reporting system. The amount of additional resources that would be required to establish and maintain such a system, however, cannot be precisely estimated. This amount would depend, first, on the degree of sophistication of the mandatory PMS system that might be developed, and given this, on the adequacy of CDC's currently available resources.

Virtually all of the costs of a mandatory PMS system for vaccines administered in the public sector would be borne by U.S. taxpayers. The Federal Government would direct and control the entire PMS effort and would rely very little, if at all, on resources from vaccine manufacturers. Any costs incurred by vaccine manufacturers, furthermore, most likely would be passed on to taxpayers in the form of higher prices for federally purchased vaccines.

Mandatory PMS activities could be a disincentive for local and State public health clinics to participate in federally sponsored public immunization programs. Such activities could cause clinics to increase their operating expenses and to divert a substantial portion of their currently limited resources from other activities.

COST-EFFECTIVENESS ANALYSIS OF VACCINATION PROGRAMS

The policy options presented below are based in part on OTA's cost-effectiveness analysis (CEA) of pneumococcal vaccination presented in chapter 4. Findings and issues related to this CEA are discussed in chapter 6. Options are categorized as follows: 1) general applications, 2) specific use in reimbursement decisions, and 3) methodological and data problems.

General Applications of CEA

Most decisions made in health care, or any field, take into account some informal weighing of costs and outcomes or benefits. Formal CEA, however, has not been widely used in health care decisionmaking. Despite a substantial increase in the rhetoric of "cost-effective decisionmaking," the technique of CEA has remained principally a phenomenon of academic journals. (See appendix 4.3.)

This state of affairs may now be changing. Increased awareness on the part of policymakers, providers, and the public of the sometimes inadequate state of knowledge about the efficacy, effectiveness, and costs of medical technologies, combined with tight budgets, may lead to increased evaluation of these technologies. Such evaluation might include the use of formal CEAs.

CEAs and benefit-cost analyses (BCAs) are explicitly included in the mission of the new National Center for Health Care Technology (NCHCT) of the Department of Health, Education, and Welfare (HEW). The legislative authority for NCHCT, however, covers only the conduct of CEAs; it does not cover their application.

Selection of the following option would likely increase the Federal Government's use of cost-effectiveness analysis.

OPTION C-1:

Federal agencies could include formal CEA in the process of allocating funds for vaccination and other health care programs.

Federal agencies that might use CEA in allocating funds for vaccine-related programs include the National Institute of Allergy and Infectious Diseases (NIAID), the Center for Disease Control (CDC), and the Health Care Financing Administration (HCFA). (See chapter 6.)

A possible advantage of this option is that, when used appropriately, cost-effectiveness criteria could lead to more rational allocation of Federal resources. Thus, the judicious use of CEA might lead to better selection of programs to reduce health care costs or improve health status. As suggested by the case study of pneumococcal vaccine, for example, vaccination would produce health benefits that could not be derived from treatment, and for some age groups, vaccination appears to be relatively inexpensive. (See chapter 4.)

No reasonable estimate can be made of potential reduction in overall health care costs that might result from using CEAs. That reduction would depend on how widely CEAs were used and for what decisions (for individual technologies, for entire programs, and so on), and on external factors such as the incentives affecting use of health care resources. If certain technologies or programs were utilized on the basis of CEA projections of savings, for example, those savings might not yield a reduction in overall health care expenditures; the funds might be diverted to other health care programs. Overall public expenditures on health care might still be determined by political, economic, and cultural forces.

A potential disadvantage of greater application of CEA information is directly related to the very strength of the technique. CEA is a technique for improving the rationality of decisionmaking—at least in terms of economic efficiency. Cost-effectiveness analysis has the potential to improve the efficiency-related aspects of resource allocation, but can do little to aid the noneconomic aspects of rationality. CEAs often exclude considerations of equity, politics, and distribution. When a bottomline dollar-figure is generated in a CEA, the excluded factors may not appear important; further, some included, but subjective, factors (such as choice of discount rate) may become hidden.

Another potential disadvantage of this option is the possibility that Government time and funds would be spent on formal CEA when an informal or less rigorous analysis would serve as well. The lack of criteria for determining the need for forma] analysis may result in overapplication of the technique.

CEA and Its Relationship to Reimbursement for Vaccinations

Only two preventive vaccines are currently marketed for general use by persons over age 65: influenza vaccine and pneumococcal vaccine. According to OTA's cost-effectiveness analysis, vaccination against pneumococcal pneumonia provides health benefits that cannot be derived from treatment of that disease. (See chapter 4.) Under most conditions, health benefits can be obtained at either a very low cost or even a small savings. Furthermore, vaccination against pneumococcal pneumonia is more cost-effective among the elderly than any other age group, Kavet has demonstrated that vaccination against influenza also yields health benefits among the elderly that treatment cannot provide; further, under certain circumstances, influenza vaccination among the elderly

might be cost-saving (Kavet, 1972). Other vaccines that likely will be designed to reduce the incidence, morbidity, and mortality of infectious diseases that affect the elderly are being developed.

The Federal Government has only one authorized mechanism to pay for preventive vaccinations among the elderly: Congress can authorize HEW to include a particular vaccine in federally sponsored public immunization programs. (See chapter 6.) In 1976 and 1978, for example, Congress authorized and funded public immunization programs against influenza with a special emphasis on vaccinating the elderly. Congress has refused, however—in part because of unresolved liability issues (see chapter 5)—to authorize HEW to establish an ongoing influenza vaccination program.

Congress could enact legislation to authorize the inclusion of pneumococcal vaccine in federally financed mass immunization programs. Mass immunization with pneumococcal vaccine, however, is not currently recommended by the Advisory Committee on Immunization Practices (ACIP), which advises CDC on immunization issues. ACIP specifically recommended that pneumococcal vaccine be administered only to individuals who are at particularly high risk of contracting or dying from pneumococcal pneumonia or bacteremia (U.S. Ex. Br., CDC, MMWR, 1978). ACIP's recommendation probably was based on the observation that pneumococcal diseases are probably not highly contagious in the general population; pneumococcal vaccine, therefore, most likely protects only those who receive it (i. e., herd immunity resulting from vaccine probably would be negligible). Traditionally, the Federal Government has directed its public immunization programs against childhood diseases, in particular against communicable infectious diseases.

An alternative or supplementary method of financing vaccinations among the elderly would be the use of Medicare. At present, however, the Medicare law specifically excludes reimbursement for vaccinations. Congressional action would be needed to change the law.

OPTION D-1:

Amend the Medicare Law to permit reimbursement for preventive vaccinations.

Congress could permit Medicare to pay for immunizations by amending the 1965 Amendments to the Social Security Act to strike the word "immunizations" from the list of benefits specifically excluded from coverage in the law [42 USC 1395(y)].

In amending the Medicare law, Congress itself could establish criteria for the selection of immunizing agents to be included in the Medicare benefit package, or it could assign this responsibility to HEW. Examples of types of agents that might be considered for inclusion in the benefit package are these:

- Agents that help prevent diseases that particularly affect the elderly.
- Agents designed for use in special high risk populations.
- Agents that are not included in publicly financed immunization programs.
- Agents that have been proved both safe and efficacious, and possibly cost-effective, when used by individuals 65 years and older.

Some type of special payment mechanism for vaccinations under Medicare might be necessary. Under the current system, Medicare beneficiaries might have to pay a substan-

tial copayment (deductible and coinsurance) before receiving a vaccination. The total cost of pneumococcal vaccination in the private sector is about $11. Because of copayment requirements, some beneficiaries might forego vaccination, thus defeating the purpose of authorizing reimbursement.

Possibly, a schedule of payments for preventive services such as immunizations could be established without copayment requirements. For preventive services, a schedule of payments without copayment requirements might be sensible, because preventive services—unlike treatment services for most diseases—are not insurable risks; on the contrary, preventive services are predictable events designed to help reduce the risks of disease in the future. Financial incentives to encourage Medicare beneficiaries to demand such services, subsequent to their inclusion in the benefit package, therefore, may be desirable.

One mechanism that could be used to encourage the use of selected vaccines by Medicare beneficiaries is the inclusion of a coupon for one or more vaccinations in a mailing of the beneficiaries' monthly Social Security checks. Subsequent to administering the vaccinations, physicians could submit these coupons to Medicare for reimbursement.

On the one hand, there appear to be several reasons to pay for preventive vaccines under Medicare. First, it seems to make little sense to pay for the treatment of infectious diseases, such as influenza and pneumococcal pneumonia, and not to pay for vaccinations to help prevent them. With treatment costs rising at unprecedented rates, the economic value of a relatively inexpensive preventive vaccine is increasing. Second, studies of pneumococcal vaccine and influenza vaccination document a benefit of vaccination that cannot be attained with treatment, namely, a gain in years of life. Moreover, the effectiveness of antibiotic treatment of pneumococcal pneumonia may be declining (Austrian, 1964; Jacobs, 1978).

On the other hand, there may be reasons not to change the Medicare law to permit payment for vaccinations. First, it is possible that Medicare payment for vaccination would not increase the total number of vaccine recipients among those over age 65. Payment might simply transfer the cost of vaccination to Medicare from those who would pay for the vaccine on their own. Second, the net cost of vaccination in publicly financed immunization programs may be lower than the cost in the private sector. Therefore, Congress may be able to encourage vaccine use more efficiently by increasing its reliance on public immunization programs, rather than expanding Medicare coverage.

CEA Methodology and Data

The methodology of cost-effectiveness analysis is still evolving and exhibits certain shortcomings. (See chapter 6.) Standardization of certain aspects of CEA methodology and research aimed at reducing methodological shortcomings might strengthen CEA as an analytical technique. Similarly, efforts to identify and collect data necessary or desirable for CEAs—many of which are currently not available or not in usable form-might enhance CEA's potential utility in improving the economic efficiency of resource al1 oca t i ons.

Selection OF the option below could facilitate the evaluation CEA as an analytical tool and might enhance the utility of this technique to the Federal Government.

OPTION E-1:

Federal agencies, including HEW, could begin to develop standardized and refined CEA methodology and basic data sets for CEAs.

The legislation creating the National Center for Health Care Technology (NCHCT) permits that agency not only to conduct CEAs, but also to develop general methodology and data for such assessments. NCHCT could conduct pilot evaluations of certain technologies that would force analysts to confront some of the methodological weaknesses (e.g., developing acceptable health status indexes) or areas of disagreement (e.g., how to account for multiple outcomes or effects).

CEA methodology and data problems could be addressed jointly by NCHCT, the National Center for Health Services Research (NCHSR), and the National Center for Health Statistics (NCHS). These three Centers are all under the authority of HEW's Deputy Assistant Secretary for Health Research, Statistics, and Technology. Thus, coordination among the three Centers and the Deputy Assistant Secretary's offices could greatly improve the feasibility of implementing this option.

Resolution of some CEA methodological shortcomings will likely require efforts by Federal agencies in addition to HEW. For example, the Office of Management and Budget (OMB) is a major force in decisions about what discount rate should be used. Some type of cooperative agreement or study would be needed to standardize such aspects of methodology .

One potential advantage of this option is that it could accelerate certain data-related activities within the three Centers mentioned above. Two examples are: 1) the development of population-based data sets regarding the incidence, prevalence, morbidity, and mortality of chronic conditions; and 2) the development of methods to reflect multiple causes of death and the interactive effects of multiple diseases.

A related advantage is that methodological and data improvements which increased CEA researchers' ability to characterize populations or medical conditions would also benefit health services research in general. Work on health status indexes, for example, might benefit the identification of medically needy, the comparison of different settings for health care, and the comparison of different delivery systems.

Standardized CEA methodologies, once developed and put into use by HEW or other health agencies, could greatly facilitate comparisons of different types of medical technologies. In general terms, agreement on methodological elements, such as types of effects to be measured and the discount rate, along with better health status data on effects could improve comparisons between technologies or programs designed to improve health but not targeted at the same disease. The economic and medical aspects of a cancer prevention technology, for example, might be compared to those of hypertension treatment. Standardized methodologies also might permit comparisons of the cost-effectiveness of various types of vaccinations at selected ages throughout life.

Potential disadvantages are associated with this option. Improvements and standardization of methodology and data sets would be expensive. Both research and administrative programs would be necessary. An intangible disadvantage might be the inconvenience to providers—and consumers—who may have to provide data at a time when there is an expressed effort to reduce burdensome Federal paperwork and regulation.

One possible weakness of this option is the difficulty that would be encountered in attempting at the same time both to improve the methodology (i.e., hasten the evolution of the technique) and to standardize major aspects of it. This is probably not a significant

enough disadvantage to counter the advantages of the option, but it is one that will have to be seriously taken into account. Overcoming this difficulty may require flexibility in setting—and revising—methodological standards. Since such flexibility is not a hallmark of bureaucracy, some form of oversight mechanism may be a desirable addition to the option.

LEGAL LIABILITY AND COMPENSATION FOR VACCINE-RELATED INJURIES

Unless Congress takes some definitive action, decisions concerning liability and compensation for vaccine-related injury will continue to be made on a case-by-case basis by the courts. (See chapter 5.) By maintaining the status quo, the Federal Government may be perpetuating a degree of uncertainty that is, or could be, leading to a reduced commitment of vaccine manufacturers, as well as State and local health agencies, to public immunization programs. Until vaccine liability issues are resolved, all participants in federally financed immunization programs proceed with caution. Manufacturers and Congress scrutinize their commitments to public immunization programs at least yearly, State and local health agencies are concerned about the malpractice risks of their employees, and the public's enthusiasm for vaccines may be waning. (See chapter 6.)

Current case law has placed ultimate liability for the "duty to warn" potential vaccinees about the statistically remote risks of serious vaccine-induced injury on the vaccine manufacturer. In its recent vaccine purchase contracts with manufacturers, however, the Department of Health, Education, and Welfare (HEW) has assumed responsibility for developing an adequate informed consent statement to be used to discharge the legal duty to warn; HEW is requiring participating State and local health agencies to use this statement and HEW guidelines before administering vaccines in federally financed public immunization programs. HEW and vaccine manufacturers disagree on who now has legal responsibility to inform potential vaccinees of the risks of vaccination.

There is no definite way to predict whether a court in any given instance will find HEW's informed consent statements, and the way in which they are used, to be adequate. If a court finds that the duty to warn has been successfully discharged, then injured vaccinees would not be legally entitled to compensation. Even if a court finds in a particular case that the duty has not been discharged, whom the court will hold 1iable is not predictable. The duty to warn may be contractually transferred from the vaccine manufacturer to other participants further down the vaccination distribution and administration chain. It is not clear, however, how this transfer may be accomplished to the satisfaction of a court.

If the Federal Government takes the position that liability for vaccine-related injury should be determined by the courts, it is doing its best to avoid assuming the responsibility for compensating the injured. If HEW successfully defends its current position that underlying responsibility for the duty to warn still rests with the manufacturers, however, vaccine manufacturers may become even more reticent than ever to continue developing and producing vaccines. If manufacturers are able to obtain liability insurance, then it is likely that they will pass the costs of such insurance on to the Federal Government and other vaccine purchasers in the form of higher vaccine prices.

Alternatively, however, if vaccine manufacturers are not able to obtain liability insurance, they may ask the Federal Government to indemnify them from all duty to warn

liability before they will produce vaccines for future federally financed public immunization programs. This is what happened under the 1976 swine flu program. Failure to meet the manufacturers' requirement(s) could lead to a further decline in, and possible termination of, vaccine production in the private sector. In this case, if the Federal Government chose to retain its commitment to public immunization programs, it might have to establish Government vaccine production programs.

By allowing vaccine liability cases to be decided by the courts, the Federal Government minimizes its administrative and legal expenses for settling liability lawsuits arising from public immunization programs. The current system also may keep the number of lawsuits for claims without merit to a minimum. Because of the expenses associated with large court cases, though, some persons truly injured in public immunization programs may never seek compensation.

The Federal Government's involvement in all phases of vaccine development, quality assurance, promotion, and use might justify the Federal Government's developing an approach to mitigate liability problems that would improve injured vaccinees' access to compensation. If Congress believes that such an approach is warranted, then it might consider adopting one of the two options presented below. A central element of each of the options below is easier access to compensation for vaccinees injured in federally sponsored public immunization programs.

OPTION F-1:

Assume responsibility for defending all claims of vaccine-induced injury incurred in public immunization programs and maintain authority to sue negligent parties.

This model is analogous to that used in the swine flu program. (See chapter 5.) Under this option, the Federal Government would become the primary defendant in all legal actions involving claims of injury sustained as a result of vaccination in a public program. The Federal Government would assume liability for the duty to warn, but would retain the right to sue other parties for negligently caused injury. Vaccine manufacturers would incur costs in assisting the Government in the preparation and defense of lawsuits under this option, but would be somewhat insulated from the expense of defending lawsuits.

As the Federal Government would be the primary focus of claims for compensation, it might relax the vigorousness of the kinds of proof that would be needed to obtain compensation. Under the legal liability system, foreseeability is a fundamental concept in assigning liability. (See chapter 5.) In its processing of claims from plaintiffs who allegedly contracted Guillain-Barre Syndrome (GBS) by participating in the 1976 swine flu program however, the Federal Government apparently is relaxing the requirement of proof of foreseeability. GBS injuries were not a foreseeable consequence of immunization at the start of the swine flu program. In order to provide compensation to injured vaccinees, the Government is requiring proof of causation between swine flu inoculation and alleged injury more than proof of foreseeability of injury. This approach is more compensation-oriented than an approach based on strict application of judicial doctrine. If the Federal Government were to decide to use a similar approach in the future, compensation would depend less on whether an adequate warning had been given than on whether significant injury had occurred as a result of immunization.

In terms of increasing injured vaccinees' chances of receiving compensation, this approach might represent an improvement for the class of injured vaccinees as a whole; however, it might not represent an improvement for the rare individual vaccinee who successfully maneuvers the current 1itigation process and receives a large award. Such a tradeoff between high individual awards and more awards of less individual worth is typical of the kinds of tradeoffs that would have to be made in either continuing the current situation or developing a more compensation-oriented system.

Immediate and direct costs to the Federal Government would increase under this option because of the administrative expense of processing, evaluating, and defending claims and because of the costs of compensating successful 1itigants. Long-term and indirect costs to the Coverrnent might or might not increase. Indirect "costs, " such as decreased public participation i n immunization programs, might be less under this option, because the Government would be taking a positive approach, or at least not a passive one, to the problem of injured vaccinees.

OPTION F-2:

Establish a federally operated program to compensate vaccinees injured as a result of being vaccinated in public immunization programs.

A frank compensation approach could take any one of several forms ranging from modifications of the legal 1iability system, to integration into existing social insurance programs, to melding with existing injury compensation approaches that have similar rationales for compensation (e. g., for the injured in medical experimentation). The details of specific Federal compensation approaches that might be developed will have to await further studies. Data currently being collectedly HEW may assist in estimating the costs of a compensation system, determining which injuries should be compensated, and which systems should be used to deliver compensation.

The four major tasks in establishing a Federal compensatic~n system would be the following. First, criteria for- the selection of vaccinees eligible for compensation would have to be established. Compensation could be limited, for example, to persons whose injuries result from vaccinations that the Government promotes to a substantial degree. This would provide compensation to injured recipients of the childhood vaccines and certain influenza vaccines, but not vaccines such as rabies.

Second, the types and severity of injury qualifying a vaccinee for compensation would have to be established. Under present legal approaches, what should be compensated is decided on the basis of individual assessment of causation, foreseeability, and severity of injury. Under a compensation approach, there would have to be some test of causality and cutoff point on the severity of injury for which compensation will be provided.

Third, the amount of compensation to be provided to injured vaccinees would have to be determined. A basic tenet of damage assessment in litigation is that damages are set according to the particular circumstances of the individual. Under the legal liability system, compensation is awarded in lump sums based on a judge's or jury's determination of the projected needs of an injured person. Under a frank compensation system, which is oriented away from the adversary process toward the assumption of societal responsibility for injury, however, compensation could not be based primarily on consideration of individual circumstances. Instead, some general standards of levels of compensation would have to be established. The compensation mechanism could be structured,

however, to pay for injured persons' needs as they occur. Further, payments could be standardized, at least within set ranges, for selected types of injuries. Efforts could be made to ensure that the schedule of payments adopted under the system is not excessively restrictive and to provide for updating the schedule of payments as needed to keep pace with increases in the cost of living.

Fourth, financing mechanisms would have to be created or selected. Prior analysis in this report has shown the difficulty of applying insurance principles to finance such a system. (See chapter 5.) Furthermore, given the limited number of injuries arising out of even mass immunization programs, it would appear that the development of a free-standing compensation system might not be warranted. The issue of how compensation should be given is a generic one in reform of the injury liability field and has been extensively studied. No amount of further analysis here will bring new insight to bear upon the exact contours of the compensation system that might be developed. Any specific approach would need clarification, public debate, and compromise.

The advantages and disadvantages of establishing a federally operated program to compensate vaccinees injured as a result of being vaccinated in public immunization programs are largely speculative at this point, but in some respects parallel those cited in Option F-1. Court costs to the Federal Government probably would be lower under this option than those under Option F-1, but administrative costs probably would be greater. In addition, under this option, injured vaccinees probably would have easier access to compensation.

APPENDIXES

Appendix 1.1
PNEUMOCOCCAL VACCINE RESEARCH AND DEVELOPMENT (1881-1966)

Early Pneumococcal Research (1881-1931)

The pneumococcus was successfully isolated for the first time in 1880 by two researchers working independently, Sternberg in the United States, and Pasteur in France (White, 1938). For the next 5 years, several investigators, notably Fried1änder and Fraenkel, debated the association between pneumococcus and lobar pneumonia, but this debate ended in 1886, with confirmation of the association by Weichselbaum.

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

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

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

Researchers using Neufeld's serological system of classification were better able: 1) to determine which types of pneumococci produce pneumonia and other infections, 2) to conduct epidemiologic studies associating pneumococcal types with disease outbreaks in different geographical locations, and 3) to assess the severity of infections produced by specific types of pneumococci. Classification of pneurnococcal types was also a prerequisite to the partially successful treatment of humans with type-specific antiserum, prepared initially in horses and later in rabbits.

Whole Cell Pneumococcal Vaccine Trials (1911-38)

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

Following Wright's clinical experiment, Lister was able to identify specific types of pneumococci found in South Africa (Lister, 19 17). Using a whole cell vaccine containing five specific types of pneumococci identified by Lister, Maynard demonstrated a 20 percent reduction in the incidence of pneurnococcal pneumonia among South African gold miners, but no significant reduction in the mortality rate (Maynard, 1915). Lister himself also demonstrated a significant protective value of this vaccine, but the design of his studies— he selected control groups from separate mines with different attack rates—was questionable (Heffron, 1939), and some scientists refused to accept his results as valid.

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

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

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

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

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

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

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

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

In 1936, the New York State Health Department established a pneumonia control program modeled after the one in Massachusetts. Under this program antisera were developed for five types of pneumococci, reports were made on 13,540 cases of pneumonia, and the fatality rate of pneumonia was reduced (Stebbins, 1940).

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

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

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

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

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

According to Dowling (Dowling 1973):

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Research on Pneumococcal Pneumonia and Bacteremia (1952-62)

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

Pneumococcal Research After 1966

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

Appendix 2.1
HISTORICAL REVIEW AND TREND ANALYSIS OF VACCINE ESTABLISHMENT AND PRODUCT LICENSURE IN THE UNITED STATES (1902-67)'

The First Golden Era of Vaccines (1903-26)

From 1903 to 1916, the number of manufacturing establishments licensed to produce vaccines in the United States rose from O to **38,** and the number of vaccine products licensed in this country rose from O to **367.**

A sharp drop in both the number of licensed establishments and the number of licensed products occurred between 1916 and 1918. During World War I, many German and other European manufacturers ceased their American activity, so their licenses were revoked.

For the 9 years after World War I, vaccine licensure in this country significantly increased. By 1926, 40 manufacturing establishments held licenses for 422 products. Two factors probably contributed to the rapid escalation of vaccine activity immediately after the war. First, the medical profession at the time had little to offer patients in terms of effective treatment of infectious diseases, so prevention of such diseases may have been accorded a higher priority than treatment. Second, medical schools were developing research capabilities on which to base their educational programs, so medical science was growing. Thus, the combination of emphasis on prevention of infectious diseases and scientifically based medical research may have led to an increase in new vaccine products.

Decline During the Depression Years (1927-31)

From 1927 to around 1931, very few licenses were issued and several were revoked. The number of licensed vaccine manufacturing establishments during this period dropped from **40** to 33, and the cumulative number of licensed products dropped from **431** to 421. Quite possibly, some vaccine manufacturers were forced out of the vaccine business by the country's economic depression.

'The number of licensed manufacturing establishments and licensed vaccine products in the United States for each year from 1903 through 1979 are represented in graphic form in figures 3 and 4 in ch. 2 of this report.

Second Golden Era of Vaccines (1932-40)

From 1932 to 1940, the vaccine business underwent tremendous growth. The number of manufacturers rose from 33 to 52, and the cumulative number of products rose from 448 to an all time high of 607. This growth may have reflected the accumulation of benefits derived from new scientific breakthroughs. Biologists and microbiologists were better able than ever before to isolate and grow organisms; vaccine technologies were improving; immunochemistry techniques were being refined; and the use of clinical trials helped scientists assess vaccine safety and efficacy in humans. With the inevitability of World War II looming, the American Government also may have encouraged the development and production of vaccines to supply U.S. armed forces.

Increasing Reliance on Antibiotics (1941-54)

A few years prior to the peak of vaccine acitivity in 1938, the first clinically successful sulfa drug, sulfapyridine, was introduced into medical practice. Within a few years, the emphasis on disease prevention through vaccination shifted to disease treatment with antibiotics. Antibiotics were often less expensive and less troublesome to administer than were vaccines, and the introduction of antibiotics eroded a growing effort to conduct epidemiologic studies of, and to prevent, pneumococcal diseases. (See appendix 1.1.)

From 1950 on, vaccine product and establishment licensure activity in this country generally declined. Several factors **may** have contributed to the overall—and continuing— decline. First, American pharmaceutical companies increased their emphasis on the discovery and development of antibiotics rather than immunizing agents. Antibiotics were popular, apparently effective, and profitable. In 1951, Congress passed the Humprey-Durham Act which gave several drugs, including antibiotics, prescription status; this may have increased the promotion and use of antibiotics. Further, the pharmaceutical industry expanded its scope of research and production into several areas of therapeutics that were more profitable than were vaccines. The discovery of chloramphenicol, the tetracycline, and synthetic penicillin furthered the emphasis 'on iFeatment- rather than prevention—of infectious diseases.

Spurt of Vaccine Innovation (1955-67)

In the late 1950's, the number of licensed vaccine products declined, but the number of licensed manufacturers increased, and several events spurred vaccine innovation. The Salk vaccine, the first against poliomyelitis, was introduced in 1955. With this vaccine, Congress initiated its now 25-year history of purchasing and promoting the use of selected vaccines. Also, microbiological techniques and culture media were improving. Isolation of organisms was made easier. The early sixties marked the development of several viral vaccines, including oral polio, measles, and mumps.

In 1962, Congress amended the Food, Drug, and Cosmetic Act, setting new standards for drug safety, and for the first time, establishing clinical efficacy as a criterion for marketing approval of prescription drugs. New safety and efficacy standards also 'were adopted for biological products. These new criteria apparently had no-immediate effect on the number of licensed vaccine products or establishments. During the next 5 years, the number of licensed products dropped very little, from **396** to **385,** the cumulative number of licensed establishments dropped by 2.

Trends in vaccine product and establishment licensure from **1968** to the present are discussed in chapter **2.**

Appendix 2.2
PROFILE OF VACCINE ESTABLISHMENTS AND PRODUCTS CURRENTLY LICENSED IN THE UNITED STATES (1979)

Eighteen of **26** vaccine manufacturing establishments licensed in the United States currently produce vaccine products. Altogether these 18 establishments hold a total of approximately 143 vaccine product licenses issued by the U.S. Government. ' Eight American pharmaceutical companies currently hold 100 **(70** percent) of these 143 licenses; seven foreign-based institutions hold **24** licenses **(17** percent); and two State governments (Michigan and Massachusetts) hold 18 licenses (13 percent); only one product license is issued to an American university, the University of Illinois.[2]

Among these 143 product licenses, about 51 distinct types of vaccine products are represented. A profile of sources of the 51 types of vaccine products currently licensed in the United States, including American pharmaceutical companies, foreign institutions, State governments, and American universities, is presented in table 2.2A.

'These 143 product I icenses do not include I icenses for immunoglobulin products made from blood fractionation.

'See table 1 inch. 2.

Table 2.2A–Typos of Establishments ThatAre Licensed To Produce Each of the 51 Types of Vaccine Products Currently Licensed in the United States (1979)[a]

Type of product	Number o product licenses held by each tvDe of establishment				
	American pharmaceutical companies	Foreign-based Institutions	American uruversities	State governments	All 'establishments combined
1 Adenovirus and influenza virus vaccines combined aluminum phosphate adsorbed	1				1
2 Adenovirus vaccine,	1				1
3 Antirabies serum,	1	1			2
4 Anthrax vaccine adsorbed				1	1
5 BCG vaccine.		2	1		3
6 Cholera vaccine	4	1			5
7 Diphtheria antitoxin	1	1		2	4
8 Diphtheria and tetanus toxoids	2				2
9. Diphtheria and tetanus toxoids and pertussis vaccine.	2				2
10. Diphtheria and tetanus toxoids and pertussis vaccine adsorbed.	6	1		2	9
11. Diphtheria and tetanus toxoids adsorbed	4	1		2	7
12, Diphtheria toxoid	3	1		1	5
13. Diphtheria toxoid adsorbed	2	1		1	4
14 Diphtheria, tetanus toxoids, pertussis vaccine adsorbed, pohomyelitis vaccine	1				1

Table 2.2A–Types of Establishments That Are Licensed To Produce Each of the 51 Types of Vaccine Products Currently Licensed in the United States (1979)[a]–continued

	Type of product	Number of product licenses held by each type of establishment: American pharmaceutical companies	Foreign-based institutions	American universities	State Governments	All establishments combined
15	Diphtheria, tetanus toxoids, pertussis poliomyelitis vaccines adsorbed	1				1
16	Gas gangrene polyvalent antitoxin	1				1
17	Influenza virus vaccine	5				5
18	Measles and mumps virus vaccines, live	1				1
19	Measles and rubella virus vaccine, live	1				1
20	Measles virus vaccine, live, attentuated	2				2
21	Measles-smallpox vaccine, live	1				1
22.	Measles, mumps, and rubella virus vaccine, live	1				1
23	Meningococcal polysaccharide vaccine, Group A	2				2
24.	Meningococcal polysaccharide vaccine, Group C	2				2
25	Meningococcal polysaccharide vaccine, Groups A and C combined	2				2
26.	Mumps virus vaccine, live	1				1
27	Pertussis vaccine	4				4
28.	Pertussis vaccine adsorbed	1			1	2
29	Plague vaccine	1				1
30	Pneumococcal vaccine, polyvalent	2				2
31	Poliomyelitis vaccine	2	1			3
32	Poliomyelitis vaccine adsorbed	1				1
33	Poliovirus vaccine, live, oral, trivalent	1	1			2
34.	Poliovirus vaccine, live, oral, Type 1	1	1			2
35	Poliovirus vaccine live, oral, Type 2	1	1			2
36	Poliovirus vaccine live, oral, Type 3	1	1			2
37	Polyvalent bacterial antigens with "no U.S. standard of potency"	1				1
38	Polyvalent bacterial vaccines with "no U.S. standard of potency"[b]	1				1
39.	Rabies vaccine	1				1
40	Rocky Mountain Spotted Fever vaccine	1				1
41	Rubella and mumps virus vaccine, live	1				1
42	Rubella virus vaccine, live	1	2			3
43,	Smallpox vaccine	3	1		1	5
44	Staphylococcus toxoid	1	1			2
45	Tetanus and diphtheria toxoids adsorbed (for adult use)	5			1	6
46	Tetanus toxoid	7	2		1	10
47.	Tetanus antitoxin	3	2		1	6
48	Tetanus toxoid adsorbed	6	2		2	10
49	Typhoid vaccine	2			2	4
50	Typhus vaccine	3				3
51	Yellow Fever vaccine					
	Totals	100	24	1	18	143

[a]Includes 2 serums and 11 antitoxin products. [b]Cutter actually holds licenses for 12 products in this category

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, 1979.

For 20 (40 percent) of the 51 types of vaccine products currently licensed in this country, there is only one currently licensed manufacturing establishment.[3] For 14 other types of products, there are only two establishments with current product licenses. For 12 products, there are three to five establishments with licenses; and for six products, there are more than five establishments.

Names of all licensed establishments that hold current product licenses for each of the *51* types of vaccine products licensed in the United States are shown in table 2.2B. Also indicated is the number of years that each manufacturer's product license has been in effect.

[3]See **table 3** in ch. *2.*

Table 2.2 B—Names of Establishments That Are Licensed To Produce Each of the 51 Types of Vaccine Products Currently Licensed in the United States (1979)"

Type of product	Licensed establishment(s)	Date license issued	Number of years licensed
1. Adenovirus and influenza virus vaccines combined aluminum phosphate adsorbed	Parke, Davis and Company.	9/22/59	20
2. Adenovirus vaccine	Parke, Davis and Company.	9/23157	22
3. Antirabies serum	Lederle Laboratories	1/24/51	28
	Instituto Sieroterapico Vaccinogeno Toscano Sclavo	6126/52	27
4. Anthrax vaccine adsorbed.	Bureau of Laboratories, Michigan Department of Public Health.	1 1/04/70	9
5. BCG vaccine	Connaught Laboratories, Ltd.	3/31/67	12
	Glaxo Laboratories, Ltd.	1/24/63	16
	University of Illinois	7/07/50	29
6. Cholera vaccine	Eli Lilly and Company.	10/31/1 7	62
	Instituto Sieroterapico Vaccinogeno Toscano Sclavo	8/19/76	3
	Lederle Laboratories	12/26/41	38
	Merck Sharp and Dohme	9/04/52	25
	Wyeth Laboratories, Inc.	7/16/52	25
7. Diphtheria antitoxin	Bureau of Laboratories, Michigan Department of Public Health.	5/11 7/26	53
	Connaught Laboratories, Inc.	1/03/78	1
	Instituto Sieroterapico Vaccinogeno Toscano Sclavo	5/12/60	19
	Massachusetts Public Health Biologic Laboratories.	3/20/1 7	62
8. Diphtheria and tetanus toxoids.	Eli Lilly and Company.	7/26/49	30
	Parke, Davis and Company.	4/08/49	30
9. Diphtheria and tetanus toxoids and pertussis vaccine.	Connaught Laboratories, Inc.	1/03/78	1
	Parke, Davis and Company.	7129152	27
10. Diphtheria and tetanus toxoids and pertussis vaccine adsorbed	Bureau of Laboratories, Michigan Department of Public Health.	5/1 3148	31
	Connaught Laboratories, Inc.	1/03/78	
	Eli Lilly and Company.	7/26/49	3
	Instituto Sieroterapico Vaccinogeno Toscano Sclavo	3131178	1
	Lederle Laboratories	3115148	31
	Massachusetts Public Health Biologic Laboratories.	4/26/50	29
	Merck Sharp and Dohme	3/31/49	30
	Parke, Davis and Company.	1/30/46	33
	Wyeth Laboratories, inc.	5/16/61	18
11. Diphtheria and tetanus toxoids adsorbed	Bureau of Laboratories, Michigan Department of Public Health.	5/1 1/51	28
	Eli Lilly and Company.	7/26/49	30
	Instituto Sieroterapico Vaccinogeno Toscano Sciavo	3131178	1
	Lederle Laboratories	3/22/54	25
	Massachusetts Public Health Biologic Laboratories.	5/23/50	29
	Parke, Davis and Company.	4/08/49	30
	Wyeth Laboratories, Inc.	7/26/49	30
12. Diphtheria toxoid	Connaught Laboratories, Inc.	1/03/78	1
	Instituto Sieroterapico Vaccinogeno Toscano Sclavo	1/04/63	16
	Massachusetts Public Health Biologic Laboratories.	7/07/32	47
	Parke, Davis and Company.	8/1 7127	52
	Wyeth Laboratories, Inc.	5/19/44	35
13. Diphtheria toxoid adsorbed.	Bureau of Laboratories, Michigan Department of Public Health.	8/18/55	24
	Instituto Sieroterapico Vaccinogeno Toscano Sclavo	2/1 7/61	18

Footnote appears at end of table

Table 2.2 B—Names of Establishments That Are Licensed To Produce Each of the 51 Types of Vaccine Products Currently Licensed in the United States (1979)[a]—continued

Type of product	Licensed establishment(s)	Date license issued	Number of years licensed
	Parke, Davis and Company. ., ...	4/28/49	**30**
	Wyeth Laboratories, Inc.	3/07/52	**27**
14. Diphtheria, tetanus toxoids, pertussis vaccine adsorbed, poliomyelitis vaccine . .	Parke, Davis and Company,	12/20/63	**16**
15. Diphtheria, tetanus toxoids, pertussis poliomyelitis vaccines adsorbed	Parke, Davis and Company.	3/29/59	**20**
16. Gas gangrene polyvalent antitoxin ., ..., ...	Lederies Laboratories	5/04/49	**30**
17. Influenza virus vaccine.	Connauaht Laboratories. Inc.	1/03/78	1
	Lederle Laboratories	12/07/45	**34**
	Merck Sharp and Dohme	1 1/30/45	**34**
	Parke, Davis and Company.	11/26/45	**34**
	Wyeth Laboratories, Inc. .	12/1 3/61	**18**
18. Measles and mumps virus vaccines, live	Merck Sharp and Dohme	7/18/73	**6**
19. Measles and rubella virus vaccine, live. ., .,	Merck Sharp and Dohme .,	4/22/71	**8**
20. Measles virus vaccine, live, attenuated.	Lederle Laboratories	5/03/66	**13**
	Merck Sharp and Dohme .	3/21/63	**16**
21. Measles-smallpox vaccine, live. ...	Merck Sharp and Dohme	11/1 7/67	**12**
22. Measles, mumps, and rubella virus vaccine, live. ...	Merck Sharp and Dohme	4122171	**8**
23. Meningococcal polysaccharide vaccine, Group A ...	Connaught Laboratories, Inc. . . .	1/03/78	1
	Merck Sharp and Dohme . . .	7/1 1/75	*4*
24. Meningococcal polysaccharide vaccine, Group C . . .,	Connaught Laboratories, Inc. .,	1/03/78	1
	Merck Sharp and Dohme	4/02/74	5
25. Meningococcal polysaccharide vaccine, Groups A and C combined.	Connaught Laboratories, I	1/03/78	1
	Merck Sharp and Dohme	10/06/75	4
26. Mumps virus vaccine, live .,	Merck Sharp and Dohme	12/28/67	12
27. Pertussis vaccine . . . . . ., ...	Connauaht “Laboratories, Inc ...	1/03/78	1
	Lederle Laboratories	**1/19/1 4**	65
	Parke, Davis and Company. .,	**/24/1 7**	62
	Wyeth Laboratories, Inc. .,	**5/19/44**	35
28. Pertussis vaccine adsorbed . .	Bureau of Laboratories, Michigan Department of Public Health	10/1 2/67	12
	Parke, Davis and Company.	2/20152	27
29. Plague vaccine	Cutter Laboratories, Inc.	5/14142	37
30. Pneumococcal vaccine, polyvalent ...	Merck Sharp and Dohme ...	*11/21/77*	2
	Lederle Laboratories	*8/15/79*	—
31. Poliomyelitis vaccine.	Connaught Laboratories, Ltd	*1/24/63*	16
	Merck Sharp and Dohme	*4/1 2/55*	24
	Parke, Davis and Company. ., ...	4/1 2/55	24
32. Poliomyelitis vaccine adsorbed	Parke, Davis and Company.	7/22/70	9
33. Poliovirus vaccine, live, oral, trivalent	Lederle Laboratories	6/25/63	16
	Pfizer, Ltd. . . . . ., . . .	10/28/66	13
34. Poliovirus vaccine, live, oral, Type 1 ..., ...	Lederle Laboratories	3127162	17
	Pfizer, Ltd. . . . . ., .,	8/1 7/61	18
35. Poliovirus vaccine live, oral, Type 2 . . . . . ., ...	Lederle Laboratories	3/27/62	17
	Pfizer, Ltd.	1 0/06/61	18
36. Poliovirus vaccine live, oral, Type 3	Lederle Laboratories	3/27/62	17
	Pfizer, Ltd.	3/27/62	17
37. Polyvalent bacterial antigens with “no U.S. standard of potency”	Delmont Laboratories.	8/31/59	20
38. Polyvalent bacterial vaccines with “no U.S. standard of potency”	Cutter Laboratories, Inc.[b]. . . . . (Hollister-Stier)	4/27/76	3
39. Rabies vaccine	Eli Lilly and Company. ., ...	**6/07/1 5**	64
40. Rocky Mountain Spotted Fever vaccine.	Lederle Laboratories . ., ...	**4/1 3142**	37
41. Rubella and mumps virus vaccine, live.	Merck Sharp and Dohme	**8/30/70**	9
42. Rubella virus vaccine, live	Merck Sharp and Dohme	**6/09/69**	10
	Recherche et Industrie Therapeutiques S.A.	**3/12/70**	9
	Wellcome Foundation, Ltd. Wellcome Research Laboratories. .	3/01/77	2
43. Smallpox vaccine ., ...	Bureau of Laboratories, Michigan Department of Public Health.	**10/01/30**	49

Footnotes appear at end of table

Table 2.2B—Names of Establishments That Are Licensed To Produce Each of the 51 Types of Vaccine Products Currently Licensed in the United States (1979)[a]—continued

Type of product	Licensed establishment(s)	Date license issued	Number of years licensed
	Connaught Laboratories, Ltd.	10/23/67	12
	Connaught Laboratories, Inc.	1/03/78	1
	Merck Sharp and Dohme	9/21/65	14
	Wyeth Laboratories, Inc.	8/21/03	76
44. Staphylococcus toxoid	Instituto Sieroterapico Vaccinogeno Toscano Sclavo	5/1 2/60	19
	Lederle Laboratories	4/03/33	46
45. Tetanus and diphtheria toxoids adsorbed (for adult use)	Connaught Laboratories, Inc.	1/03/78	1
	Eli Lilly and Company	1 1/1 4/54	25
	Lederle Laboratories	4/06/62	17
	Massachusetts Public Health Biologic Laboratories	10/18/67	12
	Merck Sharp and Dohme	8/31/70	9
	Wyeth Laboratories, Inc.	12/1 7/54	25
46. Tetanus toxoid	Connaught Laboratories, Ltd.	1/14/43	36
	Connaught Laboratories, Inc.	1/03/78	1
	Cutter Laboratories, Inc.	9/25/40	39
	Eli Lilly and Company	12/10/35	44
	Instituto Sieroterapico Vaccinogeno Toscano Sclavo	1/04/63	16
	Lederle Laboratories	6/1 5/35	44
	Massachusetts Public Health Biologic Laboratories	5/16/49	30
	Merck Sharp and Dohme	12/11/33	46
	Parke, Davis and Company	5/04/40	39
	Wyeth Laboratories, Inc.	5/10/44	35
47. Tetanus antitoxin	Connaught Laboratories, Inc.	1/03/78	1
	Instituto Sieroterapico Vaccinogeno Toscano Sclavo	5/1 2/60	19
	Lederle Laboratories	3/06/16	73
	Massachusetts Public Health Biologic Laboratories	9/1 1/50	29
	Parke, Davis and Company	1/1 3/1 5	64
	Swiss Serum and Vaccine Institute Berne	8/09/63	16
48. Tetanus toxoid adsorbed	Bureau of Laboratories, Michigan Department of Public Health	9/20/55	24
	Connaught Laboratories, Inc.	10/1 5/70	9
	Eli Lilly and Company	9/09/70	9
	Instituto Sieroterapico Vaccinogeno Toscano Sclavo	2/1 7/61	18
	Lederle Laboratories	1/05/54	25
	Massachusetts Public Health Biologic Laboratories	5/09/67	12
	Merck Sharp and Dohme	8/31/70	9
	Parke, Davis and Company	7/08/52	27
	Swiss Serum and Vaccine Institute Berne	2/1 1/70	9
	Wyeth Laboratories, Inc.	6/30/55	24
49. Typhoid vaccine	Bureau of Laboratories, Michigan Department of Public Health	7/26/26	53
	Massachusetts Public Health Biologic Laboratories	3/20/17	62
	Merck Sharp and Dohme	4/25/63	16
	Wyeth Laboratories, Inc.	5/19/44	35
50. Typhus vaccine	Eli Lilly and Company	3/11/41	38
	Lederle Laboratories	5/24/67	12
	Merck and Sharp and Dohme	12/24/41	38
51. Yellow Fever vaccine	Connaught Laboratories, Inc.	1/03/78	1

[a]Includes 2 serums and 11 antitoxin products. [b]Cutter actually holds licenses for 12 products in this category.

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, 1979.

Appendix 2.3
CHRONOLOGICAL INTRODUCTION OF TYPES OF VACCINE PRODUCTS THAT ARE STILL LICENSED IN THE UNITED STATES

The year of introduction of each of **49** of the **51** types of vaccine prducts currently licensed in the United States, alolng with the manufacturing establishment with the oldest license still in effect for each product, is shown in table 2.3 A.] For 42 (86 percent) of these 49 products, the establishment that received the original product license still holds this license. As shown in table 2.3B, American pharmaceutical companies were issued 37 (89 percent) of the original licenses for these 42 products. New or improved types of products that are currently licensed have been introduced at a fairly consistent rate of three to seven products per each 5-year interval since 1940.[2] Ten of the currently licensed products were licensed before **1940.**

[1]Only 49 of the currently licensed 51 types of licensed products are included. Polyvalent bacterial antigens with "no U.S. standard of potency" and polyvalent bacterial vaccines with "no U.S. standard of potency" are excluded.

[2]The number of currently licensed vaccine products introduced in the United States in 5-year intervals since 1940 is shown in table 5 in ch. 2.

Table 2.3A—Chronological Introduction of Types of Vaccine Products Still Licensed in the United States

Year	Type of vaccine product	Establishment with oldest product license still in effect[a]
1903	**Diphtherla antitoxin**	**Massachusetts Public Health Biologic Laboratories (191 7)**
1907	**Tetanus antitoxin**	**Parke. Davis and Company (191 5)**
1914	**Pertussis vaccine**	**Lederle Laboratories**
	Typhoid vaccine	**Massachusetts Public Health Biologic Laboratories (191 7)**
	Rabies vaccine	**Eli** Lilly and Company*
1917	**Cholera vaccine**	Eli Lilly and Company*
1926	**Diphtheria toxoid**	Parke, Davis and Company (1927)
1933	**Staphylococcus toxoid**	Lederle Laboratories*
	Tetanus toxoid	Merck Sharp and Dohme
1941	**Typhus vaccine**	Eli Lilly and Company
1942	**Plague vaccine**	Cutter Laboratories*
	Rocky Mountain Spotted Fever vaccine.	Lederle Laboratories*
1945	**Influenza virus vaccine**	Lederle Laboratories
		Merck Sharp and Dohme
		Parke, Davis and Company *
1946	Diphtheria and tetanus toxoids and pertussis vaccine adsorbed	Parke, Davis and Company •
1947	Diphtheria and tetanus toxoids	Parke, Davis and Company (1949)
1948	Diphtheria and tetanus toxoids and pertussis vaccine	Parke, Davis and Company (1952)
	Diphtheria and tetanus toxoids adsorbed	Parke. Davis and Company*
	Diphtheria toxoid adsorbed	Parke, Davis and Company"
1949	Pertussis vaccine adsorbed	Parke, Davis and Company (1952)
	Gas gangrene polyvalent antitoxin	Lederle Laboratories •
	Tetanus toxoid adsorbed	Parke, Davis and Company (1952)
1950	BCG vaccine	University of Illinois"
1951	Antirabies serum	Lederle Laboratories"
1953	Yellow Fever vaccine	Connaught Laboratories, Inc. (1978)
	Tetanus and diphtheria toxoids adsorbed (for adult use)	Eli Lilly and Company'
		Wyeth Laboratories
1955	Poliomyelitis vaccine	Merck Sharp and Dohme*
		Parke. Davis and Company*
1957	Adenovirus vaccine	Parke, Davis and Company •
1959	Adenovirus and influenza virus vaccines combined aluminum phosphate adsorbed	Parke, Davis and Company*
	Diphtheria. tetanus. toxoids. pertussis. poliomyelitis vaccines adsorbed	Parke, Davis and Company •
	Diphtheria and tetanus toxoids. pertussis vaccine adsorbed, and poliomyelitis vaccine.	Parke, Davis and Company (1963)
1960	Poliomyelitis vaccine adsorbed	Parke, Davis and Company •
1961	Poliovirus vaccine live. oral. Type 1	Pfizer, Ltd. •
	Poliovirus vaccine. live. oral. Type 2	Pfizer. Ltd. •

Footnotes appear at end of table

Table 2.3A—Chronological Introduction of Types of Vaccine Products Still Licensed in the United States (continued)

Year	Type of vaccine product	Establishment with oldest product license still in effect[a]
1962	Poliovirus vaccine, live, oral, Type 3	Ptizer, Ltd.* Lederle Laboratories*
	Measles virus vaccine live, attenuated	Merck Sharp and Dohme*
	Poliovirus vaccine live, oral, trivalent	Lederle Laboratories*
1967	Measles-smallpox vaccine, live	Merck Sharp and Dohme*
	Mumps virus vaccine	Merck Sharp and Dohme*
1969	Rubella virus vaccine, live	Merck Sharp and Dohme*
1970	Anthrax vaccine adsorbed	Bureau of Laboratories, Michigan Department of Public Health*
	Rubella and mumps virus vaccine, live	Merck Sharp and Dohme*
1971	Measles and rubella virus vaccine, live	Merck Sharp and Dohme*
	Measles, mumps, and rubella virus vaccine, live	Merck Sharp and Dohme*
1973	Measles and mumps virus vaccine, live	Merck Sharp and Dohme*
1974	Meningococcal polysaccharide vaccine, Group C	Merck Sharp and Dohme*
1975	Meningococcal polysaccharide vaccine, Group A	Merck Sharp and Dohme*
	Meningococcal polysaccharide vaccine, Groups A and C combined	Merck Sharp and Dohme*
1977	Pneumococcal vaccine, polyvalent	Merck Sharp and Dohme*

[a]Dates in parentheses indicate dates of product licensure for vaccine products for which original license holders no longer hold licenses
*Establishment issued original product license.

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, 1979.

Table 2.3 B—Establishments Holding Original Licenses for Vaccine Products Still Licensed in the United States (1979)

Type and name of establishment	Number of original product licenses
American pharmaceutical companies	
Cutter Laboratories	1
Eli Lilly and Company.	4
Lederle Laboratories	7
Merck Sharp and Dohme	14
Parke, Davis and Company	10
Wyeth Laboratories	1
Subtotal	37 (890/.)
Foreign-based institutions	
Pfizer, Ltd.	3(7%)
State governments	
Bureau of Laboratories, Michigan Department of Public Health.	1 (2°/0)
American universities	
University of Illinois	1 (2%)
Total	42 (l 00%))

SOURCE OTA's Interpretation of data provided by the Bureau of Biologics 1979

Appendix 3.1
THE DEVELOPMENT OF THE FEDERAL GOVERNMENT'S STATUTORY AUTHORITY TO REGULATE VACCINE SAFETY AND EFFICACY (1902-73)

In **1902,** Congress enacted the Virus Serums and Toxins Act to "regulate the sale of vaccines, serums, toxins, and analogous products" (Hecht, 1977). This biologics control law, which gave the Secretary of the Treasury authority to license biological products and manufacturing establishments, marked the first attempt by the Federal Government to regulate products used for disease prevention or treatment.

Congress passed the 1902 law in response to a tragic event. The year before, 10 children had died from contaminated diphtheria antitoxin that had been prepared hurriedly and in the absence of manufacturing safety standards. The main intent of the Virus Serums and Toxins Act was to mandate assumption by Federal Government of responsibility for helping to ensure the safety of biological products intended for human use. Labeling regulations under the **1902** law required manufacturers to document claims they made about the efficacy of their products; these regulations, however, did not clearly establish product efficacy as a criterion for Federal licensing of new biological products.

The Virus Serums and Toxins Act of 1902 contained several key statutory provisions that still are enforced today (Timm, 1977):

1. Mandatory Federal licensing of all biological products to be sold in the United States
2. Mandatory Federal licensing of all manufacturing establishments engaged in the production of biological products to be sold in the United States
3. Mandatory inclusion of the following items on the label of each biological product sold in the United States:
   —Proper name of product content
   —Name, address, and establishment license number of the manufacturer
   –Product expiration date
4. Federal authority to inspect establishments licensed to manufacture biological products for sale in the United States
5. Federal authority to revoke or suspend biological product and manufacturing establishment licenses
6. Federal authority to punish by fine or imprisonment violators 'of the statute's provisions.

Regulations pursuant to the Virus Serums and Toxins Act, promulgated by a board consisting of the Surgeons General of the Army, Navy, and the Public Health and Marine-Hospital Service, were these:

1. Product and manufacturing licenses are to be issued and reissued on the basis of annual inspections. (1903)
2. Criteria for suspending or revoking licenses shall include faulty methods of preparation, faulty construction or administration of manufacturing establishments, and impurities or subpotency of products as demonstrated by laboratory examination. (1903)
3. Inspectors shall be commissioned medical officers of the Public Health and Marine-Hospital Service, and their visits to manufacturers shall be unannounced. (1903)
4. Samples of products shall be examined for purity and potency. (1903)

Additional regulations issued in 1909 and 1919 included these:

1. Licensable products are defined. (1909)
2. Product importation is prohibited except from licensed establishments. (1909)
3. Manufacturers are to establish requirements for personnel training and competence assessment. (1919)
4. Manufacturers are to establish permanent records regarding production and control for each lot of vaccines manufactured. (1919)
5. Manufacturers' product labeling requirements are expanded to include, among other things, a product expiration date. (1919)
6. The Federal Government is authorized to request manufacturers to submit for examination prior to distribution samples of all lots of particular products. (1919)
7. Product distributors' labels must include the name of the product manufacturer(s). (1919)

The Virus Serums and Toxins Act of 1902 and pursuant regulations were incorporated into section 351 of the Public Health Service Act of 1944 (42 USC 262). A requirement of the 1944 law, which remains in effect, is that biological products be safe, pure, and potent.

In **1962,** Congress amended the Food, Drug, and Cosmetic Act of 1938 (42 USC 216) to include efficacy, along with increased standards for safety, as a criterion for licensure of new prescription drug products. It also amended the act to authorize the Federal Government to require manufacturers to demon-

strate the safety and efficacy of new products in controlled clinical trials. Investigational new drug (IND) regulations developed in 1963 have been applied to investigational biologics, including experimental vaccines, as well as to drugs.

In 1972, the Food and Drug Administration (FDA) combined selected elements of the Public Health Service Act with certain provisions of the 1962 amendments of the Food, Drug, and Cosmetic Act to establish regulatory procedures and standaids for licensure of biological products. Under the 1972 regulations, FDA bolstered its authority to remove from commerce products not in compliance with certain regulations, for example, those establishing standards for vaccine and efficacy, As reported in the *Federal Register* on August 18, 1972: (37 FR 16679)

> Section 351 of the Public Health Service Act does not explicitly confer the authority to deny or revoke a license on the ground that the product is ineffective or misbranded. Because all biological products are drugs, and because the Federal Food, Drug, and Cosmetic Act does contain explicit authority to control the effectiveness of misbranding of all drugs, applicable provisions of the Federal Food, Drug, and Cosmetic Act were redelegate as published in the ***Federal Register*** on February ***25, 1972 (37*** FR *4004).*

In 1973, FDA promulgated a new set of regulations authorizing FDA to review and evaluate the safety and efficacy of biological products licensed prior to July 1, 1972. Based on the findings of its safety and efficacy reviews, FDA may leave intact, modify, suspend, or revoke manufacturers' licenses for particular products already on the market. '

'Procedures and standards authorized under these regulations, which also can be applied to the evaluation of products that have not yet been marketed, are discussed in detail in ch. *3. See* also app. 3.2, 3.3, and 3.4.

Appendix 3.2
STATUTORY AUTHORITY AND PROCEDURES FDA USES TO EVALUATE THE SAFETY AND EFFICACY OF PRESCRIPTION DRUGS

Ever since 1906, the Federal Government has required legitimate drug manufacturers to demonstrate that their products can be used by humans at a level of safety acceptable to Government scientists and officials. In 1906, Congress passed the Food and Drugs Act, which banned the manufacture and interstate commerce of adulterated or misbranded food and drugs.

Thirty-two years later, stimulated by a tragic event —over 100 people died from ingesting a sulfanilamide mixture made with the deadly toxin diethylene glycol —Congress passed the Food, Drug and Cosmetic Act of 1938 (USC, Title 21). This act strengthened the Federal Government's standard for safety and expanded the scope of the 1906 law to include cosmetics.

In 1962, Congress amended the Food, Drug and Cosmetic Act of 1938, again to strengthen safety requirements, and in addition, to establish efficacy as a criterion for licensure of prescription drugs to be marketed in this country. Congressional passage of this act was stimulated, at least in part, by the thalidomide tragedy in England and other European countries.

The effect of increasingly rigid Federal standards for the safety and efficacy of prescription drugs sold in this country has been a matter of controversy since the enactment of the 1906 Food and Drugs Act. On the one hand, prescription drug manufacturers complain about the costs associated with conducting premarketing clinical trials. Some contend that the rigorous safety and efficacy criteria established and enforced by the Food and Drug Administration (FDA) discourage innovation in the development of new drugs, and further, that the American public may be deprived of potentially useful new therapeutic entities as a result (Warden, 1978). On the other hand, FDA believes that tough Federal standards for safety and efficacy are necessary to help protect the American public from potentially dangerous and inefficacious prescription drugs (Kennedy, 1978). Neither viewpoint is substantiated by overwhelmingly supportive data. Judgments regarding the value of Government standards for drug safety and efficacy, therefore, are still based on one's sense of values. Thus far, Congress appears to have valued the public's protection more than it has industry's concerns about innovation and costs.

To evaluate the safety and efficacy of a new prescription drug product, FDA's Bureau of Drugs (BOD) first requires the sponsoring manufacturer to present data from preclinical testing of the product in animals. Before initiating clinical testing (in humans), a drug manufacturer must submit to FDA an acceptable investigation new drug application (IND). If FDA approves this application, the manufacturer may proceed with Phase I, II, and 111 clinical trials. Phase I clinical trials are used to assess the safety of

the product when administered in various dosages in healthy human subjects. In Phase II trials, the drug is tested for efficacy, as well as for specific short-term toxicities. In Phase 111, the product is tested in multiple, randomized, controlled clinical trials, usually involving short-term use of the drug among 2,000 to 3,000 subjects. * Data from these three phases of clinical trials are required by FDA. (If acceptable data are available, e.g., from foreign trials, however, then FDA can reduce its requirements for one or more of the three phases.) Upon completing Phase 111 clinical trials, the manufacturer submits a new drug application (NDA) to FDA. Approval by FDA of the manufacturer's NDA is necessary before the company legally can introduce a new drug product into interstate commerce.

For the most part, FDA bases its evaluation of the safety and efficacy of prescription drug products on the results of rigorous premarketing clinical testing. Once satisfied on the basis of premarketing test data that a drug is safe and efficacious, though, FDA leaves further assessment of its safety and efficacy to medical practitioners, patients, and health insurance carriers who pay for the use of prescription drugs.

The Secretary of the Department of Health, Education, and Welfare (HEW) has statutory authority to remove an approved prescription drug from the market, providing postmarketing evidence indicates that the drug represents an "eminent hazard" to the health of its users (21 USC 355 E). Once FDA approves a prescription drug product for marketing, however, its postmarketing assessment of the product's safety and efficacy is 1imited.

Prescription drug manufacturers are required to report to FDA all reports they receive from health professionals regarding adverse reactions to their products. On occasion, FDA participates in postmarketing assessments of drug efficacy and safety. For example, it establishes scientific panels, sometimes in collaboration with the National Academy of Science / National Research Council, to study the safety and efficacy of selected products on the market, e.g., antibiotics and over-the counter (nonprescription) drugs. In addition, FDA operates a passive postmarketing surveillance system to allow voluntary reporting by health professionals of cases involving adverse reactions to approved prescription drugs. At present, FDA is seeking statutory authority to expand its postmarketing surveillance activities (See chapter 7.)

[1]The virtues and limitations of clinical trials are discussed briefly in ch. 3, 6, and 7 of this report and at greater length in another OTA report, *Assessing the Efficacy and Safety of Medical Technologies* (U.S., Cong., OTA, Sept. 1978).

Appendix 3.3
BOB'S VACCINE PRODUCT LICENSURE APPLICATION AND PRODUCT REVIEW PROCESSES'

From 1902 to 1948, responsibility for enforcing laws and establishing regulations governing the manufacture and marketing of biological products was assigned to the Public Health Service's (PHS) Hygienic Laboratory. In 1948, the Hygienic Laboratory was incorporated into the National Institutes of Health (NIH), and this responsibility was assigned to the National Microbiologic Institute. In 1955, responding to a tragedy—polio cases resulting from poliomyelitis vaccine—Congress strengthened the Federal Government's control over the manufacture and sale of vaccines in the United States by establishing at NIH a separate Division of Biologics Standards.

In **1972,** the Division of Biologics Standards was transferred administratively within the Department of Health, Education, and Welfare (HEW) from NIH to the Food and Drug Administration (FDA). The purpose of this transfer was to strengthen Federal regulatory control of biological products by separating—and thus helping to prevent potential conflicts of interest between—Federal regulatory and scientific activities. Upon being transferred to FDA, the Division of Biologics Standards was renamed the Bureau of Biologics (BOB).

BOB (technically, FDA) is authorized to help ensure the safety and efficacy of vaccine products to be used by the American public by reviewing, and either approving or disapproving, vaccine manufacturers' applications for licenses to manufacture and sell particular vaccine products. The 10 basic steps involved in BOB's vaccine 1icensure application and review process, the procedures and processes involved in each step, and the sources of BOB's regulatory and statutory authority are described below:

[1]The 10 basic steps involved in BOB's vaccine product licensure and review process described in this appendix are i llustrated in figure 7 in ch. 3.

Step 1: BOB Has Established (or Establishes) General and (for Some Existing Vaccines) Specific Regulatory Requirements for Vaccine Product Licensure

Source(s) of Authority: Virtually all BOB regulations that apply to vaccine product and establishment licenses are contained in the Code of Federal Regulations (CFR), Title 21, sections 600-680. Section 600 lists several establishment standards, general provisions, and procedures for inspection of vaccine manufacturing establishments. Section 601 outlines general provisions, procedures and processes for establishment and product licensure (including foreign ones), and procedures for maintaining confidentiality of manufacturers' information. Section 610 establishes general biological standards, and sections 620-680 establish additional standards for various types of biological Products.

Legislative authority for sections 600 through 680 comes from the Public Health Service Act of 1944 (Sec. 351,58 Stat. 702, as amended, 42 USC 262).

Procedures and Processes: BOB issues two types of licenses that a manufacturer must obtain before introducing a vaccine product into commerce—a product license and an establishment license. A manufacturer must obtain an establishment license at the same time it receives its first product license.

Step 2: Manufacturer Submits to BOB an IND Application To Test an Experimental Vaccine in Humans

Source(s) of Authority: BOB's regulatory authority to require a manufacturer to file an investigational new drug (IND) application for new vaccine products is contained in section 601.21, Title 21, CFR. Specific regulations that apply to IND procedures are found in section 312 (New Drugs for Investigational Use) of Title 21 of the CFR (21 CFR 312).

Authority for section 312 comes from the 1962 amendments to the Food, Drug and Cosmetic Act of 1938 (sec. 215, 58 Stat. 690, as amended, 42 USC 216; sees. 502, 503, 505, 701, 52 Stat. 1051, 1052, 1053, 1055, as amended (21 USC 352, 353, 355, 371); 5 USE 554).

Procedures and Processes: The extent to which BOB requires a manufacturer to complete an IND application depends on the amount of existing data concerning a particular product that BOB will accept from foreign and intrastate studies. If no such data are available, then the manufacturer will have to supply a substantial amount of data collected from IND-approved studies. If it so chooses, however, BOB can waive this step entirely from the licensing process.

Step 3: BOB Evaluates and Either Approves or Rejects Manufacturer's IND Application

Source(s) of Authority: Same as those cited in Step 2.

Procedures and Processes: During the 30-day period subsequent to the filing of its IND application, the manufacturer may conduct no clinical investigations of its product. BOB during this period conducts a two-part review of the manufacturer's IND application. First, BOB staff scientists review sections of the application and comment on the validity of submitted data and research protocols. Second, BOB's IND Branch reviews the appropriateness of the total application. For its evaluation, the IND Branch may seek the advice, not only of BOB scientists, but of scientists in governmental agencies such as the National Institutes of Health (NIH) and the Center for Disease Control (CDC).

On the basis of its two-part review, BOB decides to allow the manufacturer to proceed as proposed, to require the manufacturer to modify its application, or to reject the IND application totally. If BOB objects to any part of the IND application, it must inform the manufacturer within 30 days and specify corrective actions that are necessary for BOB's acceptance. If BOB does not object to the IND application within 30 days, the manufacturer can proceed with its clinical investigation of the product described.

Step 4: Manufacturer Tests the Experimental Vaccine in Humans and Submits Its Data and Application for Product Licensure to BOB for Evaluation

Source(s) of Authority: Same as those cited in Step 2.

Procedures and Processes: Clinical investigation authorized under an IND is performed, at maximum, in three phases, each involving progressively more extensive testing. For vaccines, Phase I testing involves a small number of human subjects and is used primarily to assess safety. This phase is required when a product has been tested only in vitro and in animals. In Phase II, the manufacturer continues safety testing, using a larger number of subjects, and also begins efficacy testing for specific medical conditions. In Phase III, more rigorous testing methods

such as well controlled clinical trials, are used to evaluate clinical safety and efficacy in a large number of subjects. There are no requirements for minimum numbers of subjects included in any phase.

BOB can 1) require a manufacturer to go through this phase-by-phase process, 2) modify IND requirements, that is, abbreviate or waive one or more phases, or 3) waive such testing, depending on the availability of valid data from prior clinical investigations. Apparently, modification is the most commonly used alternative. A manufacturer is required to submit to BOB new research protocols for each phase of testing and annual progress reports. BOB weighs safety data with efficacy data in an effort to achieve an equitable balance of caution and progress.

Once an IND application has been accepted by BOB, it usually remains open until closed by the manufacturer. Thus, the manufacturer can continue to conduct clinical investigations with the product, informing BOB of major changes in proposed research protocols.

To facilitate market entry of a product, a manufacturer can begin the product licensure process before completing clinical investigations authorized or required under the IND process.

Step 5: BOB Evaluates Safety and Efficacy Data From Clinical Trials and Processes Manufacturer's Application for Product Licensure

Source(s) of Authority: Parts ***600, 601, 610, 620, 630,*** and 680 of the CFR delineate BOB's authority to use selected procedures, processes, and standards to conduct prelicensing evaluations of new vaccine products. Sections in the CFR pertaining to regulatory functions include the following:

CFR Section Citation	*Content of* Regulation
21 CFR 600.3	Establishes definitions used throughout Title 21, e.g. safety, sterility, purity, potency, and labeling.
21 CFR 601.2	Outlines procedures for filing application for product licensure.
2 1 CFR 601.4	Gives FDA Commissioner authority to approve or deny an application.
21 CFR 601.20	Requires products and manufacturing processes to comply with all applicable standards established in Title 21.
21 CFR 601.25	Establishes general definitions and criteria to be used to evaluate a product's safety, effectiveness, risk-to-benefit ratio, and labeling requirements, also outlines procedures to be used to evaluate products and to handle manufacturers' responses. **(Note: Section 601.25 technically refers to the review only of products licensed prior to July 1, 1972, but apparently is used by BOB to evaluate new products, as well.)**
21 CFR 601.51	Establishes conditions and procedures for maintaining confidentiality of selected data submit ted by manufacturers.
21 CFR **610**	Establishes general standards and procedures for tests conducted on biologi - cal products to help ensure their general safety, potency, sterility, purity, identity, and stability.
21 CFR *620*	Establishes additional standards for bacterial products.
21 CFR *630*	Establishes additional standards for viral vaccines.
21 CFR *680*	Establishes additional standards for miscellaneous products.

The statutory authority for these regulations is derived from the Public Health Service Act of 1944 (see. 351, 58 Stat. 702, as amended, 42 USC 262).

Procedures and Processes: BOB uses at least seven basic procedures to process a manufacturer's application for licensure of a vaccine product.

1. BOB's Licensing Branch screens the entire application to ensure completeness and compliance with all elements of CFR sections 601.2 and 601.
2. BOB forms an Ad Hoc License Review Committee comprised of BOB scientists, which assesses data produced from clinical trials and other testing procedures. Examples of scientific disciplines represented on the committee are microbiology, virology, bacteriology, immunology, epidemiology, and pathology. This committee is responsible for assessing various aspects of a product, including its safety and effectiveness, and relies on data from IND clinical investigations. If no IND investigation has been conducted, the committee may rely on data from clinical trials conducted in foreign countries.
3. BOB's Division of Control Activities conducts several types of tests on samples submitted from at least three lots of the experimental product. Tests are conducted to assess sterility, potency, stability, and biological and chemical purity and pyrogen content. Other BOB laboratories may conduct tests to confirm the manufacturing process.
4. BOB staff conduct a prelicensing establishment inspection. They investigate manufacturing procedures (e. g., processing, testing, storing, dispensing, and recording), inspect the manu-

facturer's equipment and facilities, and interview appropriate personnel.

5. Upon review of all test data, manufacturing procedures, and inspection findings, the chairman of the Ad Hoc License Review Committee recommends to BOB's Licensing Branch, with the concurrence of appropriate scientific division directors within BOB, either issuance or denial of the product license application,
6. BOB's Licensing Branch ensures that all data, including labeling, have been submitted by the manufacturer and reviewed by BOB. It conducts an administrative review for compliance with regulatory standards. In addition, the Licensing Branch ensures that, prior to issuance of the license, the manufacturer has prepared a batch of the new vaccines for release on the market.
7. If the Licensing Bureau concurs with the findings of the Ad Hoc License Review Committee, it recommends licensure to the BOB Director, who then makes a recommendation to the FDA Commissioner regarding the manufacturer's application.

In addition to relying on in-house procedures to review a manufacturer's product application, BOB often, on an informal basis, enlists the aid of scientists and clinicians from other Government agencies, e.g., the Center for Disease Control (CDC), the National Institute of Allergy and Infectious Diseases (NIAID), and from selected professional organizations, e.g., the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and certain infectious disease groups in medicine. The BOB Directol also may seek the services of outside advisory panels, such as those established under section 601.25.

In addition to using the general standards described in sections 601 and 610, and the additional standards in sections 620 and 630 of Title 21 of the CFR, to evaluate new vaccine products submitted for licensure, BOB uses specific guidelines issued by its staff and minimum requirements (particularly for potency) established at NIH before 1972.

Step 6: BOB (FDA) Issues Product License to Manufacturer

Source(s) of Authority: Section 601.4 of Title *21* of the CFR authorizes the FDA Commissioner to issue or deny either a product or an establishment license. This authority and its accompanying procedures were published in the *Federal Register* (FR) on January 25, 1977 (42 FR *4718),* and published as amended on May 22, 1977 (42 FR 15676), and on April 12, 1977 (42 FR 19142).

Procedures **and** Processes: If the FDA Commissioner approves the manufacturer's product application, BOB completes the license forms, and licensure remains valid until suspended or revoked. If the FDA Commissioner denies the application, however, he or she must inform the manufacturer of the reasons for denial and offer the manufacturer a public hearing on the matter.

Step 7: Manufacturer Markets the Newly Licensed Product

Source(s) of Authority: Not applicable.

Procedures and Processes: Not applicable.

Step 8: Manufacturer Is Required, Once Having Marketed the Licensed Vaccine Product, To Remain in Compliance With at Least Four Regulations That Help BOB Monitor the Product

Source(s) of Authority: As a condition of product licensure, BOB requires manufacturers' continuing compliance with the following regulations:

CFR Section Citation	*Content of Rcgulation*
21 CFR 610.1	Requires manufacturers to test samples from each lot of vaccines for compliance with BOB's standards for selected product qualities, e.g., potency, sterility, and labeling, and to report all deficiencies to BOB.
21 CFR 610.2	Requires manufacturers to submit samples and data from, and to obtain BOB's approval to release, each lot of vaccines produced.
21 CFR 601.12	Requires manufacturers to obtain BOB's approval to change selected aspects of vaccine production, e.g. manufacturing methods and product labeling.
21 CFR 600.12 and 21 CFR 600.22	Requires manufacturers, for 5 years, to maintain records of clinical reports of adverse reactions to their vacccines, and to give FDA inspectors access to these records. (Note: BOB is attempting to establish its regulatory authority to require manufacturers to submit reports of adverse reactions to vaccines.)[2]

Procedures and Processes: No comment.

[2]See chs. 6 and 7.

Step 9: BOB Monitors Manufacturer's Compliance With Established Regulations; BOB Reviews the Safety and Efficacy of Licensed Vaccines

Source(s) of Authority: For products licensed before July 1, 1972, BOB uses 21 CFR 601.25 to establish review procedures to determine that licensed products are safe, effective, and not misbranded under prescribed, recommended or suggested conditions of use. For all licensed products, FDA can use 21 CFR 601.5 to revoke a license and 21 CFR 601.6 to suspend a 1icense. Implicit] y, these two sections give FDA authorit, to establish product review procedures.

Procedures and Processes: Under 21 CFR 601.5, the FDA Commissioner can determine the appropri - ateness of any licensed biological product based on the following criteria:

- Uninspectable conditions of manufacturing facilities
- No product available for inspection
- Failure of manufacturer to report major changes as described in 21 CFR 601.12
- Failure of manufacturer to comply with standards for product characteristics such as safety, purity, and potency
- Evidence that the product is either misbranded, unsafe, or ineffective for all intended uses.

Federal regulations do not precisely specify the procedures the FDA Commissioner uses to collect data to evaluate which, if any, of these criteria are met. Some evaluation appears to be clone by BOB staff; some may be done with the assistance of advisory panels. The FDA Commissioner also may hold public hearings (2 I CFR 601 .7).

Under 21 CFR 601.25, the FDA Commissioner uses the following procedures to review at his or- her discretion at least those biological products licensed prior to 1972:

1. Appoints advisory review panel(s) to do the following:
   —Evaluate the safety and efficacy of licensed products
   —Review the labeling of licensed products
   —Advise the Commissioner as to which products are safe, effective, and not misbranded.
2. Solicits data and views from the public regarding licensed biological products through the *Federal Register*.
3. Considers the conclusions of the advisory review panel.
4. Publishes in the Federal ***Register*** a proposed order that designates which products should remain licensed without further testing, which need further testing, and which should be withdrawn from interstate commerce.
5. Receives and reviews comments, and 60 days after publication of the proposed order, publishes in the Federal *Register* a final order.

Step 10: Based on Its Findings in Step 9, BOB Acts in One of Three Ways:

- **Leaves License Intact Without Requiring Further Testing**
- **Requires Manufacturer To Conduct Further Testing**
- **Removes Product From Commerce**

Source(s) of Authority: BOB derives its authority to revoke a product license from 21 CFR 601.5 and its authority to suspend a license from 21 CFR 601.6. Other authorities to remove a product from commerce are 21 USC 334 (seizure) and 21 USC 331 (injunction). Also, 21 CFR 601.25 permits the FDA Commissioner to revoke a license based upon data from a formal review.

Procedures and Processes: No comment.

Appendix 3.4
TYPES OF DATA BOB USES TO EVALUATE THE SAFETY AND EFFICACY OF BIOLOGICAL PRODUCTS

1. Product label(s) and all other labeling (including labeling for export)
2. Representative advertising used during the past 5 years
3. Complete quantitative composition of the product
4. Animal safety data
   - Individual active components
     —COnt rolled studies
     —Partial] y controlled or uncontrolled studies
   - Combinations of the individual active components
     –Controlled studies
     —Partially controlled or uncontrolled studies
   - Finished biological product
     —Controlled studies
     —Partially controlled or uncontrolled studies

5. Human safety data
   - Individual active components
     —Cent rolled studies
     —Partial] y controlled or uncontrolled studies
     —Documented case reports
     —Pertinent marketing experiences that may influence a determination as to the safety of each individual active component
     —Pertinent medical and scientific literature
   - Combinations of the individual active components
     —Controlled studies
     —Partially controlled or uncontrolled studies
     —Documented case reports
     —Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components
     —Pertinent medical and scientific literature
   - Finished biological product
     —Controlled studies
     —Partially controlled or uncontrolled studies
     —Documented case reports
     —Pertinent marketing experiences that may influence a determination as to the safety of the finished biological product
     —Pertinent medical and scientific literature
6. Efficacy data
   - Individual active components
     —Controlled studies
     —Partial] y controlled or uncontrolled studies
     —Documented case reports
     —Pertinent marketing experiences that may influence a determination as to the efficacy of each individual active component
     —Pertinent medical and scientific literature
   - Combinations of the individual active components
     —Controlled studies
     —Partially controlled or uncontrolled studies
     —Documented case reports
     —Pertinent marketing experiences that may influence a determination as to the effectiveness of combinations of the individual active components
     —Pertinent medical and scientific literature
   - Finished biological product
     —Controlled studies
     —Partially controlled or uncontrolled studies
     —Documented case reports
     —Pertinent marketing experiences that may influence a determination as to the effectiveness of the finished biological product
     —Pertinent medical and scientific literature
7. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the biological product and its components and the scientific basis (or lack thereof) for the conclusion that the biological product, including its components, has been proven safe and effective and is properly labeled for the intended use or uses. If there is an absence of controlled studies in the materials submitted, an explanation as to why such studies are not considered necessary or feasible shall be included.
8. If the submission is by a licensee, a statement signed by the responsible head (as defined in §600.10 of this chapter) of the licensee shall be included, stating that to the best of his knowledge and belief, it includes all information, favorable and unfavorable, pertinent to an evaluation of the safety, effectiveness, and labeling of the product, including information derived from investigation, commercial marketing, or published literature.

   If the submission is by an interested person other than a licensee, a statement signed by the person responsible for such submission shall be included, stating that to the best of his knowledge and belief, it fairly reflects a balance of all the information, favorable and unfavorable, available to him pertinent to an evaluation of the safety, effectiveness, and labeling of the product.

SOURCE, 21 CFR 601.,25

Appendix 3.5
TYPES OF STUDIES BOB USED TO EVALUATE THE SAFETY AND EFFICACY OF POLYVALENT PNEUMOCOCCAL VACCINE

Epidemiologic Studies

In 13 of the 26 studies on which BOB based its evaluation of the new polyvalent pneumococcal vaccine, investigators attempted to determine the distribution of pneumococca] serotypes among U.S. and foreign study subjects with pneumococcal disease. [1]

[1] Investigators in other epidemiologic studies, most notably Robert Austrian in a study funded by NIAID, surveyed the distribution {)1 pneumococcal serotypes in the United States (Austrian, 1978), but the extent to which BOB relied on data from other investigations was not assesed in this report.

These 13 studies, most of which were sponsored by the U.S. Government (e. g., the National Institute of Allergy and Infectious Diseases (NIAID)) or academic institutions, involved about 13,000 cases of pneumococcal disease; one U.S. study alone involved 12,000 cases.

Determining the types of pneumococci that produce pneumococcal pneumonia is a difficult task for at least two reasons. First, there is no simple, inexpensive, and reliably accurate diagnostic technique that can be used to isolate and identify specific types of pneumococci in the lungs of persons with pneumococcal pneumonia. Second, in few, if any, epidemiologic studies are data collected in a manner that permits investigators to calculate for a defined population the rate of occurrence of new cases of pneumococcal pneumonia, i.e., the pneumococcal pneumonia incidence rate.

The problem in ascertaining which type of pneumococcus produces a given case of pneumonia is this: The most reliable diagnostic technique, which involves extracting pneumococci from the lung (transtracheal aspiration), is a difficult, expensive, and potentially harmful procedure; alternative techniques, though, have serious limitations and usually do not yield reliably accurate results. The latter include examining cultures of throat and sputum samples (simple and inexpensive, but itself an inaccurate indication of infection in the lungs), examining cultures of blood samples (simple, inexpensive, and accurate, but only when, as occurs in about 25 percent of pneumococcal pneumonia cases, a person has bacteremia), and assaying of antibodies in blood (dependent on skilled personnel and specific technology, expensive, and accurate only when a person has bacteremia).

If a reliable, accurate, inexpensive, and safe diagnostic technique for isolating pneumococci from the lungs of persons with pneumococcal pneumonia were available, epidemiologic studies to determine incidence rates of diseases produced by each type of pneumococcus could be conducted more easily and more accurately than they can be at present. A population could be defined (e. g., by age, geographical location, or disease state) and monitored for pneumococcal disease for a specified time period. Then the number of cases of pneumonia (or other types of pneumococcal infection) among the defined population caused by each of the 83 types of pneumococci could be determined. Annual incidence rates for diseases caused by each type of pneumococcus subsequently could be tabulated as follows:

Type of pneumocoocus	Incidence *rate* of pneumococcal pneumonia
Type 1	X cases per 100,000 persons per year
Type 8	Y cases per 100,000 persons per year

To date, thorough epidemiologic investigations to determine the incidence of pneumococcal pneumonia in the United States have not been conducted on a national basis. Furthermore, in some studies conducted at present, researchers do not identify or describe the base population from which they have extracted pneumonia cases and pneumococcal types. Pneumococcal pneumonia incidence rates, therefore, especially among specified populations such as the elderly, have not been possible to calculate.

Partly because of the low rates of occurrence of pneumococcal diseases in this country, U.S. epidemiologic studies of these diseases consist primarily of investigations of case reports. Such case reports are generated by investigators who select one of the diagnostic techniques described above, and identify and record the types of pneumococci they isolate from a selected group of pneumonia patients. Data from various epidemiologic studies are often not comparable. Because diagnostic techniques used to isolate and identify pneumococcal types vary dramatically, each study produces case reports based on different assumptions.

Notwithstanding these problems, BOB used epidemiologic studies as a basis for its decision, made jointly with the manufacturer, regarding the formulation of the currently licensed 14-valent pneumococcal vaccine. This formulation was based primarily on results from epidemiologic studies in which blood cultures of pneumococci and serum assays of pneumococcal antibodies were used to determine which types of pneumococci were present in patients with pneumococcal bacteremia and pneumonia.

Immunogenicity Studies

The immunogenicity of experimental pneumococcal vaccines was evaluated in 20 of the 26 studies on which BOB based its evaluation. Thirteen of the studies, were sponsored by industry, mostly by Merck Sharp and Dohme, and these studies involved about 4,000 subjects in foreign countries. In a study sponsored by NIAID, Austrian measured antibody responses in another 4,000 subjects in the United States.

Immunogenicity studies were conducted for each serotype of antigen in the 14-valent vaccine. The purpose of these studies was to ascertain the level of protective antibody production that was induced in persons receiving polyvalent polysaccharide pneumococcal vaccine. Overall, the vaccine produced a good antibody response in most subjects except those under 2 years of age. [2]

[2]Apparently, children under 2 years old have not yet fully developed an immune system that reacts sufficiently to polysaccharide antigens to produce consistently good antibody titers.

BOB used data from immunogenicity studies to help determine the efficacy of pneumococcal vaccine before, during, and after it was used in clinical trials. Its rationale for using such studies is this: If a vaccine does not produce good antibody response, it most likely will not protect an individual from a target disease.

Correlation between a quantifiable immunogenic response and a predictable level of protection has not yet been fully established for pneumococcal vaccine. For some vaccines, certain patterns of antibody responses can be correlated with some level of protection, but the minimum level of circulating antibodies necessary for protection against the target disease is not known. This situation applies to pneumococcal vaccine. Immunogenicity studies were included in some clinical trials of pneumococcal vaccine, and using data from these trials, BOB did attempt to correlate levels of pneumococcal antibody production with protection against pneumococcal disease. BOB's attempts at correlation continue today.

Clinical Trials

By law, BOB must require manufacturers to submit data from clinical trials to be used in its prelicensing evaluation of the safety and efficacy of new vaccines. The purpose of clinical trials of pneumococcal vaccines was to test the experimental vaccines' clinical safety and efficacy in defined human populations. The eight premarketing clinical trials on which BOB based its evaluation of the new polyvalent pneumococcal vaccine altogether involved about 43,000 U.S. and foreign subjects, including about 18,767 vaccinees (7,120 domestic, 11,647 foreign).3

[3]For a description of the methods and results of these premarketing clinical trials and other studies of experimental pneumococcal vaccine (excluding epidemiologic and immunogenicity studies), see app. 3.6.

Each clinical trial study population was divided into at least two groups: 1) an experimental group, which received the pneumococcal vaccine that was being evaluated; and 2) one or more control groups, which received either a placebo vaccine or a type of vaccine that differed substantially from the one being tested. In some studies, subjects were assigned to the experimental or control group on a random basis. Additionally, in some studies, subjects were paired on the basis of certain characteristics before being assigned to the experimental or control group. Furthermore, in some double blind clinical trials, neither the investigators nor the test subjects knew which vaccine was being administered to a given subject. The most ideal clinical trials were randomized, controlled, and double blind (Hales, 1979).

In clinical trials of pneumococcal vaccines, investigators observed subjects during a designated time period for adverse reactions and the presence or absence of disease. They then tabulated and analyzed data regarding the vaccine's safety and efficacy. Pneumococcal vaccine's relative safety was evaluated by measuring and comparing the incidence of acute adverse reactions in the experimental group with the incidence of similar reactions in the control group(s). Similarly, the vaccine's efficacy in most studies was determined primarily by measuring and comparing the incidence of pneumococcal pneumonia in the experimental group with the incidence in the control group(s).[4] To help assess efficacy in some trials, investigators also measured vaccinees' antibody responses to pneumococcal vaccine. Data generated in the trials were subjected to various types of statistical analysis.

[4]In one study, investigators measured the incidence of LRTI rather than pneumococcal pneumonia.

Appendix 3.6
REVIEW OF PREMARKETING CLINICAL TRIALS AND STUDIES BOB USED TO EVALUATE THE SAFETY AND EFFICACY OF POLYVALENT PNEUMOCOCCAL VACCINE

INDUSTRY-SPONSORED TRIALS

Merck Sharp and Dohme—Two South African Trials, 1973-76

From 1973 to 1976, Merck Sharp and Dohme (MSD) conducted two major clinical trials of pneumococcal vaccines among gold miners in South Africa (Smit, 1977). In the first trial, No. 315, investigators assessed the safety and efficacy of a 6-va]ent **polysaccharide vaccine (Types** 1, 2, 4, 8, 12, 25); in the second, No. 315A, they tested a 12-valent vaccine (Types 1,2,3,4,6,8,9,12,25, 51,56, 73).

Study No. 315.—In study No. 315, 983 subjects were given the 6-valent pneumococcal vaccine; 1,051 were given meningococcal A vaccine, and 985 were

given a saline (placebo) vaccine. The latter two groups served as controls. Subjects were randomly assigned to study groups, and all subsequent testing was done blindly, that is, without knowledge of the subjects' group assignment.

Researchers watched for the occurrence of pneumococcal pneumonia for about 24 months after immunization. Among subjects receiving pneumococcal vaccine who were studied for more than 2 weeks after vaccination, the attack rate of pneumococcal pneumonia was 9.2 cases per 1,000 persons. Among control subjects, the attack rate was 38.3 cases per 1,000 persons. The protective efficacy rate, that is, the percent reduction in type-specific pneumococcal pneumonia among those receiving pneumococcal vaccine, was 76 percent ($p < .001$).

Investigators also measured antibody responses to the pneumococcal vaccines. At least 74 percent of a subgroup of 40 subjects receiving pneumococcal vaccine developed antibodies to each type of pneumococcus represented in the vaccine.

To assess the incidence and nature of adverse reactions, investigators in study No. 315 observed vaccinees for 3 days following vaccination. Reported adverse reactions were minor. [1]

Study No. 315 A.—Study No. 315A was conducted in much the same manner as study No. 315. In study No. 315A, ***540*** subjects received a 12-valent pneumococcal polysaccharide vaccine; 585 received meningococcal A-C vaccine, and 550 persons received a saline (placebo) vaccine. Among subjects receiving the 12-valent pneumococcal vaccine, the attack rate of pneumococcal pneumonia was 1.8 cases per 1,000 persons, as compared to 22.0 cases per 1,000 persons in the control group. Thus, the protective efficacy rate was 92 percent ($p < .004$). At least 83 percent of those receiving pneumococcal vaccine developed antibodies to each of the 12 types of pneumococci represented in the vaccine. Again, the reported incidence of adverse reactions was low. [2]

In both of these Merck studies, informed consent was obtained from each participant. Miners who reported to the dispensary for medical attention were evaluated clinically for pneumococcal pneumonia, and if the clinical findings were positive, they were followed-up with chest X-rays and laboratory diagnostic work on serum and sputum samples. When indicated, medical treatment was provided.

Merck/Papua (Riley)—New Guinea Highlands Trial, 1973-76

From 1973 to 1976, I. D. Riley conducted a study of Merck's 14-valent vaccine (Types 1, 2, 3, 4, 5, 6, 7, 8, 12, 14, 18, 23, 25, and 46) in the New Guinea Highlands surrounding Papua (Riley, 1977). This study was cosponsored by Merck Sharp and Dohme, and the Papua Department of Public Health.

A total of 5,946 persons in Riley's study received the 14-valent pneumococcal vaccine; another 6,012 persons received a saline (placebo) vaccine and served as controls. Subjects' consent to participate was verified by thumbprint.

To assess morbidity in this study, investigators conducted bimonthly household surveys of half of the study subjects. Vaccinees were observed for the onset of pneumonia, which was diagnosed mostly clinically and, when possible, by X-ray.

Criteria used in this study to measure the difference in the incidence of pneumococcal pneumonia between vaccinees and controls were not as well defined as in Merck's two South African studies. To assess the incidence of morbidity, researchers in Riley's study used pneumonia or lower respiratory tract infection (LRTI) instead of type-specific pneumococcal pneumonia. Among the 5,373 people observed for morbidity for 16 months, 138 of the 2,660 observed control subjects developed LRTI, as did 114 of the 2,713 observed vaccinees. The difference in the incidence of LRTI between vaccinees and controls, therefore, was only 18 percent ($p < .05$).

In general, there was very little difference in vaccine-type pneumococcal isolation rates from among vaccinees and controls. Antibody responses were measured in 22 ,recipients of pneumococcal vaccine. A twofold increase in serum antibody titers, using prevaccination vs. postvaccination geometric mean titers, was demonstrated for 10 of **14** serotypes.

In the 3 years of this study, 303 subjects died—133 vaccinees and 170 control subjects. This was a 22 percent difference ($p < 0.05$). Forty-two percent (68) of the vaccinees and 55 percent (94) of the control subjects died from respiratory illnesses.

Vaccine-related side effects were studied only in the first 133 subjects receiving the pneumococcal vaccine; side effects were not reported for the control subjects. Of the 133 vaccinees observed for adverse reactions, 75 percent (98) reported no side effects, 42 percent (31) complained of a sore arm, 7 percent (9) complained of fever, and 3 percent (4) complained of a swollen arm. [3]

Merck Sharp and Dohme (Weibel)—Five Small U.S. Studies, 1967-77[4]

The results of five small studies that Merck conducted in the United States were reported by Robert

[1] See tables 7 and 8 in ch. 3.
[2] See tables 7 and 8 in ch. 3.
[3] See tables 7 and 8 in ch. 3.
[4] Merck studies reported by Weibel, No 384, No. 431, No. 454, No. 482, and No. 497, were not controlled clinical trials.

Weibel and associates (Weibel, 1977). Collectively, these five Merck studies, No. 384, No. 431, No. 454, No. 482, and No. 497, involved a total of 104 subjects.

All five were designed: 1) to measure the incidence of vaccine-related side effects to 12-valent (Types 1, *3, 4, 6, 8, 9, 12, 14, 19, 23, 51, 56)* or 14- valent (Types 1, 2, 3, 4, 6, 8, 9, 12, 14, 19, 23, 25, 51, 56) pneumococcal vaccines; and 2) to measure antibody titer responses.

In general, vaccine side effects observed in these studies were mild and local (redness, swelling or pain at injection site), but also quite common. Nearly all of the *42* vaccinated children and *86* percent of the 50 vaccinated adults reported some type of reaction. Most reactions began 4 hours after vaccination, About 40 percent of the children and 14 percent of the adults reported a mild fever (99° to 100.9° F). One child experienced headache, myalgia (muscle pain), and a maximum temperature of 104°F for 1 day; her local reactions lasted 5 days. [s]

[s]See tables 7 and 8 inch. 3.

FOREIGN-SPONSORED TRIALS

Chamber of Mines of South Africa (Austrian) —Three South African Trials, 1972-76

From 1972 to 1976, the Chamber of Mines of South Africa financed clinical testing of polyvalent pneumococcal vaccines among newly recruited workers in the East Rand Preparatory Mines in Boksburg, South Africa (Austrian, et al., 1976). Three major trials were conducted under the guidance of Robert Austrian, University of Pennsylvania, who tested two pneumococcal polysaccharide vaccines produced under NIAID contract by Eli Lilly: a 6-valent vaccine (Types 1,3,4,7, 8, 12) and a 13-valent vaccine (Types 1,2,3, 4, 6,7,8,9,12,14, 18,19, 25).

The three trials involved a total of 12,000 mine workers, assigned randomly to groups. About 4,000 received a pneumococcal vaccine; another 4,000 received a Group A meningococcal vaccine, and yet another 4,000 received a saline (placebo) vaccine. The major purpose of these trials was to assess the efficacy and safety of Lilly's 6- and 13-valent pneumococcal vaccines, using the meningococcal and saline vaccine groups as controls.

In one study, 1,493 subjects received the 13-valent pneumococcal vaccine; 1,527 received the Group A meningococcal vaccine, and 1,480 received the saline placebo. Vaccine recipients were observed for several months, and the incidence of putative pneumococcal pneumonia or pneumococcal bacteremia among them was recorded. Seventeen cases of pneumococcal pneumonia or bacteremia were diagnosed among recipients of the pneumococcal vaccine; 77 cases were diagnosed among recipients of the meningococcal vaccine, and 83 cases among recipients of the placebo. Based on these findings, the efficacy rate of the 13-valent pneumococcal vaccine was calculated to be 78.5 percent ($p < .0001$.)

Analyses of combined data from all three trials indicated that the vaccines tested had an overall *82.3* percent rate of efficacy against pneumococcal bacteremia caused by vaccine types of pneumococci, In other words, the incidence of pneumococcal bacteremia caused by serotypes of pneumococci represented in the vaccine was 82.3 percent lower among pneumococcal vaccinees than the incidence of such bacteremia among controls. The reported incidence of vaccine-related side effects was very low.[b]

[b]See tables 7 and 8 inch. 3.

U.S. GOVERNMENT-SPONSORED TRIALS

The National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) funded two major clinical trials of pneumococcal vaccine. In addition, NIAID Partially supported other small trials. Data from at least the two of NIAID-sponsored trials discussed below were used by BOB to evaluate the safety and efficacy of pneumococcal vaccine.

NIAID (Austrian)—San Francisco (Kaiser) Trial, 1975-77

Austrian, with the cooperation of Marvin A. Fried, conducted a large clinical trial involving 13,600 subjects 45 years of age and older enrolled in the Kaiser Permanence Health Plan in San Francisco, California (Austrian, et al., 1976). A total of 6,850 subjects received a 12-valent vaccine (Types 1, 3, 4, 6, 7, 8, 9, 12, 14, 18, 19, 23) produced by Eli Lilly, and 6,750 subjects received a saline placebo.

Data from this study have not been completely analyzed, so there is as yet no conclusive evidence from this study of this vaccine's efficacy in preventing pneumococcal pneumonia. Nonetheless, two findings can be reported. First, no cases of pneumococcal bacteremia caused by the serotypes represented in the vaccine were reported among vaccine recipients, whereas four such cases were reported among controls. Second, about 60 percent of those who received pneumococcal vaccine reported no adverse reactions, about 40 percent experienced discomfort or pain at the injection site, 35 percent developed redness at the injection site, and 3.4 percent developed a mild fever (Austrian, et al., 1976).[7]

NIAID (Ammann)—San Francisco (Univ. of Calif.) Trial, 1974-76

Arthur Ammann tested the safety and efficacy of a Lilly-produced 8-valent pneumococcal polysaccharide vaccine (Types 1, 3, 6, 7, 14, 18, 19, and 23) among children believed to be at high risk of contracting pneumococcal disease (Ammann, 1977). These children, who had either sickle-cell anemia or inadequate spleen function, were vaccinated at the University of California, San Francisco Medical Center.

Ammann administered Lilly's 8-va]ent pneumococcal vaccine to 96 high risk children: 77 patients with sickle-cell anemia and 19 with inadequate spleen function. He then measured and compared antibody responses to the vaccine among these unhealthy children with antibody responses elicited by the vaccine among 44 healthy children.

Ammann also immunized another 38 healthy young people and observed them specifically for adverse reactions. Further, during a 2-year postimmu - nization period, Ammann compared the incidence of pneumococcal infection among the 77 vaccinated sickle-cell patients with that among ***106*** unvaccinated sickle-cell patients.

Antibody titer responses to pneumococcal vaccine among the ***96*** high risk children were good and did not differ significantly from the responses among the 44 healthy children. Among the 77 sickle-cell patients, the mean fold increase in indirect hemagglutination titers (i. e., the postimmunization titer divided by preimmunization titer) ranged from ***1.65*** (Type 19) to 12.55 (Type 3). Among the 19 asplenic children, the corresponding mean fold increase in titers ranged from 1.46 (Type 19) to 18.36 (Type 3). Among both these groups of patients, a mean fold increase of ***2.00*** or more was recorded 3 to 4 weeks after immunization for six of the eight types of pneumococci represented in the vaccine. A mean fold in-. crease of ***2.00*** or more for six of the eight types also was recorded among both groups of patients 1 year after immunization.

The only adverse reactions Ammann found were local pain at the injection site and one case of brief fever ***(38 °C).*** During a 2-year postimmunization period, he found no cases of pneumococcal infection among the 77 vaccinated sickle-cell patients and eight cases among the 106 unvaccinated sickle-cell patients who served as controls.

Based on his results, Ammann's conclusions were that 1) the 8-valent pneumococcal polysaccharide vaccine stimulates type-specific antibody formation in patients with inadequate spleen function, 2) the vaccine may help reduce the incidence of pneumococcal infection in sickle-cell patients and 3) the vaccine produces very few adverse reactions.

[7] See tables *7* and *8* in ch. *3*.

Appendix 3.7
CDC'S PASSIVE, VOLUNTARY CASE REPORTING SYSTEM FOR MONITORING ADVERSE REACTIONS TO LICENSED VACCINES[1]

Introduction

Vaccinations are recommended and administered to millions of children and other individuals each year on the presumption that the benefits far outweigh the risks. The benefit side of the equation is straightforward: vaccinations can prevent serious disease. The risk side is not as straightforward, since it includes factors that are known and others that

[1] This appendix (apart from the title) is a verbatim reproduction of CDC's official written description of its system for monitoring and reporting adverse reactions to licensed vaccines.

may exist but have not yet been discovered. It is necessary, therefore, to maintain surveillance of potential risks of vaccination to continually reevaluate whether individual vaccinations are, on balance, good for people. Such surveillance is important, not only to provide potential vaccinees with accurate information about the consequences of vaccination, but also to stimulate improvements in the vaccination process or recommendations that will minimize or eliminate the risks.

The surveillance of these risks, or adverse reactions to vaccination, can be carried out actively or passively. In the active approach, systematic and intensive efforts are made to obtain reports of all adverse effects following vaccination. An example of this is a clinical field trial, required for licensure of a new vaccine. In the passive approach, a mechanism is established by which individuals may voluntarily report vaccine reactions. The active approach is comprehensive, but costly in terms of personnel time and other resources. The passive approach is not comprehensive, but it can be reasonably efficient at detecting severe and uncommon reactions without substantial expenditures of time and resources since it makes maximum use of existing reporting mechanisms and procedures.

The following discussion describes a passive system for monitoring adverse reactions to vaccination that should be used by all immunization projects. Included will be a form for reporting adverse reactions to the Center for Disease Control where a National Adverse Reactions Monitoring System will be maintained.

System Description

The system description will center around these topics:

- designation of adverse reaction coordinators,
- establishment of a reporting mechanisms,
- stimulation of reporting,
- Ž criterion for reporting, and
- • submission of reaction reports to CDC.

Designation of Adverse Reaction Coordinators

The responsibility for establishing an Adverse Reaction Monitoring System is that of each Immunization Project Office. The first step is to designate an individual on the Immunization Project staff to serve as System Coordinator. This individual will then be responsible for establishing the system in the Project area and for coordinating its operation.

In establishing the system, the first task of the System Coordinator should be to have Adverse Reaction Coordinators designated in each local health jurisdiction within the Project area. These could be individuals in county health departments or large public clinics. In addition, Adverse Reaction Coordinators should be designated in hospital emergency rooms wherever possible and representatives of the State and local medical societies and pediatric organizations should be invited to serve as liaison people to the system to promote the reporting of reactions from the private sector. (The establishment of these contacts can be delegated to the local coordinators.)

The designation of Adverse Reaction Coordinators will create a surveillance network which can be used to collect information about vaccine reactions and channel the reports to the points at which analysis can be carried out. These local Coordinators will have the specific responsibilities of implementing a reporting mechanism in their areas, of stimulating reporting by the public and local immunization providers, and of making sure that reports are submitted promptly and correctly to the Immunization Project Office. The System Coordinator in the Central Office may be the logical person to be responsible for monitoring all phases of the operation and for submitting reaction reports to the Center for Disease Control. Copies of the reports should be forwarded to the Regional Offices.

Establishment of a Reporting Mechanism

The next task of the System Coordinator is the establishment of a mechanism through which the public and immunization providers can easily report vaccine reactions. One possibility is the installation of a toll-free telephone which can be called without charge from anywhere within the Project area. Another possibility is the designation of local telephones in each health jurisdiction for receiving reaction reports. Both methods may be used conjointly.

The telephones should be attended during regular business hours by the designated Coordinator or other health professionnal. A supply of the form, "Report of Illness Following Vaccination" (Exhibit One),[2] should be kept near the telephone(s) so that reports can be documented on it directly. Consideration should be given to the use of tape recording units to handle calls made after hours.

Telephone communication should be the primary mechanism for receiving reaction reports in a Project Area. It may be supplemented, however, by a mechanism for receiving reports through the mail, primarily from immunization providers. This can be effected by supplying providers with the report form

[2] CDC's "Report of Illness Following Vaccination" form (Exhibit One) appears in this appendix as figure 3.7A.

(Exhibit One) and business reply envelopes. Another possibility is the inclusion of a line for reporting vaccine reactions on the morbidity report form used in the Project area. Such reports would be followed up to obtain the more detailed information required.

Stimulation of Reporting

To be effective, the mechanism for reporting vaccine reactions must be made known to the public and to the public and private immunization providers. The stimulation of reporting, therefore, is an important responsibility of each Adverse Reaction Coordinator.

Where it is used, the "Important Immunization Information" statement provides a basic means of stimulating reporting since i t must contain a name or telephone number for reporting adverse events following vaccination. In addition, when the "Important Immunization Information" statement is explained to parents, the importance of being alert to possible reactions and using the telephone number to report any that occur should be emphasized specifically.

Ongoing efforts should be made to encourage reporting by the immunization providers themselves, especially in the private sector. This may be done by advertising the toll-free, or other, telephone number in the periodic newsletters that go from the State Health Department to physicians. Also, the "Report of Illness Following Vaccination" form may be reprinted in such a newsletter or in newsletters published by the respective medical organizations.

An important aspect of stimulating reporting by providers is feedback from the system. Providers should always be consulted when reaction reports are received from their patients. Also, any interesting analyses of reports should be shared with providers (through mechanisms like communicable disease newsletters) to show what happens to the information that they provide to the system.

Some use of the news media may be considered to promote reporting, but care should be taken not to overplay the negative aspects of the immunization process. In this context, the Adverse Reaction Monitoring System can be cast in a positive light as cooperative effort between parents and providers to maintain "quality control" in the immunization process. In general, the best use of the media will be low-key, but ongoing.

Criterion for Reporting

The types of reaction reports to be expected will include those that are obviously unrelated to vaccination, those that are known to be vaccine-related, and those that may or may not be currently recognized as vaccine-related. One important purpose of the Adverse Reaction Monitoring System is to detect previously unrecognized vaccine reactions. It is desirable to screen from the system reactions that are known to be insignificant. For this purpose, the following criterion for documenting reported reactions on the "Report of Illness Following Vaccination" form has been established: Only those *reactions* that are *serious enough to require hospitalization or a visit to a physician or public health facility are to be reported.* One qualification to this rule should be observed: *Any reaction involving only soreness, red*ness *or swelling at the point* of *injection should not be reported even if a physician was visited.*

Submission of Reaction Reports to CDC

All reaction reports, meeting the above criterion, that are generated at any point in the surveillance network should be collected centrally in the Immunization Project Office and submitted to the Center for Disease Control at the beginning of each month. The reports should be sent to:

The Center for Disease Control
Attn: Surveillance& Assessment Branch
Immunization Division, BSS
1600 Clifton Road
Atlanta, GA 30333

The reports that **are** *sent to the Center for Disease Control must not contain any information that would identify the individual involved.* The "Report of Illness Following Vaccination" form is designed as a two-part carbonized record in which the CDC copy does not contain any individual identification fields. If the form is not available in this format, the draft form shown in Exhibit One may be used, provided that the fields identifying the individual are removed. This may be done by photocopying the original report and cutting off, or masking, the top two lines. The original report should be kept on file in the Immunization Project Office. The System Coordinator may be the logical person to be responsible for seeing that all reports are submitted promptly and properly, according to the instructions shown in Exhibit One. Any reports alleging death as a result of vaccination should be telephoned immediately to the Immunization Division of the Center for Disease Control at (404) 329-3071. After hours, call (404) 923-4226.

The Immunization Division will maintain a computerized file of all reports. Crude adverse reaction rates will be determined and special analyses will be made of unusual reactions and clusters. Quarterly, the Immunization Division will send to each Immunization Project a report, showing a line listing and tabulation of all reports submitted by the Project and a national summary of reactions reported from all

Projects. This will assist projects in the analysis of accumulated reports.

At the national level, the Center for Disease Control will collaborate with the American Medical Association and the American Academy of Pediatrics to promote the reporting of vaccine reactions by private physicians. Also, cooperative arrangements with vaccine manufacturers and other Government agencies, like the Food and Drug Administration, will be sought to obtain vaccine reaction reports received by them. In this way, it is hoped that the Adverse Reactions Monitoring System will become a definitive source of information about the risks of vaccination.

Figure 3.7A-CDC'S "Report of Illness Following Vaccination" Form and Guidelines for Completion (Exhibit One)

Guidelines for Completing the "Report of iliness Folloing Vaccination"

1. **The "Report of Illness Following Vaccination" form should be completed if and only if the reaction was severe enough to require hospitalization or a visit to a physician or public health facility.**
2. **Reactions involving only soreness, redness or swelling in the immediate vicinity of the injection should not be reported even if a physician was visited.**
3. **Most of the items on the form are self-explanatory. The following ones may need some explanation:**

PATIENT Section

State: A two-digit code (see attachment).

Report *Number;* Each report should be assigned a number, serially, from 0001 through 9999.

VACCINES Section

Enter the date the vaccinations were given. Check the type of provider and enter the name on the line underneath. Then record, in the spaces below, all the vaccines given on that date.

Type: Type of vaccine, e.g., DTP, Td, polio, influenza, measles-mumps-rubelia, etc.

***Manufacturer;* Vaccine manufacturer, e.g., Merck, Sharp & Dohme, Merrell-National, Wyeth, Parke-Davis, Lederle, Connaught, etc.**

Lot *Number:* Vaccine lot number, recorded on vaccine vial or important Immunization information Statement.

***Route:* Subcutaneous (SC), intramuscular (IM), intradermal (ID), Oral (0) or Unknown (U).**

Method: Needle & Syringe, Oral, Jet Gun, Unknown.

Site: Left arm, right thigh, buttocks, etc.

Note: For orally administered vaccines, enter "O" on the **Route" line and leave the "Method" and "Site lines blank.**

PREVIOUS HISTORY Section

In each box, enter "Y", "N" or "U" for "Yes", "No" or "Unknown," respectively.

4. **After 7 days, a follow-up enquiry should be made to determine the condition of the patient. Enter the date and the results of the enquiry in the "7-Day Follow-Up" Section. Additional comments should be recorded on a separate sheet and attached to the report form.**
5. **Accumulated reports should be submitted at the end of each month. The top copy should be retained by the Reporting Agency. The bottom copy should be sent to:**

Center for Disease Control
Attn: Immunization Division
Surveillance & Assessment Branch
1600 Clifton Road
Atlanta, GA 30333

Forms should not be sent until the follow-up is complete. However, if follow-up has not been completed within 30 days after the initial report, forms should be submitted without completing the "7-Day Follow-Up" Section.

6. **In the case of a death allegedly resulting from a vaccination, call the Center for Disease Control immediately at (404) 329-3071.**

(Suggested Prototype)

REPORT OF ILLNESS FOLLOWING VACCINATION

PATIENT

Date of Birth: ☐☐☐☐☐☐ (mo dy yr) Sex: M F State: ☐☐ Report Number: ☐☐☐☐

County of Residence: _____ Date of Report: ☐☐☐☐☐☐ (mo dy yr)

REPORTING SOURCES

Patient's Physician: _____ Phone: ☐☐☐-☐☐☐-☐☐☐☐ (a.c. exc. num.)

Physician's Address: _____

Person Making Report: _____ Phone: ☐☐☐-☐☐☐-☐☐☐☐ (a.c. exc. num.)

VACCINES

Vaccination Date: ☐☐☐☐☐☐ (mo dy yr) Provider: ☐ Public ☐ Private ☐ Military ☐ Other

Below, enter all vaccines given on the above date. Name of Provider: _____

Vaccine:	#1	#2	#3	#4
Type				
Manufacturer				
Lot Number				
Route				
Method				
Site				

ILLNESS

Onset Date: ☐☐☐☐☐☐ (mo dy yr) Diagnosis: _____

Brief Description of Illness: _____

_____

Hospitalized: YES NO UNK If Yes, Name of Hospital: _____

Laboratory Results: _____

PREVIOUS HISTORY

❑ Previous Illness or Reaction to Vaccination ❑ educations Taken

❑ History of Convulsions in Patient ❑ History of Convulsions In Family

Describe: _____

7 DAY FOLLOW-UP

Date: ☐☐☐☐☐☐ (mo dy yr) Condition: ☐ Recovered ☐ Partial Recovery ☐ Ill ☐ Death

Comments: _____

Record additional comments on a separate page and attach to this form.

CDC COPY

(Suggested Prototype)
REPORT OF ILLNESS FOLLOWING VACCINATION

PATIENT

Patient Name: _____ Phone: ☐☐☐-☐☐☐☐

Patient Address: _____

Date of Birth: ☐☐☐☐☐☐ (mo dy yr) Sex: M F State: ☐☐ Report Number: ☐☐☐☐

County of Residence: _____ Date of Report: ☐☐☐☐☐☐ (mo dy yr)

REPORTING SOURCES

Patient's Physician: _____ Phone: ☐☐☐-☐☐☐-☐☐☐☐ (a.c. exc. num.)

Physician's Address: _____

Person Making Report: _____ Phone: ☐☐☐-☐☐☐-☐☐☐☐ (a.c. exc. num.)

VACCINES

Vaccination Date: ☐☐☐☐☐☐ (mo dy yr) Provider: ☐ Public ☐ Private ☐ Military ☐ Other

Below, enter all vaccines given on the above date. Name of Provider: _____

Vaccine:	#1	#2	#3	#4
Type				
Manufacturer				
Lot Number				
Route				
Method				
Site				

ILLNESS

Onset Date: ☐☐☐☐☐☐ (mo dy yr) Diagnosis: _____

Brief Description of Illness: _____

_____

Hospitalized: YES NO UNK If Yes, Name of Hospital: _____

Laboratory Results: _____

PREVIOUS HISTORY

☐ Previous Illness or Reaction to Vaccination ☐ Medications Taken

☐ History of Convulsions in Patient ☐ History of Convulsions in Family

Describe: _____

FOLLOW-UP

Date: ☐☐☐☐☐☐ (mo dy yr) Condition: ☐ Recovered ☐ Partial Recovery ☐ Ill ☐ Death

Comments: _____

Record additional comments on a separate page and attach to this form.

REPORTING AGENCY COPY

Appendix 4.1
FACTORS THAT CAN AFFECT CONSUMERS' AND PHYSICIANS' USE OF VACCINES

Factors That Can Affect Consumers' Vaccine-Seeking Behavior

> ***The demands of this poor public are not reasonable, but they are quite simple. It dreads disease and desires to be protected against it. But it is poor and wants to be protected cheaply . . . What the public wants, therefore,*** *is* ***a cheap*** *magic charm to prevent, and a cheap* ***pill or potion to cure, all*** *disease . . .*
>
> *Thus it was really the public and not the medical profession that took up uaccination with irresistible faith . . .*
>
> George Bernard Shaw
> ***The Doctors Dilemma***
> **1911**

The American public's enthusiasm for vaccines may have declined since Shaw's time. Research has demonstrated that public demand for vaccines now depends on such factors as the public's general attitudes concerning the dangers of specific diseases and benefits of vaccination, beliefs regarding the safety and efficacy of a particular vaccine, and the convenience of being vaccinated (Glasser, 1958; Clausen, 1954; Rosenstock, 1959; Deasey, 1956). (See figure 4.1 A.) Researchers also have identified demographic variables that can be correlated with vaccine-seeking behavior (ORC, 1978; Rosenstock, 1959, Pearman, 1978). As discussed below, the cost of vaccination may also influence public demand for vaccines (Luft, 1978).

Investigations to identify factors that affect the public's demand for vaccines began in the 1950's, when researchers attempted to identify the factors that were influencing the demand for polio vaccine. In 1959, Rosenstock and associates used the findings of six studies to help explain why people were not seeking vaccination against poliomyelitis (Rosenstock, 1959). Rosenstock divided behavioral factors into two major categories: 1) personal readiness factors, and 2) social and situational factors. The first category includes personal attitudes that may affect an individual's willingness to seek vaccination: a) perceived personal susceptibility to a particular disease (includes perceived likelihood of local occurrence of the disease), b) perceived seriousness of the disease, and c) perceived safety and efficacy of the vaccine. The second category, social and situational factors, includes: a) social pressure and b) convenience of vaccination. In one of his studies, Rosenstock concluded (Rosenstock, 1959):

> Readiness and social factors may operate with a degree of independence of each other or they may interact . . . The evidence to date suggests, that among the currently unvaccinated, personal readiness to obtain poliomyelitis vaccination is so weak that rather strong social supports may be needed to modify their behavior in the short run. Education for increased personal readiness can probably be effective.

A more recent study, entitled *Public Attitudes Toward Immunization: August 1977 through February 1978*, was conducted for the Center for Disease Control (CDC) by Opinion Research corporation (ORC). [1] The purposes of **ORC's Public survey were (ORC) 1978):**

1. To determine the relationships between individuals' past experiences with immunizations and their desire to receive, or have their children receive, other immunizations.
2. To establish baseline data regarding:
   - Consumers' desire to receive specific immunizations;
   - Consumers' belief in likelihood of a disease occurring in their local area;
   - Consumers' belief in the seriousness of a disease;
   - Consumers' belief in their vulnerability to a disease;

Figure 4.1A.— Factors That Can Affect Consumers' Vaccine-Seeking Behavior

Personal readiness factors
- Perceived susceptibility to a disease
- Perceived likelihood of local occurrence of a disease
- Perceived seriousness of a disease
- Perceived safety and effectiveness of the vaccine

Social and situational factors
- Social pressure
- Convenience
- Demographic characteristics

Vaccine costs and health insurance

SOURCE: OTA's interpretation of data from Rosenstock, 1959; ORC, 1978; Luft, 1978.

[1] ORC's study was developed and funded by CDC's Bureau of Health Education (BHE) under HEW contract No. 200-77-0723. Reprint requests for that report should be addressed to BHE, CDC, in Atlanta, Ga., not to ORC.

- Consumers' belief in the safety and efficacy of various vaccines; and
- The effect of local laws and regulations on consumers' acceptance of vaccines.

Data from ORC's study appear to verify, at least in part, Rosenstock's findings in the late 1950's regarding the importance of selected factors that influence consumers' vaccine-seeking behavior. First, people must be convinced of a reasonable likelihood that a disease is going to occur in their local area and that they are susceptible to the disease. (Sometimes, individuals perceive themselves, at times falsely, to be protected from a given disease.) Second, people must be convinced that a disease is serious, Third, people must be convinced of at least the safety, if not the efficacy, of a vaccine before they will tend to accept it.

Using a multivariate statistical analysis, ORC attempted to predict the intent of respondents to seek vaccination for themselves and their children. Intent is difficult to predict and has not yet been statistically correlated with actual future behavior, but in its analysis, ORC did identify at least a few important discriminating variables. (See table 4.1 A.) These variables are beliefs or events that may influence a person's decision to seek or avoid vaccination. By themselves, these variables cannot be used to predict a person's behavior; however, they do indicate the basis on which consumers' decisions will likely be made. (ORC researchers did not attempt to study interactions among these discriminating variables or the potential influences of such interactions on people's behavior. They did recommend, however, that an analysis of interacting variables be included in future research.)

Those attempting to mount a successful vaccination program probably should consider all factors identified in Rosenstock's and ORC's investigations. Launching a television campaign to educate people about the evils of disease and virtues of vaccines, for example, probably would show little return on investment, if a community's biggest obstacle to an im-

Table 4.1A.—Factors (Discriminating Variables) That Influence ORC-Surveyed Consumers' Vaccine-Seeking Behavior

Factor (discriminating variable)[a]	P value	Type of vaccine: Diphtheria	Tetanus	Polio	Smallpox	Asian flu	Influenza B	Swine flu	Total number of vaccines
1. Race	< .05	X	—	X	X	X	X	X	6
	< .10	—	—	—	—	—	—	—	0
2. Perceived *likelihood* of local occurrence of disease	< .05	X	X	X	X		—	X	5
	< .10	—	—	—	—	—	—	—	0
3. Perceived personal *susceptibility* to the disease (includes prior case of, or immunization for, the disease)	< .05	—	—	X	X	X	X	X	5
	< .10	X	X	—	—	—	—	—	2
4. Perceived *safety* of the vaccine (includes prior adverse reaction experience)	< .05	—	—	X	X	X	—	X	4
	< .10	—	—	—	—	—	—	—	0
5. Perceived *seriousness* of the disease	< .05	X	—	—	X	—	—	X	3
	< .10	—	—	—	—	—	—	—	0
6. Household income	< .05	X	—	X	X	—	—	—	3
	< .10	—	—	—	—	—	—	—	0
7. Sex	< .05	—	X	—	—	—	—	X	2
	< .10	X	—	—	—	—	—	—	2
8. Age	< .05	X	—	—	—	—	—	—	1
	< .10	—	—	—	—	—	—	—	0
9. Education	< .05	—	—	—	—	—	—	—	0
	< .10	—	X	—	—	—	—	—	1
10. Belief in mass immunization programs	< .05	—	—	—	—	—	—	—	0
	< .10	—	—	—	—	—	X	—	1
Total number of factors	< .05	5	2	5	6	3	2	6	—
	< .10	2	2	0	0	1	1	0	—

[a]Factors (discriminating variables) found in ORC's survey are listed in descending order according to the number of vaccines per factor.

SOURCE: OTA's interpretation of data from *Public Attitudes Toward Immunization: August 1977 Through February 1978.* Opinion Research Corporation, 1978 (See ORC, 1978.)

munization program is a lack of public transportation. Likewise, funding a worksite immunization program might be futile, if the intended vaccine recipients do not perceive the vaccine as beneficial. Another factor that might be considered in mounting a vaccination program is the cost of vaccination to vaccine recipients.

Personal Readiness Factors

As noted above, personal readiness factors were divided in the system of classification of factors developed by Rosenstock into the following major categories: a) perceived susceptibility to a disease (which includes perceived likelihood of local occurrence of the disease), b) perceived seriousness of a disease, and c) perceived safety and efficacy of the vaccine (Rosenstock, 1959). Rosenstock's categories are used to classify various researchers' findings in the discussion below.

PERCEIVED SUSCEPTIBILITY TO A DISEASE AND PERCEIVED LIKELIHOOD OF LOCAL OCCURRENCE OF A DISEASE

Many people who did not seek polio vaccination during the 1950's believed they were at low risk of contracting poliomyelitis (Glasser, 1958). Many adults, for example, apparently perceived themselves to be at low risk for contracting polio, because most polio vaccine campaigns were targeted at children.In general, the advertising of high risk target populations tended to reinforce perceptions of safety from polio among individuals not identified as being at high risk. As Rosenstock stated, "It is known that behavior is determined more by one's beliefs about reality than by reality itself, and that people vary markedly in their interpretation of reality" (Rosenstock, 1959).

Results reported by ORC regarding the importance of interviewees' "perceived susceptibility to disease" and "perceived likelihood of local occurrence of disease" are shown in tables 4.1B and 4.lC. As shown in table 4.1A, at the 95 percent level of confidence, perceived personal susceptibility to a disease and perceived likelihood of local occurrence of a disease share equally the second most significant degree of discriminating power. At the 90 percent level of confidence, perceived susceptibility appears to be the most important variable.

PERCEIVED SERIOUSNESS OF A DISEASE

One important influence on an individual's willingness to seek protection from a disease is that person's belief about the seriousness of the disease. In 1959, a study commissioned by the National Foundation for Infantile Paralysis showed that those adults (mostly men) who believed that polio was milder in adults than in children tended not to be vaccinated (Rosenstock, 1959).

As shown in table 4.1A, in ORC's survey, perceived seriousness of disease ranks as the fifth most discriminating variable. Data from ORC's survey regarding the perceived seriousness of diseases for

Table 4.1 B.—ORC Interviewees' Perceptions of Their Personal Susceptibility to Particular Diseases

"For the following disease, please tell *me ho w likely you think it would be that you might* **catch** *it if it occurred extensively in your local area. "*

	Percent of ORC interviewees responding			
	"Very likely"	"Some chance"	"Very likely"	"Some chance"
Disease	February 1978 N = 2,080		August 1977 N = 2,006	
Asian flu	10%	51%	10%	44%
Influenza B	10%	47%	9%	44%
Swine flu	10%	43%	8%	37%
Diphtheria	7%	19%	5%	21%
Mumps	5%	23%	5%	19%
Pertussis	5%	20%	4%	18%
Measles	5%	21%	5%	17%
Tetanus	4%	23%	4%	24%
Rubella	4%	20%	5%	18%
Typhoid	4%	18%	6%	19%
Smallpox	4%	17%	4%	15%
Rabies	3%	24%	5%	23%
Polio	2%	15%	4%	16%

SOURCE: *Public Attitudes Toward Immunization: ...ust 1977 Through Febru·ary 1978,* Opinion Research Corporation, ...'8. (See ORC, 1978.)

Table 4.1 C.—ORC Interviewees' Perceptions of the Likelihood of Particular Diseases' Occurring in Their Local Area

"For each disease, please tell *me how likely it will be that each will occur in your local area during the next 12 months. "*

	Percent of ORC interviewees responding			
	"Very likely"	"Some chance"	"Very likely"	"Some chance"
Disease	February 1978 N = 2,080		August 1977 N = 2,006	
Measles	26%	49%	29%	47%
Mumps	20%	50%	20%	50%
Influenza B	19%	46%	16%	42%
Rubella	19%	45%	21%	40%
Asian flu	15%	52%	14%	43%
Swine flu	14%	40%	10%	33%
Pertussis	8%	28%	8%	31%
Tetanus	7%	31%	11%	32%
Rabies	7%	31%	6%	34%
Smallpox	5%	16%	5%	18%
Diphtheria	5%	12%	3%	14%
Polio	4%	19%	5%	21%
Typhoid	4%	14%	3%	13%

SOURCE: *Public Attitudes Toward Immunization: August 1977 Through Febru·ary 1978,* Opinion Research Corporation, 1978. (See ORC, 1978.)

adults are displayed in table 4.lD. Five diseases, polio, rabies, typhoid, smallpox, and tetanus, were perceived as very serious for adults by 50 percent or more of the respondents in at least one of the two surveys. No type of flu was perceived as very serious by a majority of the respondents in either survey: Swine flu was perceived as very serious by an average of 32.4 percent, Asian flu by an average of 21.5 percent, and influenza B by 15 percent.

With few exceptions, ORC survey respondents generally perceived the diseases that they believed to be the most serious as the diseases least likely to occur in their local area and as the diseases they would be least likely to contract. Polio, rabies, typhoid, and smallpox, for example, were perceived as the four most serious diseases, but also as the four diseases respondents believed they were least likely to contract. Contrastingly, most respondents perceived "flu" to be among the least serious diseases, but also the disease most likely to occur in respondents' local area and most likely to be contracted by respondents.

PERCEIVED SAFETY AND EFFECTIVENESS OF THE VACCINE

An individual's belief about the safety and effectiveness of a vaccine may influence that person's decision to seek vaccination as much as does the individual's perception regarding either personal susceptibility to, or seriousness of, a disease. Three studies have documented the significance of an individual's doubt about the safety and effectiveness of polio vaccine as a major reason for the individual's unwillingness to receive this vaccine (Clausen, 1954; Deasy, 1956; Glasser, 1958).

In 1978, Pearman reported the results of a household survey (N = 342) designed to assess the willingness of the public to participate in future influenza immunization projects, especially in light of the negative image of the swine flu program (Pearman, 1978). In the aggregate, 52 percent of respondents in this survey had participated in the swine flu program; 59 percent anticipated participating in a future immunization program if convinced that a flu outbreak was pending; and 53 percent thought people should take flu shots. Although approximately half of the respondents generally favored flu shots; 24 percent thought people should not take flu shots; and 25 percent said they would not participate in future programs.

As shown in table 4.1A, in the ORC study, perceived vaccine safety ranks as the fourth most discriminating variable. ORC researchers reported the data displayed in tables 4.lE and 4.lF regarding the perceived safety of vaccines. Overall, respondents in ORC's study perceived vaccines as relatively safe: About 90 percent perceived vaccines as either very or moderately safe. (See table 4. IE.) ORC survey respondents with lower incomes (less than $5, 000 per year), respondents with less than a high school education, and nonwhite respondents tended to doubt the safety of vaccines more than their richer, better educated, and white counterparts did. Nearly 32 percent of the respondents felt that some specific vaccines were unsafe or a threat to one's health; about 57 percent said that there were not specific vaccinations which they felt were unsafe. (See table 4.1F.)

Long-term effects of the highly publicized adverse reactions to swine flu vaccine on the public's use of

Table 4.1D.—ORC Interviewees' Perceptions of the Seriousness of Particular Diseases

"For each of the following diseases, please tell me how serious you think it would be if an adult caught it."

Disease	Percent of ORC interviewees responding "Very serious" February 1978 N = 2,080	August 1977 N = 2,006
Polio	68%	64%
Rabies	63%	61%
Typhoid	51%	49%
Smallpox	51%	47%
Tetanus	47%	49%
Diphtheria	41%	38%
Rubella	36%	36%
Mumps	31%	32%
Swine flu	29%	36%
Measles	26%	28%
Pertussis	23%	21%
Asian flu	20%	23%
Influenza B	15%	15%

SOURCE: *Public Attitudes Toward Immunization: August 1977 Through February 1978*, Opinion Research Corporation, 1978. (See ORC, 1978.)

Table 4.1E.—ORC Interviewees' Perceptions of the General Safety of Immunizations

"In general, how safe do you think vaccinations and immunizations are?"

Degree of safety of immunizations	Percent of ORC interviewees responding February 1978 N = 2,080	August 1977 N = 2,006
Very safe	54%	51%
Moderately safe	36%	37%
Somewhat safe	5%	6%
Not safe at all	1%	1%
Don't know	4%	4%
No response	—[a]	1%

[a]Less than .5%.

SOURCE: *Public Attitudes Toward Immunization: August 1977 Through February 1978*, Opinion Research Corporation, 1978. (See ORC, 1978.)

Table 4.1 F.—ORC Interviewees' Perceptions of the Safety of Specific Immunizations

"Are *there any specific vaccinations or immunizations which you fee/ are unsafe or a threat to one health? Which ones?"*

Response	Percent of ORC interviewees responding February 1978 N = 2,080	August '1977 N = 2,006
Yes (major mentions)	320/~ (N = 733)	36% (N=722)
Swine flu	59°4	78%
Flu (nonspecific)	300/o	110/0
Asian flu	30/0	3%
Smallpox	30/0	—a
No	570/0	54%
Don't know	**10°/0**	90/0
No response	1%	**10/0**

[a]Less than 5%

SOURCE *Public Attitudes Toward Immunization August 1977 Through February 1978*, Opinion Research Corporation 1978 (See ORC 1978)

future vaccines are not known. A major influence on public behavior may be the amount and types of information about the safety and efficacy of a vaccine that is presented to a person before vaccination. The Department of Health, Education, and Welfare (HEW) may require that vaccine recipients be informed of vaccine safety and efficacy through patient information sheets (and possibly, patient informed consent forms) before they are vaccinated in any publicly financed immunization program. The impact of the provision of vaccine safety and efficacy information on individuals' vaccine-seeking behavior is unknown. The Food and Drug Administration (FDA) plans to expand the use of PPIs and to study the effects of their use on several factors, including patients' drug-consuming behavior and physicians' drug-prescribing behavior. Vaccines could be included in FDA's studies.

Social and Situational Factors

As noted above, Rosenstock **divided social and situational factors that can affect consumers'** vaccine-**seeking behavior into two categories: a) social pressure, and** b) convenience (Rosenstock, 1959). Rosenstock and others (e. g., Pearman, 1979; ORC, 1978) also have attempted to measure the influence of demographic characteristics on public demand for vaccines.

SOCIAL PRESSURE

Analyses of some data indicate that an individual's decision to seek vaccination maybe influenced by the social pressures applied by other persons who are important to that individual. Belcher showed in one community that people who held presumably respectable positions (e. g., school teachers, ministers, and physicians) effectively encouraged individuals to seek vaccination against polio (Belcher, 1958). Glasser verified the potential influence of physicians on people's vaccine-seeking behavior (Glasser, 1958).

CONVENIENCE

As stated by Rosenstock, "For any individual with a degree of readiness to be vaccinated, the ultimate decision will be facilitated the more convenient, simple, and inexpensive the action is" (Rosenstock, 1959). In this context, convenience includes such factors as travel time and distance, hours of operation, and acceptability of the facilities in which vaccination is performed.

Validating Rosenstock's findings that both social pressure and convenience are important influences on people's vaccine-seeking behavior, Pearman's study showed that employed men, more often than women, stated that they received swine flu shots because: (Pearman, 1978)

1. Shots were available at their work place (convenience factor).
2. Coworkers pressured them to take shots (social pressure).
3. They perceived participation in immunization to be company policy (social pressure).

DEMOGRAPHIC CHARACTERISTICS

Both Pearman and Rosenstock found a positive relationship between an individual's amount of formal education and his or her participation in vaccination programs (Pearman, 1978; Rosenstock, 1959). In general, both of these investigators found that the more formal education a person completes, the more positive a person tends to be about immunization.

With the exception of race, ORC researchers found demographic factors to be much less discriminating than interviewees' perceptions of personal susceptibility to disease, seriousness of disease, and vaccine safety (ORC, 1978). At the 95-percent level of confidence, household income was more discriminating than sex, age, or level of education. (See table 4.1 A.) At the 90 percent level, sex was slightly more discriminating than income, age or education.

Vaccine Costs and Health Insurance

The effect of the cost of vaccination for the consumer on the public's use of vaccines has not been assessed in any study published to date. In general, the cost of vaccination is low relative to the costs of many other types of medical procedures. The average fee for administering a vaccine in a private physician's office in 1978 has been estimated by the Office

of Technology Assessment (OTA), to be $6.47 (Schieber, 1976; CMA, 1969).[2] Product costs add another $.50 to $5 per dose, depending on the vaccine (Risky, 1978; Beck, 1978).[3] In a publicly financed immunization program, vaccinations can be performed either free-of-charge or at a reduced cost for the consumer. It should be noted that, while the price of a single vaccination may be low, for large families, the price of a series of vaccinations could be substantial.

The extent to which health insurance carriers pay for vaccinations is unknown. Typically, health insurance plans pay for the costs associated with the diagnosis and treatment of medical problems. Most plans, however, do not pay for the provision of preventive services such as vaccinations.

In the public sector, for example, Medicare, specifically excludes payment for immunizations to prevent disease:[4]

> **Immunizations.—Vaccinations or inoculations are excluded as "immunizations"** unless they are directly related to the treatment of an injury or direct exposure to a disease or condition, such as antirabies treatment, tetanus antitoxin or booster vaccine, botulin antitoxin, antivenin sera, or immune globulin. In the absence of injury or direct exposure, preventive immunization (vaccination or inoculation) against such diseases as smallpox, polio, diphtheria, etc., is not ***covered.*** (Flu injections are administered as a preventive measure and are excluded from coverage without regard to a patient's particular susceptibility to influenza.) In cases where a vaccination or inoculation is excluded from coverage, the entire charge should be denied,
>
> (Medicare *Carriers Manual*, paragraph C, section 2050.5C, 2050 services and supplies, 2050.5 drugs and biological)

Medicaid may or may not pay for immunizations, depending on the discretion of a particular State. Immunizations are not a service mandated by the Federal Government as a condition for State participation in the Medicaid program. Presumably, the Federal Government jointly finances immunizations with those States that include vaccinations in their Medicaid benefit packages. Another federally mandated health program, Early and Periodic Screening, Diagnosis and Treatment (EPSDT), designed to pay for preventive health services for Medicaid beneficiaries under 21 years old, does not pay for immunizations. A program designed to replace EPSDT, the Child Health Assessment Program (CHAP), if enacted by Congress, would pay for immunizations.

The extent of coverage for vaccinations by either commercial health insurance companies or Blue Cross and Blue Shield is not known. According to a Health Insurance Survey in 1977, 20 of the 28 companies responding offered coverage for some types of preventive services (Jones, 1978; Lutins, 1978). No data indicate the percentage of policies or insurers with preventive coverage. Most companies do not cover immunizations (Jones, 1978; Lutins, 1978). Likewise, individual Blue Cross/Blue Shield plans may cover preventive services in some of their contracts, but the number of people with such coverage is unknown (Buckley, 1978; Mitchner, 1978). A Safeco health insurance plan marketed in California and Washington State and the Blue Shield- Blue Cross Plan for New Jersey both include immunizations as services to be covered by primary care providers reimbursed in a prospective capitalization payment mechanism (Fairity, 1978).

The extent to which vaccinations are provided by health maintenance organizations (HMOs) is also unknown. Theoretically, HMOs have financial incentives to immunize their members, because the cost of vaccination usually is much less than the cost of treating a preventable infectious disease. Factors such as turnover of members (due to mobility and choice of plans), however, may reduce the benefits to HMOs of providing immunizations. The Health Maintenance Act Amendments of 1976 mandate the provision of specific preventive services, but the use of vaccines is excluded. An HMO may offer supplemental health services, including vaccinations, at its own discretion.

No major study has examined the effect of insurance coverage on the extent to which people seek vaccination. Results from investigations into the effect of insurance coverage on ambulatory care services (Roemer, 1975) and preventive services (Luft, 1978), however, may help to predict the relationship between insurance coverage and vaccine use. Briefly, these studies show that, in general, insurance coverage positively influences the demand for ambulatory and preventive services. In general, although data are mixed, enrollees in HMOs probably use preventive services more than do those insured in fee-for-service insurance plans (Luft, 1978).

Factors That Can Affect Physicians' Provision of Vaccines

In a discussion of physician-induced demand for medical care, Harvard economist Jerry Green wrote: (Green, 1978)

> Looking for the effects of availability on the utilization of medical resources is similar to tracking the abominable snowman. The evidence is fragmentary,

[2] See ch. 4.

[3] See app. 4.5 for further discussion of the prices of vaccines for public programs and private physicians.

[4] Whether the Medicare law should be amended to permit reimbursement for preventive vaccinations is an issue discussed in ch. 6. Amending the Medicare law is a policy option presented in ch. 7.

and though the search is exciting and fraught with danger, no one is quite sure what to do were the beast ever confronted face to face.

To some, this statement may reflect the state-of-the-art of efforts to explain how and why physicians prescribe the treatments and use the procedures that they do. Just as the behavioral research literature is bountiful with attempts to describe the behavior of health care consumers, it is filled with descriptions of selected physician behaviors. Some researchers offer theories based on economics (Green, 1978); others offer explanations based on professional motives; and still others use explanations driven by malpractice concerns.

Unfortunately, few studies have analyzed the factors that determine physicians' prescribing of vaccines. Certain factors that may influence such behavior are shown in figure 4.lB. The factors shown in this figure are basically the same factors that affect consumers' vaccine-seeking behaviors, but are presented from the perspective of the physician. The first three items reflect concern for a patient's health status; the fourth, concern for the patient's economic status; and the last two, concern for the physician's own liability and economic status.

Factors that physicians may consider in assessing a given patient's need for a particular vaccine include these:

1. The likelihood of the patient's being exposed to a particular disease-producing organism.
2. The patient's vulnerability to the disease once having been exposed to the organism.
3. The extent to which contracting the disease will disrupt the patient's life.

Sometimes, physicians' decisions to vaccinate individuals are mandated. Most States, for example, have mandated the administration of certain vaccines to children entering public schools.[5] Similarly, the Federal Government mandates the use of vaccines for travelers to and from certain countries with endemic diseases.

Evans has theorized that physicians consider the ability of their patients to pay for a medical procedure or use of a technology before prescribing it (Evans, 1974). The effect of this factor on the use of vaccines is not known. The factor may be of minor concern, because of the low cost of vaccines. As discussed above, however, most health insurance carriers do not pay for vaccinations, so in most cases, the cost is assumed directly by the vaccinee.

Physicians derive their knowledge and attitudes about a given disease or a certain vaccine from multiple sources. (See figure 4.1C.) The risks and benefits of vaccination against certain diseases—measles, rubella, diphtheria, mumps, typhoid, polio, and tetanus—have been known for many years. Physicians often learn about vaccination against these diseases in their formal training. In addition, the epidemiology and potential harm of these diseases have been studied for many years, so physicians have large data bases to use in deciding whether or not to vaccinate their patients. For other diseases, such as pneumococcal pneumonia, data bases are limited, and physicians must often speculate about a given patient's risk of contracting the disease and need for vaccination. For data regarding new vaccines, as well as new data regarding old vaccines, physicians rely largely on contemporary sources of information, such as professional literature, Government publications, peers, and vaccine manufacturers. In spite of widespread communications and product advertising among physicians, their acceptance of vaccines, particularly new ones, can be quite slow (Pantell, 1979).

An increased level of awareness about vaccine-related injury (e.g., Guillain-Barre Syndrome (GBS) caused by swine flu vaccine, and polio caused by poliovirus vaccine) possibly has influenced physicians' use of vaccines for two reasons. First, adverse reactions obviously influence the welfare of the vaccinee, and potential injuries may alter the benefit-risk ratio of certain types of vaccinations for some people, at least in the minds of their physicians. New concern about the potential dangers of pertussis (whooping

Figure 4.1 B.— Factors That Can Affect Physicians' Provision of Vaccines

- Attitudes and knowledge about targeted diseases
- Attitudes and knowledge about the safety and efficacy of certain vaccines
- Perceptions about a patient's need for vaccination
- Consideration of a patient's ability to pay for vaccination
- Consideration of revenue generated by vaccination
- Consideration of the potential liability for vaccine-related injury

Figure 4.1C.— **Sources of Information That Physicians Receive About Vaccines**

- Formal medical school and postgraduate training
- Contemporary professional literature and texts
- Peers
- Government publications
- Vaccine manufacturers
- Formal continuing education programs
- Personal experiences of their patients

[5] See table 17 in ch. 5.

cough) vaccine, for example, has led to a sharp decline in its use in England. [b]

Second, in this era of mounting malpractice liability problems, some physicians may be hesitant to administer vaccines that are known to be more dangerous than others, especially when vaccination is perceived to be of marginal benefit to a particular patient. Physicians' liability for vaccine-related injury rests on at least two responsibilities:

1. To warn the vaccinee about potential adverse reactions[7]
2. To administer the vaccine without negligence.

Increased public awareness of vaccine-related injury could increase physicians' vulnerability to legal action. An increased risk of being sued could impede physicians' use of vaccines in general.

[b]Unfortunately, the decline in pertussis vaccine use has led to a substantial increase in the incidence of whooping cough. Some authorities believe the dangers of this disease are more worrisome than the side effects of the vaccine

[7]In three major court cases, *Davis v. Wyeth, Reyes v. Wyeth,* and *Givens v. Lederle,* however, the duty to warn obligation has been assigned to the vaccine manufacturer, In the swine flu program, the duty to warn obligation was assumed by the Federal Government. Topics related to vaccine liability issues are discussed in chs. 5, 6, and 7 of this report.

Appendix 4.2
THE IMPACT OF FEDERALLY FINANCED STATE AND LOCAL IMMUNIZATION PROGRAMS ON THE INCIDENCE OF MEASLES (1962-78)

Federal Support of State and Local Measles Immunization Programs

By *1962,* licensed vaccines in the United States included vaccines to prevent four major childhood diseases—polio, diphtheria, whooping cough (pertussis), and tetanus. Probably as a result of vaccine use, the incidence of these diseases had been decreasing. Some authorities, however, believed that national levels of protection against these diseases were too low; levels of protection were especially low among lower income groups not reached by the private sector fee-for-service health care delivery system (Lemke, 1977). Responding to these concerns, in *1962,* Congress passed the Vaccination Assistance Act, which authorized the Federal Government to provide financial assistance to States for the specific purpose of implementing vaccination programs to help prevent these four diseases.

Children at the time remained unprotected against one prevalent childhood disease for which no vaccine had yet been licensed—measles. About 3.5 million cases of measles occurred annually (Sencer, 1973). This disease is often mild and usually not fatal, but sometimes causes deafness and other neurological disorders. When not prevented, measles results in substantial loss of school days and significant use of medical resources (Sencer, *1973).*

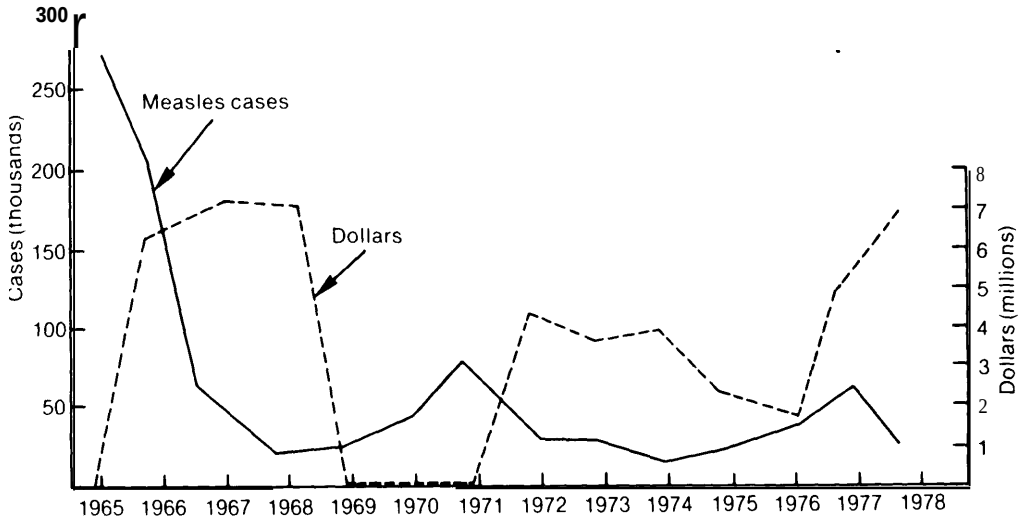
In *1963,* the Federal Government licensed an American pharmaceutical company, Merck Sharp and Dohme, to produce and sell a measles vaccine in the United States. Two years later, Congress passed the Community Health Services Extension Amendments of 1965, which added measles to the list of diseases which the Federal Government was seeking to prevent through the provision of Federal funds for State vaccination programs. Between early 1963 and the middle of 1966, approximately 15 million children were vaccinated with the new measles vaccine, and the incidence of reported cases of measles dropped by about **50** percent (Sencer, 1973). (See figure 4.2A.)

Based on this success, in 1966, the Public Health Service (PHS) launched a national campaign to eliminate measles from the United States. This campaign, which was coordinated by the Center for Disease Control (CDC) with the support of professional and voluntary health organizations, emphasized community immunization programs. in 1967 and 1968, the Federal Government spent about $14.5 million to control measles in the United States. (See figure *4.2A.)* Approximately 11.7 million doses of measles vaccine were distributed, and the incidence of measles dropped from an estimated **900,000** cases in 1967 to 250,000 cases in 1968 (Sencer, *1973).*

For fiscal years *1969* and 1970, Congress authorized no Federal funds for community immunization programs. Apparently, the lack of Federal funds for such programs substantially curtailed the distribution of measles vaccine. During these **2** years, only 9.4 million doses of measles vaccine were distributed, and the number of measles cases rose from 290,000 cases in 1969, to 533,000 in *1970,* to *847,000* in 1971 (Sencer, 1973).

Because of the rising incidence of measles, and possibly, because proportionately fewer children in poverty areas than children in nonpovert y areas were

Figure 4.2A—Measles Cases[a] and Federal Grant Funds[b] Obligated for Measles Control Programs in the United States by Year (1965 .78)[c]



[a]Calendar year
[b]Fiscal year
[c]1978 data provisional
SOURCE Center for Disease Control, Bureau of Immunization 1978

being vaccinated, Congress passed the Communicable Disease Control Amendments of 1970. Under this legislation, Federal appropriations for State and local immunization programs targeted against the five diseases mentioned above and rubella (German measles) were authorized for fiscal years 1971 and 1972. Apparently, Congress believed that when Federal assistance for community immunization programs was cut back, the levels of national protection against targeted communicable diseases decreased, and that a resumption of Federal assistance might improve national levels of protection. This perception, at least in the case of measles, proved to be accurate. In 1971 and 1972, the Federal Government provided about $8 million to the States to enable them to re-establish their immunization programs. (See table 4.2A.) During this period, 16.5 million doses of measles vaccine were distributed (Sencer, 1973), and the estimated incidence of measles dropped from **847,000** cases in 1971 to about 400,000 cases in **1972. (See** figure 4.2A.)

Based on the success of this 1971-72 program, Congress passed the Communicable Disease Control Amendments Act of 1972, which detailed the State assistance program for immunizations. Under this legislation, Federal funds for grants to States, inducting separate amounts for measles programs, were authorized through fiscal year ***1975*** (Lemke, ***1977).*** Congress continued to authorize Federal funding for immunization programs by enacting the National Consumer Health Information and Health Promotion Act of 1976, under Title 11, Disease Control Amendments of 1976. This act extended and expanded the Federal Government's program of grants to States for disease control. Current immunization programs operate under its provisions and authorizations.

Since 1972, the inversely proportional relationship between the amount of Federal grant funds obligated for measles control programs and the incidence of measles has continued. Federal spending for measles control declined from about $4 million in 1972 to slightly less than $2 million in ***1976;*** correspondingly, the number of reported cases of measles rose from about **31,000 in 1972,** to **39,000 in 1976, to 60,000 in 1977. (See** figure 4.2A.) Federal spending for measles control rose continually throughout 1977 and nearly reached $7 million in ***1978;*** the incidence of measles began to drop substantially during the last 3 months of 1977, and reported measles activity (number of cases) during the first 26 weeks of 1978 was approximately 40 percent of that reported for the corresponding time period in 1977 (U.S. Ex. Br., CDC, MMWR, 1978).

Three factors probably contributed to this most recent decline in the incidence of measles. First, because measles activity rose during the period 1974-77, fewer children were left susceptible to the disease. Second, the total number of doses of measles vaccines administered in public clinics during 1977 in-

creased 52.8 percent from 1976. Third, several States enforced school immunization laws requiring that children have adequate documentation of measles vaccination in order to enter or stay registered in school .

State Use of Federal Funds for Immunization Programs

During the past 40 years, the Federal Government has legislated hundreds of programs in health, education, manpower, and social welfare. Federal funding for such programs was particularly made available during the late 1960's and early 1970's. Many of the programs were created through categorical grant mechanisms whereby Federal funds are given to State and local health agencies.

Some authorities believe that the largely unplanned and uncoordinated proliferation of narrow categorical programs, in some instances, can reduce the flexibility needed at the State and local levels to meet the comprehensive needs of individual citizens (Price, 1978). In spite of a possible lack of coordination and loss of flexibility among Federal, State, and local government agencies, however, most States have managed to implement some types of public vaccination programs.

As reported in **1976 by the Association of State and** Territorial Health Officials (ASTHO), in 1974, 41 State health agencies supported identifiable immunization programs; most States included some immunization services in their general communicable disease programs (ASTHO, 1976). Most immunization programs, as well as programs for general communicable diseases and venereal diseases, were targeted primarily to women and children.

One State that operates an effective measles control program is Oregon (Francis, 1978). This State has combined a mandatory routine measles vaccination program for all children entering public schools with a comprehensive measles surveillance program. In addition, it has established a measles containment program to vaccinate susceptible individuals who have been exposed to a newly discovered measles case. A key element of Oregon's successful program is a combined State-county effort to continually assess the levels of immunity to measles among children entering public school. In addition to cooperation between State and county health departments, two other key elements of Oregon's measles control program are: 1) strictly enforced school immunization laws, and 2) an ongoing assessment of all programs to identify and correct problems. During a 5-year period of this program's operation, from 1971 to 1976, the percent of entering first-grade students with a history of measles or measles vaccination (i. e., who were immune to measles) rose from **76.5** percent to 92.2 percent.

Alan Hinman described the measles control program in the State of New York from 1963 through 1971 (Hinman, 1972). According to Hinman, termination of Federal financial assistance can terminate a State's commitment to a public immunization program, leading to an unanticipated rise in the incidence of a disease thought to be under control. When Congress stopped funding measles control programs in **1969,** Hinman noted, the State of New York did likewise, shifting State funds to rubella control programs. As a consequence, the number of measles immunizations in New York State public clinics dropped from 258,232 in 1968 to **180,187** in **1970;** subsequent to this drop in measles immunizations, the incidence of measles in New York rose from 4.14 cases per 100,000 persons in 1970 to 11.08 cases per 100,000 persons in 1971. Hinman believes that measles control requires a strong continuous commitment from the Federal Government.

The history of measles control in this country clearly demonstrates a relationship between increased Government financing for mass immunization and reduced incidence of disease. It strongly suggests that continued long-term Federal financing of State and local immunization programs is needed to effectively control certain communicable diseases.

Appendix 4.3
HISTORICAL CONTEXT OF COST-EFFECTIVENESS ANALYSIS

Historical Background

From the early 1900's, laws in the United States required statements of costs and benefits for river and harbor projects. Later such statements were required for flood-control projects. The political climate during the 1930's supported governmental undertakings to which benefit-cost analysis (BCA) applied. Pigou provided a theoretical underpinning by contrasting private costs and benefits with social ones, and the shortsighted view of individuals with the longer perspective of government and society (Pigou, **1965).**

The popularity of benefit-cost studies dates from the late 1950's (Klarman, 1974), and through the mid-1960's the most common subjects were water and transport projects (Prest, 1965).

In the early 1960's, two developments stimulated the Federal Government's interest in the application of cost-effectiveness analysis (CEA) in the health sector. As part of its planning, program, and budgeting (PPB) approach, the Defense Department adopted the use of cost-effectiveness analyses in 1961 (Klarman, 1974), and in 1965, President Johnson extended PPB to all Federal agencies (Wildavsky, 1966). Concurrently, benefit-cost and cost-effectiveness studies appeared in the health field. The first ones concerned mental health, tuberculosis, and polio—medical areas in which the Government had traditionally been involved (Fein, 1958, Weisbrod, 1961).

The mid-1960's and the introduction of Medicare marked a substantial extension of governmental activities in this field, beyond public health to individual medical care. The Department of Health, Education, and Welfare (HEW) applied cost-effectiveness analysis to compare the payoffs from programs to control certain medical problems: cancer of different parts of the body, syphillis, motor vehicle accidents, arthritis, and alcoholic driving, early detection of handicaps among children, and childhood tooth decay. Some of the results led to Legislation: The 1967 Social Security Amendments provided for early detection and treatment of children with handicaps (Grosse, 1972).

Analyses of Preventive Services

The public health literature distinguishes among three kinds of preventive services: 1) primary, which prevent occurrence of a disease; 2) secondary, which detect and treat incipient disease; and 3) tertiary, which deal with rehabilitation during the advanced stages of a disease. All are preventive in the sense of altering the ordinary progression of disease (Mausner, 1974).

Pneumococcal vaccine and other immunizations fall into the category of primary prevention; they are intended to prevent the very occurrence of disease. The Office of Technology Assessment's (OTA) 1979 CEA of vaccination to help prevent pneumococcal pneumonia is presented in chapter 4.[1]

Previous studies indicate both the applicability of CEAs and BCAs to preventive services and the diversity of acceptable methodologies. More important for policy implications, these studies illustrate that the application of preventive technologies is not *ipso facto* cost-saving. Many of the findings of these studies suggested that a specified preventive technology would be cost-effective or yield net benefits under certain circumstances. These circumstances, however, are often the very substance of policy decisions and include choices among: 1) alternative programs (e.g., treatment of a disease after it occurs, use of one or another preventive technology, different use of the same preventive technology); 2) rates of use (e. g., different acceptance rates by the target population, different rates resulting from public or private initiatives); and 3) target populations (e.g., different age groups, those with certain pre-existing medical conditions, females or males, blacks or whites).

An example of primary prevention, influenza vaccination has been the subject of both cost-effectiveness and benefit-cost analyses. Kavet conducted a BCA in which he used epidemiologic data for an estimate of death attributed to influenza (Kavet, 1972). Recognizing the variability of certain factors, Kavet constructed alternative calculations for different efficacy rates, vaccination rates, high risk and non-high risk groups, and degrees of severity of the annual influenza outbreaks. The livelihood approach was taken to value years of life and working years saved; average earnings were used to convert these years to dollars. Kavet's analysis indicated that net benefits of influenza vaccination for the high risk group exceeded those for the non-high risk group. Redirecting influenza vaccines to high risk recipients therefore would raise net benefits.

Building on Kavet's work, Klarman and Guzick performed a CEA of influenza vaccination for people more than 65 years old, an age group in which everyone is considered high risk (Klarman, 1976), In this analysis, a vaccination program was compared to the existing situation of partial vaccination (19 percent) of the aged. Existing vaccinations were taken into account, and estimates of lower costs per life-year gained were derived. In recognition of the great variability in influenza incidence from year to year, a composite year in the 1960's was taken as the basis for the calculations. The authors used an intermediate approach between the livelihood estimates of BCA and life-year equivalents of CEA. They did not impute a dollar value to life years saved, but like Kavet, they did value days of sickness or death averted (as distinct from the deaths themselves) in dollars by using average earnings. Thus, their calculations of cost per death averted ($3,237 to $7,241) and cost per life year gained ($311 to $696) referred to net costs reduced $11 billion to $16 billion (or 25 to 44 percent) by the loss in earnings that would be averted by a vaccination program.

[1] The potential utility and application of OTA's analysis are discussed in chs. 6 and 7.

The analysis of a swine influenza program by Schoenbaum, McNeil, and Kavet also drew on Kavet's original work (Schoenbaum, 1976). Analysts in this study used the benefit-cost framework and valued mortality and morbidity by average earnings. With 70-percent efficacy of the vaccine and IO-percent probability of an epidemic, the net benefits of a public vaccination program would have been greatest for the high-risk group, if vaccination rates were between 24 and 59 percent. With higher vaccination rates, a public program would attain maximum net benefits if targeted to people 25 years and older. A program for the general population had the lowest cost per case averted ($65), but the highest cost per life year saved ($13,000). A program for the high-risk population alone had the highest cost per case averted ($410), but the lowest cost per life year saved ($1,000).

Other studies of vaccines have been in the realm of BCAs, in which mortality and morbidity averted are valued by livelihood measures. As early as 1961, Weisbrod analyzed costs and benefits connected with polio vaccine (Weisbrod, 1961). Weisbrod in this study pioneered in devising methodology that has since been widely used in analyses of medical technologies, preventive and treatment alike. Among other things, he stressed the importance of including costs of a vaccination program in the calculations. The subject of Weisbrod's analysis, however, was not the use of the vaccine, but return on investment in the research that generated that vaccine.

In another study, Schoenbaum and his colleagues compared alternative strategies for rubella vaccination and concluded that vaccination of females at age 12 (either with or without vaccination of both sexes at age 2) would yield greater net benefits than the existing policy of a single vaccination at an early age (Schoenbaum, 1976). These results held for both 100-percent and 80-percent vaccination rates.

Sencer and Axnick calculated one element of a BCA of rubella vaccination; the social costs of a rubella epidemic (Sencer, 1973). These researchers, however, did not include in their calculations such costs as the treatment of side effects and the cost of vaccination.

More recently, Merck Sharp and Dohme (MSD) has developed a framework for benefit-cost studies of pneumococcal vaccine (Beck, 1978). Here it is noteworthy that the methodology used by MSD resembles that of Sencer and Axnick in including only a partial list of crucial variables. Excluded, for example, are side effects of the vaccine and efficacy rates below 100 percent.

Cost-effectiveness and benefit-cost analyses of secondary preventive technologies abound. Schweitzer and Luce explored the cost-effectiveness of Pap smears to detect cervical cancer (Schweitzer, 1978). Eddy considered the cost-effectiveness of screening for various cancers: breast, cervical, colon, lung, and bladder (Eddy, 1978). Other evaluations include the cost-effectiveness of the stool guaiac, a test for colon cancer, and the benefit-cost of phenylketonuria (PKU) screening, a test for a genetic deficiency (Neuhauser, 1976, Steiner, 1973).

The study of hypertension by Weinstein and Stasson represents not only a very thorough analysis of a technology, but also, in many respects the extent of the development of the cost-effectiveness methodology (Weinstein, 1977). The effect specified in this analysis was quality-adjusted life years (QALYs), an index developed for weighting years of life and years of illness. Both screening for hypertension and its treatment (secondary prevention) were considered. Findings from Weinstein and Stasson's analysis of hypertension suggested that, given a fixed budget, stress on improving adherence to the treatment regimen —at least on cost-effectiveness grounds—be preferable to screening for this disease. Also, the cost-effectiveness of treatment for males and females showed a different relationship with age: For females, the cost-effectiveness ratio declined with advancing age; the reverse was true for males—a reflection of age differences between the sexes in strokes and heart attacks.

Another example of CEA studies include Klarman's analysis of syphillis control (Klarman, 1965). There he attempted to value the intangible element of the disease, in that case the stigma of having syphillis, and used psoriasis as an analogous disease for estimation.

Treating chronic kidney disease can be considered tertiary prevention. Treatment may tide the patient over to transplantation or dialysis itself may lengthen or improve life. Studies of these modalities agree that home dialysis is more cost-effective than center dialysis (Klarman, 1968, Strange, 1978). As noted previously, with new data on survival, the views of transplantation changed from the 1968 to the 1978 study .

Appendix 4.4
VALUES ASSIGNED TO SELECTED VARIABLES IN OTA'S COST-EFFECTIVENESS ANALYSIS OF VACCINATION AGAINST PNEUMOCOCCAL PNEUMONIA

The assumptions, rationales, and data sources used to develop values assigned to **8** of the 12 variables used in the cost-effectiveness analysis in chapter 4 are described in this appendix. Variables described below include: 1) QALY weighings, 2) discount rate, 3) cost of vaccination, 4) percent of pneumonia that is pneumococcal, **5)** percent of pneumococcal pneumonia caused by the 14 types of pneumococci represented in the licensed pneumococcal vaccine, 6) vaccine efficacy rate 7) side effects associated with use of the vaccine, and 8) duration of immunity. The remaining four variables, i.e., rate of pneumonia death, rate of decline for pneumonia deaths, rate of hospital cases of pneumonia, and rate of ambulatory visits for pneumonia, are not discussed in this appendix. Data sources for these four variables are cited in chapter 4.

QALY Weighings

In OTA's cost-effectiveness analysis in chapter 4, the measure quality-adjusted life years (QALYs) was used to quantify the effects of a pneumococcal vaccination program. QALYs are a measure recently developed to quantify, in common measurable units, changes in health status resulting from a reduction or an increase in years of illness or life expectancy. As noted in chapter 4, QALYs incorporate rankings of different disability states in terms of their relationship to complete health, on the one hand, and death, on the other. Thus, for example, on a scale where a year of complete health is ranked 1 and death is O, a year of minor illness might rank as .9, and a year of serious illness might rank as .2.

Weighings of different disability states used to calculate QALYs can be developed by asking people, "Taking into account your pain and suffering immobility, and lost earnings, what fraction of a year of life with a specific disability would you be willing to trade in order to spend the remaining fraction of the year disability-free?" (Weinstein, **1977).** If, for example, an individual would be willing to give up a quarter of a year of life with stomach ailments in order to have three-quarters of a year of life disability-free, then a year of life with stomach ailments would rank as .75.

Very little work has been done in the area of developing weighings of different disability states that reflect more than the subjective evaluations of one or two individuals. An exception, however, is the empirical work done by Bush, Chen, and Patrick (Bush, 1973; Patrick, 1973). By asking groups of students and medical professionals to rank various states of functional disability, these investigators have developed a number of social indexes of changes in health status and quality of life.

QALY weighings used in OTA's cost-effectiveness analysis of pneumococcal vaccination were based on the weighings of particular disability states that Bush, Chen, and Patrick derived from a survey of students in their analysis of a phenylketonuria (PKU) screening program (Bush, 1973). Selected rankings of the 30 levels of functional disability that were differentiated in this analysis are presented in table 4.4A.

In the base case analysis, weighings used to calculate QALYs were as follows: a year of total health was valued at 1; a year of nonbed disability, .6; **a** year of bed disability, .4; and death, O. The .6 value

Table 4.4A.—Selected Rankings of Functional Disability States Derived From a Survey of Students by Bush, Chen, and Patrick

Functional status			
1	2	3	Weight[a]
Traveled freely	Walked freely	Performed major and other activities	1.000
Confined to house	Walked freely	Performed self-care, but not major activity	.594
Confined to house	In bed or chair	Performed self-care, but not major activity	.534
In hospital	In bed or chair	Performed self-care, but not major activity	.428
In hospital	In bed or chair	Required assistance with self-care	.343
Death	Death	Death	0.000

[a]The weightings of functional disability states derived by Bush, Chen, and Patrick are probably the best quality scale currently available These weightings, however, are a value rather than a utility function They have not been subjected to the probabilistic tests, based on probabilities of different combinations of health states, required of a true utility function (Shepard, 1979)

for nonbed disability is the value Bush, Chen, and Patrick derived for disabilities that confine a person to home. The .4 value for bed disability is an intermediate value between the values they derived for hospital-bed disabilities and home-bed disabilities. With nonbed disability valued at .6 and total health valued at 1, eliminating nonbed disability would improve quality of life by .4 (l-.6); eliminating bed disability would improve quality of life by .6 (l-.4).

Two sets of values for weighings used to calculate QALYs in the sensitivity analysis were derived: 1) by using the square root of each of the weights used in the base case (i. e.,= and=); and then 2) by using the square of each weight (i. e., $(.4)^2$ and **(.6)2). Use** of the square root of each weighting made the vaccine slightly less cost-effective, and use of the square of each weighting made vaccination slightly more cost-effective. [1]

To quantify the effects (i.e., changes in morbidity and mortality) of pneumococcal vaccination in terms of QALYs, an initial assumption was made that a single day was worth 1 /365 the value of a year. Thus, for example, a day of perfect health was assumed to be worth 1/365 the value of a year of perfect health. Similarly, the value of a day of serious illness was assumed to be worth 1/365 that of a year of serious illness.

Projections were made of the reduction in days of pneumococcal pneumonia morbidity that would result among the vaccinated population. Then excess days of pneumococcal pneumonia morbidity among the unvaccinated population were multiplied by the weighings discussed above. In the base case, excess nonbed-disability days among the unvaccinated were multipled by .4, and excess bed-disability days were multipled by .6. In the sensitivity analysis, one time, excess nonbed-disability days were multiplied by $\sqrt{.4}$ and excess bed-disability days by $\sqrt{.6}$; another time, they were multiplied by $(.4)^2$ and $(.6)^2$, respectively. To produce QALY equivalents, weighted days of excess pneumonia morbidity were then divided by 365.

To convert into QALYs both the effect of vaccine side effects and the effect of illnesses not prevented by pneumococcal vaccination among vaccinees in extended years of life, the same general approach, weighings, and assumptions described above were used. To estimate the latter effect, individuals whose lives were extended by vaccination were assumed to have the same average number of disability days per extended year of life as other individuals in their age group,

[1]See table 4.4 in ch. 4.

Discount Rate Applied to Costs and Effects Occurring After 1978

Cost-effectiveness ratios for pneumococcal vaccination that OTA calculated in chapter 4 were based on a one-time, hypothetical pneumococcal vaccination program conducted in June **1978.** Many of the costs and effects of the hypothetical program would not be realized in **1978,** but would occur in subsequent years. In the base case analysis, these costs and effects were discounted at the rate of 5 percent. In the sensitivity analysis: 1) a 10-percent discount rate was used; and then 2) no discount rate was used.

Discounting (i.e., valuing future costs and effects at less than their present worth) is a standard economic procedure. The practice of discounting the costs of public programs usually is based upon two related rationales. First, discounting takes into account social time preference, reflecting the fact that individuals generally would prefer to receive benefits now rather than in the future. Second, discounting takes into account the social opportunity costs of capital, reflecting the fact that money invested in a public program could have been invested in a private enterprise and received a real rate of return (e. g., interest).

Much has been written on discounting procedures, but there is still no consensus on the most appropriate method for selecting a discount rate. In the base case analysis of pneumococcal vaccination in chapter **4,** costs and effects occurring after 1978 were discounted at a 5 percent rate, because this rate was believed to be a fairly accurate reflection of the societal discount rate. The 10-percent rate used in the sensitivity analysis is the rate that the Office of Management and Budget (OMB) recommends for discounting the costs of Government projects (U. S., Exec. Off. Pres., OMB, 1971). The effects of using no discount rate were calculated in the sensitivity analysis for purposes of comparison.

One of the conflicts in economics literature concerns the appropriate discount rate to use for costs and effects when the social opportunity cost of capital and the social time preference rate diverge, due to taxes and market imperfections. In OTA's analysis in chapter 4, effects of pneumococcal vaccination were discounted at the same rate as costs. [2]

[2]It may be quite rational for the discount rates applied to costs and QALYs to be different, and for some programs to be delayed as a result. Many existing Federal programs technically could have been implemented long ago, but were not thought by the Congress to be sufficiently worthwhile in relation to their costs. As a society becomes more affluent, its members are probably willing to spend more to save (or "buy") one QALY; therefore, a program that is not sufficiently cost-effective to be implemented now may be worthwhile in the future.

This approach was used to maintain a constant trade-off between dollars and life years (Weinstein, 1977). Theoretically, if a program's effects are not discounted at the same rate as its costs, the program's cost-effectiveness can be improved simply by delaying the program's starting date.[3]

The assumption of constant costs was made throughout OTA's analysis. Discount rates used in both the base case and the sensitivity analysis were net of inflation.

Cost of Vaccination

The cost of each pneumococcal vaccination was calculated by adding the retail cost of a dose of pneumococcal vaccine to a medical fee for administering a single dose. In the base case, it was assumed that pneumococcal vaccinations would be administered through the private sector at a total cost per vaccination of $11.37. The cost of each dose of pneumococcal vaccine was assumed to be $4.90, the price charged in the private sector by Merck Sharp and Dohme (Beck, 1978). The medical fee for administering each dose through the private sector was assumed to be $6.47. OTA derived this cost from the California relative value scale for injections, in which the charge for an injection is half the charge for a limited-examination followup visit (CMA, 1969). The charge for a limited-examination followup visit was estimated to be $12.97, an amount that is a 1978 update (reflecting changes in the consumer price index (CPI)) of the prevailing Medicare charge for such a visit in 1975 (Schieber, 1976).

In the sensitivity analysis, it was assumed that pneumococcal vaccinations would be administered through a public immunization program at a total cost per vaccination of $3.45. Under a mass public immunization program, with State or local governments buying pneumococcal vaccine in large quantities, the cost per vaccine dose very likely would be less than the cost in private sector. Fewer middlemen such as wholesale drug houses and pharmacists would be involved, manufacturers' packaging and distribution costs would be lowered, and manufacturers would be better able to time production with sales. For the sensitivity analysis, the cost of each vaccine dose was estimated to be about half the cost in the private sector, $2.45. This estimate was based on the average difference in prices charged to private physicians and to public programs for other vaccines, including influenza, measles, mumps, and rubella (Chin, 1978; Beck, 1978).[4] The medical fee for administering each vaccine dose would be less under a public immunization program, because pneumococcal vaccinations could be performed in large numbers; special clinics could even be used to administer the injections. In the sensitivity analysis, the cost of administering each dose of pneumococcal vaccine through a public immunization program was assumed to be $1,00, the estimated per dose cost of administering vaccines in other public vaccination programs (Hinman, 1978).

Percent of Pneumonia That Is Pneumococcal

A number of researchers have attempted in various hospital and ambulatory settings to determine the percentage of pneumonia cases that are caused by pneumococcal organisms (Roden, 1978). In many studies, percentage estimates have been derived directly from the isolation rates of pneumococci, i.e., from the percent of pneumonia cases in which pneumococci are isolated. Because of the problems discussed below, however, estimates based solely on pneumococcal isolation rates maybe unreliable.

Pneumococci can be isolated and identified by any one of three procedures: 1) blood tests, [5]2) transtracheal aspiration (lung puncture), or 3) sputum culture (throat culture). Each method has drawbacks. When pneumococci are found in the blood of patients with pneumonia, a diagnosis of pneumococcal pneumonia can accurately be made. Pneumococci enter the bloodstream, however, in only about 25 percent of persons with pneumococcal pneumonia, in those with severe cases of pneumococcal bacterenua. Blood tests, therefore, cannot be used to diagnose pneumococcal pneumonia in the approximately 75 percent of pneumonia patients whose pneumococcal infections are not bacteremic. Transtracheal aspiration can be used to diagnose pneumococcal pneumonia more accurately, but lung puncture is a potentially risky, unpleasant, and costly procedure. Sputum culture is an easier and more commonly used method of isolating pneumococci, but a number of authorities have questioned the reliability of this method—especially when used alone— in diagnosing pneumococcal pneumonia. On the one hand, healthy persons often carry pneumococci in their throats (Lund, 1971). The presence of pneumococci in a sputum culture, therefore, is not necessarily diagnostic of pneumococcal pneumonia

[3]For example: A program begun in 1978 might result in the immediate saving of one life at an immediate cost of $1,000. Its cost-effectiveness ratio for 1978 thus would be $1,000 per life. If the same program were delayed until 1979, and a 5-percent discount rate were applied only to costs, then the present value cost-effectiveness ratio for the 1979 program would be $950 per life.

[4]The prices of vaccines for public programs and private physicians are discussed in app. 4.5

[5]Blood tests include bacteriological tests, hemagglutination, and radioimmunoassay. (See Schiffman, 1971.)

(Barrett-connor, 1971; Austrian, 1975). On the other hand, patients with pneumococcal pneumonia sometimes do not show pneumococci in their sputum (Barrett-Connor, 1971).

A rate of attributable risk can be derived by comparing the sputum culture pneumococcal isolation rate (i. e., the percent of cases in which pneumococci are isolated from sputum samples) in a group of pneumonia patients to the comparable isolation rate in a group of non-pneumonia patients. [b] An estimate of the proportion of pneumonia cases caused by pneumococci can be based on the differences in pneumococcal carriage rates among patients with pneumonia and those without pneumonia. Basing estimates of attributable risk on differences in pneumococcal carriage rates, although arithmetically neat, involves making a considerable leap of faith. In fact, estimates of attributable risk that are based on differences in pneumococcal carriage rates may not be valid. As explained by David Fraser, M. D., of the Center for Disease Control (CDC) (Fraser, 1979)

> The bacterial flora of the throat are in a delicate balance which can be tipped by the use of antibiotics or the occurrence of various infections. It may be that viral infections increase the chance of colonization of the throat with pneumococci (or the chance of recovering pneumococci that are present) without necessarily leading to pneumococcal pneumonia. Alternatively, estimates could be based on data generated from examinations of Gram-stained sputum from patients with pneumonia. The diagnosis of pneumococcal disease could be based on the characteristic appearance of polymorphonuc]ear leukocytes, alveolar macrophages, and Gram-postive diplococci with a positive Quellung test or on demonstration of pneurnococcal organism or capsular antigens in blood or other body fluids. Few such studies have been done, however, and those that are available are based on small numbers and highly selected populations.

Most of the isolation rates and attributable risks reported in studies conducted in the United States suggest that the percent of pneumonia that is caused by pneumococcal organisms is between 12 and 62 percent:

1. A study of pneumonia cases among members of Group Health Cooperative, a prepaid group practice in Seattle, yielded an estimate of about 13 percent (Fey, 1975). In this study, 24 percent of the 100 pneumonia patients carried pneumococcal isolates, in comparison with 12.2 percent of the controls.
2. In a study of 100 adult pneumonia patients admitted to a large general hospital in Baltimore, 62 percent were diagnosed as having pneumococcal pneumonia, based on clinical diagnostic criteria (Fekety, 1971). Pneumococci were isolated from nasal or sputum samples in 68 percent of the 96 pneumonia patients and in 15 percent of the 78 control subjects.
3. In a study of 148 pneumonia patients at Milwaukee County General Hospital, pneumococci were isolated from the blood or sputum of 53 percent of the patients (Dorff, 1973).
4. In a study of pneumococcal vaccine at a San Francisco prepaid medical group, it was shown that 15.6 percent of all cases of clinical pneumonia among an unvaccinated group of patients were accompanied by pneumococcal isolates (Austrian, May 1, 1976).
5. In an Atlanta study at Grady Memorial Hospital, the isolation rate for pneumococci among pneumonia patients was reported to be 35 percent (Sullivan, 1972).
6. A study of children developing pneumonia in the Chapel Hill area of North Carolina showed pneumococcal isolates among 65,3 percent of hospitalized children with pneumonia and among 39.6 percent of the control group of hospitalized children without respiratory illness, demonstrating an attributable risk of 25.7 percent (Loda, 1968). In the same study, among children treated for pneumonia at private pediatric offices, 39.6 percent had pneumococcal isolates.
7. Finally, in a study of pneumonia at a chronic care hospital in New York, the percentage of pneumonia that was pneumococcal was found to range from 10.1 percent to 23 percent during four separate study periods (Bentley, n.d.).

In OTA's cost-effectiveness analysis of pneumococcal vaccination in chapter 4, in the base case, it was estimated that 15 percent of all cases of pneumonia are caused by pneumococci. This estimate, which may be conservative, was based on—in addition to consideration of the data discussed in the preceding paragraph—discussions with three infectious diseases researchers (Austrian, 1979; Filice, 1979; Fraser, 1979), and the results of two unpublished studies (Filice, n.d.; Bentley, 1979). In one of the unpublished studies, conducted under the auspices of the Center for Disease Control (CDC), Gregory Filice, M. D., conservatively estimated the incidence of pneurnococcal pneumonia to range from 12 to 37 cases per 100,000 persons per year (Filice, n.d.). Filice's estimate was based on the incidence of documented pneumococcal bacteremia in Charleston County, S.C. To the extent that pneumococcal bacteremia in this county had not been diagnosed, this estimate is likely to be unrealistically low, In the other unpublished study, David W. Bentley, M. D., of the Monroe Community Hospital, in Rochester, N. Y.,

[b] For a description of one manner in which attributable risk can be calculated, see app. 4.6.

attempted to quantify the incidence of pneumococcal pneumonia in institutionalized populations, mostly comprised of elderly patients (Bentley, 1979). From data collected in a 1974 study, he found that out of 157 patients with pneumonia, 27 (17 percent) had pneumococcal pneumconia. From data collected in a 1975 study, he found that out of 160 patients with pneumonia, 20 (13 percent) had pneumoctlccal pneumonia. More recently, he studied 95 patients with pneumonia and found that 20 (2 I percent) had pneumococcal pneumonia as diagnosed by transtracheal aspiration.

In the sensitivity analysis in chapter 4, the low estimate of 10 percent was selected to represent the low incidence of pneumococcal pneumonia reported in the studies cited earlier. The high estimate of 35 percent was based on the results of a survey of 45 medical practitioners and scientists that was conducted by Pracon, Inc. (Roden, 1978).

Percent of Pneumococcal Pneumonia Caused by Types of Pneumococci Represented in the Vaccine

The currently licensed pneumococcal vaccine contains antigenic polysaccharides from-and produces various levels of protection against pneumonia caused by—14 serotypes of pneumococci. Currently, however, there are at least 83 known pneumococcal types. In the base case analysis, it was assumed that 75 percent of all cases of pneumococcal pneumonia among all age groups are caused by the 14 types of pneumococci represented in the vaccine. In the sensitivity analysis, however, it was assumed: 1) that 50 percent of such cases among all age groups are caused by these 14 types; and 2) that 100 percent are. The potential effects of varying percentages among different age groups were not ascertained in OTA's analysis.

The 75 percent estimate for the base case analysis was based on data derived from several recent U.S. studies in which pneumococci were isolated from patients with pneumococcal pneumonia and typed.

1. In one study, conducted at a prepaid health plan in Seattle in 1971 and 1972, 73 percent of the 40 pneumococcal isolates recovered from ill patients were types found in the 14-valent vaccine (Fey, 1975).
2. A separate study conducted at a San Francisco prepaid health plan between 1974 and 1976 yielded similar results: 72 percent of the pneumococcal isolates extracted from unvaccinated patients with X-ray positive pneumonia contained types of pneumococci represented in the vaccine (Austrian, May 1, 1976).
3. In a third study, carried out between 1974 and 1976 at a chronic care hospital in New York, it was found that 72 percent of pneumococcal isolates recovered from 50 pneumonia patients were represented in the vaccine (Valenti, 1978).[7]
4. In addition, data from a multi-institutional study of bacteremic pneumococcal infection conducted in several American cities from 1967 to 1975 showed 78.6 percent of 3,644 isolates were types represented in the 14-valent pneumococcal vaccine (Austrian, et al, 1976).

The percentage of pneumonia caused by different types of pneumococci also was investigated in a number of earlier U.S. studies (Austrian, 1964; Finland, 1937). Because of evidence that incidence of pneumococcal infections caused by different types of pneumococci have been changing over the years, however, the results of these studies may not be directly relevant. In a study conducted between 1929 and 1935 at Boston City Hospital, for example, it was found that pneumococcal Types 1, 2, and 3 accounted for about 70 percent of the cases of bacteremia (Finland, 1973.) Several more recent studies, though, have found that the distribution among pneumococcal types is more disperse (Mufson, 1974).

The future impact of pneumococcal vaccine may be significantly influenced by variations over time in the relative incidence of diseases produced by various types of pneumococci. At some point in the future, a shift might occur in the percent of pneumococcal pneumonia cases among unvaccinated populations that are caused by the 14 types represented in the licensed pneumococcal vaccine. In the absence of any method for predicting the direction or extent of shifts in the incidence of pneumonia caused by specific types of pneumococci, however, for purposes of OTA's analysis in chapter 4 (in both the base case and sensitivity analysis), it was assumed that the percentage of pneumococcal pneumonia cases caused by the 14 types of pneumococci represented in the current vaccine would remain constant. If the duration of immunity conferred by the vaccine is only a few years, then this assumption is probably valid. If the vaccine confers lifetime immunity (an assumption used in the sensitivity analysis), however, then the assumption may not be valid.

Another assumption made in OTA's analysis, that the incidence of type-specific pneumococcal pneumonia caused by each of the 14 different types of pneumococci represented in the vaccine does not

[7] The 72 percent is an average of the percent of vaccine-type isolates in confirmed and putative cases of pneumonia. Seven-V percent of the 33 confirmed cases and 76 percent of the 17 putative cases were vaccine-type isolates. (See Valenti, 1978).

vary among different age groups, also may be incorrect. At present, however, there exist no age-specific incidence data for type-specific pneumococcal pneumonia which can be used either to validate or invalidate this assumption.

Pneumococcal Vaccine's Rate of Efficacy Against Type-Specific Pneumococcal Pneumonia

The efficacy of pneumococcal vaccine against type-specific pneumococcal pneumonia has been investigated in a number of clinical trials.[8] On the basis of evidence from these trials, in the base case analysis, pneumococcal vaccine was assumed to be 80 percent effective against type-specific pneumococcal pneumonia. In the sensitivity analysis, two different assumptions used for comparative purposes were that: 1) the vaccine's efficacy rate might be as low as 40 percent; or 2) it might be as high as 100 percent.

The 80-percent efficacy rate used in the base case analysis was based mainly on results of clinical trials conducted among South African gold miners (Smit, 1977; Austrian, et al., 1976). These South African trials, some early U.S. studies (Kaufman, 1947), and a study with sickle-cell patients (Ammann, 1977) were used as a basis for the 14-valent pneumococcal vaccine's licensure by the Food and Drug Administration (FDA). Also taken into consideration were data from immunologic studies in which the vaccine consistently increased vaccinees' antibody levels following immunization (Ammann, 1977; Weibel, 1977).

While an 80-percent effectiveness rate for pneumococcal vaccine was fairly well substantiated in the studies conducted in South Africa, this rate was not confirmed in two clinical trials conducted in the United States. In one trial, conducted at the Dorothea Dix Hospital in Raleigh, North Carolina, 608 subjects were immunized with two 6-valent vaccines, and 693 subjects received a saline placebo (Austrian, 1978). There was a 53 percent reduction among vaccinees in radiologically confirmed, vaccine-type pneumonia, but this reduction was only barely statistically significant ($p < .041$). In the other trial, conducted at the San Francisco Kaiser Permanence Medical Center, 6,850 subjects were given a 12-valent vaccine, and 6,750 subjects were given a saline placebo (Austrian, 1978; Austrian, May 1, 1976; Austrain, May 28, 1976). No apparent or statistically significant difference between the incidence among controls and vaccinees of radiologically confirmed, type-specific pneumococcal pneumonia was demonstrated. Difficulties in these two U.S. trials possibly may have resulted from the relatively low incidence of pneumococcal pneumonia in the study groups.

Vaccine Side Effects

Pneumococcal vaccine appears to be generally safe, with minimal side effects reported to date.[9] In one trial in New Guinea, 131 vaccinees were monitored for adverse reactions (Riley, 1977). Seventy-five percent of these 131 vaccinees reported no side effects, 24 percent reported a sore arm; 7 percent, fever; and 3 percent, a swollen arm. In field trials in San Francisco, over 6,000 adults were given the vaccine (Austrian, May 1, 1976; Austrian, et al., 1976). Sixty percent experienced no adverse reactions; 40 percent showed some discomfort; 30 percent developed a local rash; and 3 percent had a mild fever for a day.

Pneumococcal vaccine has been on the market since February 1978. According to the Center for Disease Control (CDC), the number of adverse reactions reported since then has been small. According to CDC'S estimate, between February and September of 1978, less than one case of severe systemic reaction per 100,000 vaccinees was reported (Broome, 1978). There have been few reports of possible anaphylaxis (severe allergic reaction) and no reports of deaths directly attributable to the vaccine.[10]

For OTA's cost-effectiveness analysis in chapter 4 (in both the base case and sensitivity analysis), probabilities of having a systemic reaction to pneumococcal vaccine were developed on the basis of estimates from CDC, while probabilities of experiencing a minor reaction were developed on the basis of data from the trials in New Guinea and San Francisco cited above. The assumption was made that there would be one case of severe systemic reaction per 100,ooo vaccinees and five cases of fever per 100 vacinees. It was assumed that vaccine recipients experiencing severe adverse reactions would spend 2 days in the hospital (2 days of bed disability), at a total cost of $396, and an additional day recuperating at home (1 day of bed disability). For fever, it was assumed that the patient would suffer 1 day of nonbed disability, but would require no special medical attention, The side effects and risk of local reactions (e.g., pain or redness at the site of injection) were considered too minor to alter quality of life or cost considerations, so these were not taken into account.

[8] Studies used to evaluate the efficacy of pneumococcal vaccine are discussed in ch. 3 and described more fully in app. 3.5 and 3.6.

[9] Studies used to evaluate the safety of pneumococcal vaccine are discussed inch. 3 and described more fully in app. 3.5 and 3.6.

[10] See discussion of postmarketing data regarding the safety of pneumococcal vaccine in ch. 3.

In the base case analysis, it was assumed that the neurological disorder Guillain-Barre Syndrome (GBS)[11] would not be among the adverse reactions caused by pneumococcal vaccine. GBS has been observed as an adverse reaction to rabies, DPT, polio, and most notably, swine flu vaccine; however, these are all whole cell vaccines. Pneumococcal vaccine is a polysaccharide vaccine, and therefore is more pure (i.e., free from contaminants) than whole cell virus vaccines; at least theoretically, this vaccine may be less likely to cause GBS (Hill, 1978),

In the sensitivity analysis, the assumption was made that GBS would sometimes be a side effect. It was assumed that the incidence of GBS associated with pneumococcal vaccination would be comparable to the excess incidence of GBS among swine flu vaccinees (Schoenberger, 1979).12 For persons under 18 years of age, no excess incidence was reported. For persons 18 to 24, an increased incidence of four cases per million doses of vaccine was observed. For persons over 24 years old, the increased incidence was found to be 9 or 10 cases per million.

Knowledge regarding the effects of GBS is limited, although a few data do exist. Patients with GBS are initially treated at an acute hospital. One neurologist estimates that the average patient is hospitalized for 21½ months, but that following initial hospitalization, he or she usually needs no further medical or special home care (Asbury, 1978). According to some estimates, however, about 5 to 10 percent of GBS patients discharged from hospitals do have some lasting residual impairment after their release (Asbury, 1978). Approximately 5 percent of patients who develop GBS do die from the disease. Available data from the swine flu program indicate that GBS mortality rates are different for particular age categories. GBS mortality rates by age groups under the 1976 swine flu program were as follows: age 18-24, 3.5 percent; age 25-44, 2.4 percent; age 45-64, 5.8 percent; and age 65 and over, 12.7 percent (Schoenberger, 1978). No pattern as to the timing of death in the course of the illness has been described.

For purposes of the sensitivity analysis, it was assumed that vaccinees developing GBS would be hospitalized for an average of 75 days (75 days of bed disability) at a total cost of $15,640. Estimates of the probability of some GBS patients' dying following hospital discharge were based on mortality rates reported during the swine flu program. The assumption was made that 10 percent of the vaccinees developing GBS would have a residual disability (comparable to a permanent, restricted activity, nonbed disability). GBS survivors were assumed not to require additional special care subsequent to their hospital discharge.

Duration of Immunity Conferred by Pneumococcal Vaccine

The duration of immunity conferred by pneumococcal vaccine is not known. No clinical investigators to date have followed their vaccinated subjects for more than 8 years to establish a clinically based estimate of the duration of the protection conferred by the vaccine against death from pneumococcal pneumonia.

In a recent study in New Guinea, investigators found that pneumococcal vaccine afforded some protection against lower respiratory tract infection (LRTI) for a minimum of 3 years (Riley, 1977). Investigators in this study, however, did not attempt to demonstrate the maximum period during which immunity would last.

A study conducted in the 1940's using 3- and 6-valent vaccines demonstrated that these vaccines produced sustained serum antibody levels, and hence, possibly afforded protection, 8 years after vaccination (Heidelberger, 1953). In that study, the antibody levels in subjects' blood sera were examined at periodic intervals following vaccination. Antibody levels among subjects who had been vaccinated from 3 to 6 years previously ranged from one-fifth to one-half or more of their maximum value, and abundant residual antibodies remained in the blood of the few subjects who had been vaccinated 8 years previously.

Some scientists maintain that pneumococcal vaccine might provide protection for even longer intervals than 8 years (Hill, 1978; Robbins, 1978). Their estimates—ranging from 20 years to a lifetime—are based, not on observed cases, however, but on biological evidence and intuitive reasoning.

In the base case analysis in chapter 4, pneumococcal vaccine was assumed to offer protection for an average of 8 years. It seemed reasonable to assume that the duration of immunity would vary slightly for different individuals, so an assumption was arbitrarily made that duration of immunity would follow a normal distribution with the standard deviation equal to the square root of the mean. In the sensitivity analysis, two different assumptions regarding the duration of immunity were used: 1) that immunity would last only 3 years; and 2) that it would last for 72 years (a lifetime).

[11] Guillain Barre Syndrome (GBS) is discussed in app. 5.1.

[12] See discussion of the excess incidence of GBS among swine flu vaccinees in app. 5.1.

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Appendix 4.5
PRICES OF VACCINES FOR PUBLIC PROGRAMS AND PRIVATE PHYSICIANS

The Center for Disease Control (CDC) estimated that it was able to buy vaccines from manufacturers for about half the price paid by private physicians (Hinman, 1978). Prices paid by CDC between October 1977 and September 1978 and prices paid in 1978 by private sector purchases are shown in table 4.5A.

Merck Sharp and Dohme reported that some of their recent contracts to CDC have included a surcharge for liability. For example, rubella vaccine cost CDC **$0.60** in the contract year from October 1976 to September 1977; the same vaccine cost CDC $0.71 in the fiscal year's contract running from October 1977 to September **1978. In a recent contract,** the price for measles, mumps, and rubella vaccine to CDC was $2.35 per single dose. The price would have been even less, but for the surcharge imposed by Merck.

In 1977, the State of California paid $6.45 for a 10-dose vial of influenza vaccine (Grant, 1978). In 1977, Wyeth was supplying lo-dose vials to private physicians for $9.50 each. Wyeth representatives listed the following as reasons why the price was lower to the State of California: 1) the policy forbidding returns of vaccines purchased by public programs, 2) the ability of the manufacturer to time production and sales under public programs, and 3) the lower shipping weight that results from reduced bulk in packaging (Cahill, 1978).

James Chin, State epidemiologist, California State Department of Health, Berkeley, estimated that the military pay about one-half of the price paid by the private sector for vaccines (Chin, 1978). Private physicians buy small amounts and pay various types of middlemen; furthermore, many hospitals buy vaccines on a returnable basis. Public purchasers, however, buy directly from the manufacturer on a nonreturnable basis. They also receive a discount for the large amount of their purchase. As a result, public purchasers benefit from lower prices.

Table 4.5A.—Public and Private Prices Paid for Vaccines

	CDC	Private sector[a]	
Type of vaccine	Oct. 1977-Sept. 1978	Before June 1, 1978	After June 1, 1978
Measles, mumps, rubella	$2.35/single dose vial[b] $1.88/ten-dose vial	$5.91/ten single dose vials	$6.16/ten single dose vials
Measles, rubella	$1.20/single dose vial[a] $0.95/ten-dose vial[a] $0.56/fifty-dose vial[a]	$3.56/ten single dose vials	$3.81/ten single dose vials
Measles	$0.87/single dose vial $0.68/ten-dose vial $0.39/fifty-dose vial	$2.02/ten single dose vials	$2.27/ten single dose vials
Rubella	$0.71/single dose vial[b] $0.46/ten-dose vial[b] $0.42/fifty-dose vial[b]	$2.22/ten single dose vials	$2.47/ten single dose vials
Mumps	$1.40/single dose vial[b] $1.11/ten-dose vial[b]	$2.81/ten single dose vials	$3.06/ten single dose vials

[a]No liability surcharge.
[b]Liability surcharge included.

SOURCE: Beck, Merck Sharpe and Dohme, 1978 (Beck, 1978.)

Appendix 4.6
A METHOD OF CALCULATING ATTRIBUTABLE RISK FOR PNEUMOCOCCAL PNEUMONIA[1]

Attributable risk from the Foy and Fekety studies can be calculated using the procedure described below (Fey, 1975, Fekety, 1971). In the Foy study, it was reported that pneumococcal isolates were present in 24 percent of the pneumonia cases and in 12.2 percent of the non-pneumonia control cases. From this information, the table below can be constructed:

[1]This explanation of this method of calculating attributable risk was provided by Donald Shepard, Ph. D., Harvard University (Shepard, 1979).

Pneumonia Cases: Pneumococcal Isolates and Types of Pneumonia

	Pneumococcal isolate(s)		
	yes	no	Totals
Pneumococcal pneumonia	a		x
Other pneumonia	b		y
All pneumonia	24%		100

a = the percent of pneumococcal pneumonia cases which have pneumococcal isolates
b = the percent of other pneumonia cases which have pneumococcal isolates
x = the percent of pneumonia cases which are pneumococcal
y = the percent of pneumonia cases which are not pneumococcal

We are interested in the variable x, the percent of pneumonia cases which are pneumococcal. In order to solve for the variable x, we need to postulate a number of relationships. First, we can assume that a = x, or that pneumococcal isolate is present in all cases of pneumococcal pneumonia. Second, from the Foy study we know that pneumococcal isolates were present in 12.2 percent of the control cases, and we assume they are present in 12.2 percent of the non-pneumococcal pneumonia cases. Therefore, b = .122y. Third, from the Foy study we know that a + b = .24, or that pneumococcal isolates are present in 24 percent of all pneumonia cases. Fourth, it is obvious that x + y = 1.00, or the percent of pneumonia cases which are pneumococcal plus the percent which are not pneumococcal must sum to 100 percent. From these relationships we can solve for x.

(1) $b = .122y$, so $y = b/.122$

(2) $x + y = 1.00$, so $x + b/.122 = 1.00$
so $b = .122(1.00-x)$

(3) $a + b = .24$, so $a + .122(1.00-x) = .24$

Since a = x, then

(4) $X + .122\ (1.00-x) = .24$

then solving for x,

(5) $x = \frac{(1-.122)}{.878} = .134 = 13.4\%$

In a similar manner, using the data from the Fekety study we can calculate that the attributable risk in this study is 62 percent.

Appendix 5.1
GUILLAIN-BARRE SYNDROME

Guillain-garre Syndrome (GBS) is a neurological isorder of unknown etiology, which sometimes has een observed to follow certain types of vaccinaons, notably, swine flu, Semple rabies, and more irely, DPT and polio vaccinations (Asbury, 1978, amontaigne, 1978).

GBS is characterized by paralysis that beginsin the gs and later involves the trunk of the body, arms, and neck. GBS patients may experience a wide range f disability. The average GBS patient spends about I/z months in the acute care hospital, experiencing aralysis for about 2 weeks. After about 3 weeks, the atient is taken to rehabilitation, and once sufficient- recovered, returns home. Unlike patients with oinal cord injuries, most of those who contract GBS and not to be permanently disabled. About 5 to 10 ercent of those afflicted, however, do experience me kind of residual disability, the extent of which m vary greatly. Mortality rates from GBS run out 5 percent. No pattern as to the timing of death 1 the course of the illness has been described Asbury, 1978).

The average treatment cost for GBS is equivalent the cost of about 75 days of hospitalization. GBS atients tend not to require institutionalization in a aronic care facility and not to continue to need special care at home (Asbury, 1978).

According to the Center for Disease Control CDC), the estimated incidence of GBS occurring in the general population prior to the 1976 swine flu immunization program was **6 to 19** cases per million ersons per annum (Schoenberger, 1978). This estiate was drawn from five or six studies conducted at ~rious places including the Mayo Clinic.

Recently, an analysis of the incidence of Guillain-Barre Syndrome during the 1976 swine flu program was published (Schoenberger, 1979). Increases in the incidence of GBS among swine flu vaccinees were observed over about a l0-week period of risk (i. e., the duration of the swine flu program). In about 90 percent of the excess cases (i. e., those in excess of the expected incidence), GBS occurred in the first 6 weeks following vaccination. Among the small group of swine flu vaccinees under 18 years of age, there was no documented rise in the incidence of GBS. Among swine flu vaccinees between the ages of **18 and 24, an** increased incidence of four cases of GBS per million doses of administered vaccine was observed. Among swine flu vaccinees over 25 years old, **9** to 10 additional cases of GBS per million doses of administered vaccine were observed. While the reported incidence of excess GBS among swine flu vaccinees over the age of 25 did not rise substantially with age, GBS mortality rates did. (See table 5.1 A.)

Table 5. IA—Mortality Rates Among Swine Flu Vaccinees With G BS (1976-77)

Age group	Mortality rate
0-17 years	0.8%
18-24 years	3.5%.
24-44 years	2.4°10
45-64 years	5.8°10
65+ years	12.7%

SOURCE: Schoenberger, Center for Disease Control, 1978

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