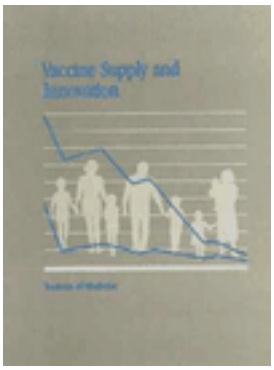

Vaccine Supply and Innovation

Division of Health Promotion and Disease Prevention, National Research Council
ISBN: 0-309-58152-4, 210 pages, 8.5 x 11, (1985)

Vaccine Supply and Innovation

Division of Health Promotion and Disease Prevention
Institute of Medicine

NATIONAL ACADEMY PRESS
Washington, D.C. 1985

NATIONAL ACADEMY PRESS 2101 CONSTITUTION AVENUE, N.W. WASHINGTON, DC 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competencies and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 congressional charter responsibility to be an adviser to the federal government and its own initiative in identifying issues of medical care, research, and education.

The study was supported under contracts with the Food and Drug Administration (223-83-1109), the Department of the Army (DAMD17-83-G-9558), and the Centers for Disease Control (200-83-0609), and grants from Lederle Laboratories, the Mericux Institute, Inc., and Merck Sharp & Dohme. Additional support was provided by the National Research Council (NRC) Fund, a pool of private, discretionary, nonfederal funds that is used to support a program of Academy-initiated studies of national issues in which science and technology figure significantly. The NRC Fund consists of contributions from a consortium of private foundations including the Carnegie Corporation of New York, the Charles E. Culpeper Foundation, the William and Flora Hewlett Foundation, the John D. and Catherine T. MacArthur Foundation, the Andrew W. Mellon Foundation, the Rockefeller Foundation, and the Alfred P. Sloan Foundation; the Academy Industry Program, which seeks annual contributions from companies that are concerned with the health of U.S. science and technology and with public policy issues with technological content; and the National Academy of Sciences and the National Academy of Engineering endowments.

Library of Congress Catalog Card Number 85-60772
International Standard Book Number 0-309-03544-9

Publication No. IOM 85-02
Printed in the United States of America

Committee on Public-Private Sector Relations in Vaccine Innovation

JAY P. SANFORD (*chair*), School of Medicine, Uniformed Services University of the Health Sciences
MARSHALL H. BECKER, Department of Health Behavior and Health Education, University of Michigan, Ann Arbor
ROGER B. DWORKIN, School of Law, Indiana University, Bloomington
BERNARD N. FIELDS, Department of Microbiology and Molecular Genetics, Harvard Medical School
JERE E. GOYAN, School of Pharmacy, University of California, San Francisco
HENRY G. GRABOWSKI, Department of Economics, Duke University
SAMUEL L. KATZ, Department of Pediatrics, Duke University Medical Center
EDMUND KITCH, University of Virginia School of Law, Charlottesville
LOUIS LASAGNA, Sackler School of Graduate Biomedical Sciences, Tufts University Medical School
MARTHA L. LEPOW, Department of Pediatrics, Albany Medical College
DAVID W. MARTIN, JR., Genentech, Incorporated, South San Francisco
DONALD N. MEDEARIS, JR., Department of Pediatrics, Harvard Medical School
THOMAS C. MERIGAN, JR., Division of Infectious Diseases, Stanford University School of Medicine
EDWARD A. MORTIMER, JR., School of Medicine, Case Western Reserve University
JANE SISK, Office of Technology Assessment, United States Congress
GENE H. STOLLERMAN, School of Medicine, Boston University
THOMAS H. WELLER, Department of Tropical Public Health, Harvard School of Public Health

See Appendix I for further information on committee members and consultants.

Consultant

LAWRENCE M. DeBROCK, Department of Economics, University of Illinois, Champaign

Government-Industry Liaison Panel

ROBERT F. ACKER, National Foundation for Infectious Diseases
DAVID W. BARRY, Burroughs Wellcome Company
A. JOHN BEALE, Wellcome Research Laboratories, United Kingdom
JOHN H. BRYANT, National Institutes of Health
FRANCIS R. CANO, Lederle Laboratories
JAMES P. CARLOS, National Institutes of Health
PINYA COHEN, Merieux Institute
CIRO C.A. de QUADROS, Pan American Health Organization
DAVID A. ESPESETH, United States Department of Agriculture
LEONARD D. FENNINGER, American Medical Association
JEROME GOLD, Wyeth Laboratories
GEORGE F. GRADY, Massachusetts Public Health Biologics Laboratories
MAURICE R. HILLEMAN, Merck Sharp & Dohme Research Laboratories
ALAN HINMAN, Centers for Disease Control
NEIL HOLLANDER, Blue Cross/Blue Shield Association
DAVID L. HUXSOLL, United States Army Medical Research Institute of Infectious Diseases
DONALD R. JAFFEE, Parke-Davis
WILLIAM S. JORDAN, National Institutes of Health
JOEL KAVET, Department of Health and Human Services
JEFFREY P. KOPLAN, Centers for Disease Control
ROBERT E. LOUIE, Cutter Laboratories
SUSAN H. MATHER, Veterans Administration
DONALD P. METZGAR, Connaught Laboratories, Limited, Canada
JOHN R. MITCHELL, Michigan Department of Public Health
GARY NOBLE, Centers for Disease Control
PAUL D. PARKMAN, Food and Drug Administration
CORNELIUS W. PETTINGA, Eli Lilly and Company
M. SUSAN UEBER RAYMOND, Center for Public Resources
MICHAEL A. RIDDIOUGH, Springfield, Virginia
DAVID ROBINSON, United States Army Medical Research and Development Command
JOHN ROBBINS, National Institutes of Health
PHILIP K. RUSSELL, Fitzsimons Army Medical Center
MARTIN H. SMITH, American Academy of Pediatrics
GASTON S. TAWIL, Pan American Health Organization
KENNETH S. WARREN, The Rockefeller Foundation
DONALD A. YOUNG, Health Care Financing Administration

Institute of Medicine Staff

ROY WIDDUS, Study Director
ENRIQUETA C. BOND, Director, Division of Health Promotion and Disease Prevention
CYNTHIA HOWE, Research Assistant
EVE K. NICHOLS, Editor
JUDE C. PAYNE, Research Assistant
GAIL E. SPEARS, Administrative Secretary

Preface

Vaccines are an elegant solution to one of the perennial problems of the human race—infectious disease. The body's own protective mechanisms are primed by specific interventions to thwart the invasion or multiplication of pathogens. Lewis Thomas has described this immunization process as one of the genuinely decisive technologies of modem medicine—it is effective, relatively inexpensive, relatively simple, and relatively easy to deliver.

In the United States, the contribution of vaccines to improved public health has been recognized by all 50 states in laws requiring preschool immunization. In addition, many studies have affirmed the benefits and cost-effectiveness of immunization programs for adults (Office of Technology Assessment 1979, 1980, Pneumococcal and Influenza Evaluations).

Today's vaccines protect millions of people from the ravages of disease, and new developments offer the possibility of widening their scope even further. It is unlikely, however, that any existing vaccine will soon repeat the feat of the smallpox vaccine—total worldwide eradication of a disease—although this ultimately may be possible for diseases such as measles, polio, and rubella. For many other diseases, continuing immunization programs will be required because the pathogens occur in reservoirs from which they are difficult to eliminate, e.g., the environment or other animals. Also, no existing vaccine is universally effective or risk free; hence, research efforts must continue to further minimize undesirable side effects. Finally, vaccines are not available for some major diseases; extending the benefits of immunization will require efforts to encourage the development of new vaccines.

The process of vaccine innovation in this country, including basic research, development, testing, production, and marketing, involves numerous organizations in both the public and private sectors. In general, however, the availability of vaccines for public use depends entirely on the willingness of commercial manufacturers to undertake production. Numerous studies over the past two decades have raised the concern that our reliance on market incentives to ensure vaccine availability may lead to a failure to meet public health needs. Also, these incentives may not result in optimal levels of vaccine innovation (National Immunization Work Groups, 1977).

These concerns and others involving the application of advances in biotechnology to vaccine production led the Institute of Medicine to establish the Committee on Public-Private Sector Relations in Vaccine Innovation.[*] The committee, convened in May 1983, was charged with

[*] The activities of this committee complemented the work of the Institute of Medicine's Committee on Issues and Priorities for New Vaccine Development. The latter's charge was to design a comprehensive approach to setting priorities for accelerated vaccine development. Its first report, *New Vaccine Development: Establishing Priorities, Volume 1* (1985), describes application of the committee's model to diseases of importance in the United States; Volume 2 will evaluate the usefulness of the model in setting priorities for vaccines needed by technologically less developed nations.

analyzing and making recommendations about current institutional arrangements supporting the research, development, supply, and promotion of vaccines. Specifically, the committee was asked to

- suggest ways of improving interactions among federal agencies involved in vaccine research, regulation, and utilization; the pharmaceutical industry; and other interested parties, such as medical specialty organizations and the Advisory Committee on Immunization Practices
- define measures for fostering a more active exchange between the public and private sectors in development of vaccines for the United States and foreign markets
- consider means for reversing the decline in the domestic capability for vaccine production, including evaluation of the practicability and desirability of federally supported production facilities
- explore ways of encouraging the development of vaccines of low commercial potential and of improving existing vaccines
- address the legal issues involved in the testing, manufacture, and marketing of vaccines for domestic and foreign markets—including antitrust matters, proposed changes in the patent laws, and liability for vaccine-related injuries
- examine the process used in developing recommendations for vaccine use and for national deployment strategies

Careful selection of members produced a committee with collective expertise in infectious disease, internal medicine, pediatrics, epidemiology, public health, vaccine development, sociology, ethics, economics, law, and public policy. A government-industry liaison panel was established to assist the committee, and additional comments were invited from other individuals on specific topics. The committee also reviewed the extensive testimony given before congressional heatings on proposals for the establishment of a vaccine injury compensation system.

In November 1983, the committee sponsored a conference on Barriers to Vaccine Innovation, attended by more than 80 participants from the United States and abroad. A range of vaccine development case histories and position papers were prepared for the conference. During the meeting, working groups identified and discussed means of reducing barriers and disincentives to vaccine research and development, production and supply, and utilization. As a result of the conference, our study committee defined two goals that became the framework for its recommendations: (1) to facilitate the control of infectious diseases by ensuring the continued innovation, production, and use of vaccines and (2) to ensure that this goal is achieved in a socially responsible and just manner.

All of the committee's discussions were based on the premise that a domestic vaccine industry is essential to ensure vaccine innovation and availability in the United States. This assumption derived from an understanding of the unique features of vaccine production: the difficulty of quality control for biological products, the length of the production cycle, and specific problems that would be created by sole reliance on foreign manufacturers.

The committee believes that the information and approaches suggested in this report may contribute to the solution of problems that it could not address because of time and resource constraints. The economic analysis presented in Chapter 4, for example, should provide useful background information for a conference planned in 1986 on Preventive Biomedical Technologies (a symposium to be convened by the National Academy of Engineering). In addition, the national vaccine commission proposed in this report would be an appropriate body to deal with some of the issues presented in Chapter 7, including the special problems surrounding the development of vaccines for use in less developed countries, and the possible need for government facilities for vaccine production.

Many of the issues on which the committee sought information or data to use as a basis for policy

recommendations touched areas of commercial sensitivity. The committee is grateful to manufacturers for providing information that is not usually made public. This is presented in an aggregate form in the report.

Not all of the information sought by the committee could be obtained, however. The conclusions presented in this document represent a synthesis of data, subjective information, and interpretation. The committee has tried to characterize the current environment surrounding vaccine innovation and production as objectively and honestly as possible.

The Committee on Public-Private Sector Relations in Vaccine Innovation would like to take particular note of support provided by the Institute of Medicine staff and study director Roy Widdus. The support of the study's sponsors also is gratefully acknowledged.

JAY P. SANFORD
CHAIRMAN

Contents

Vaccine Supply and Innovation

1

Summary

The Committee on Public-Private Sector Relations in Vaccine Innovation was established on the premise that maintaining and extending the control of infectious diseases through immunization is an important national health objective. In compliance with its charge, it undertook a comprehensive study of vaccine research and development, production and supply, and utilization. It paid particular attention to the institutional arrangements and interactions required to ensure vaccine availability and use, and reviewed previous efforts to identify and resolve problems in these areas.

The committee found that vaccine development and immunization efforts are dependent on an intricate system in which many public and private participants have traditional roles and responsibilities. Although some of these participants communicate regularly, the system lacks any formal means to coordinate the establishment and attainment of goals in the effort to combat infectious diseases. The committee identified a variety of problems that result from the absence of such a mechanism.

The history of previous ad hoc groups convened to address problems related to vaccine availability has been discouraging. In general, their recommendations for specific actions have not been implemented, for a variety of reasons unrelated to the potential utility of the recommendations. When these groups dissolved, interest in the topics they studied waned. Unfortunately, the problems remained and, in some areas, worsened.

In light of that experience, the committee chose to emphasize the need for establishment of a continuing body to anticipate and resolve problems in vaccine development, supply, and use; it recommends the creation of a national vaccine commission. To aid in the activities of such an oversight body, the committee conducted a broad analysis of current scientific, economic, legal, and ethical concerns related to vaccine availability. Two fundamentally different approaches to ensuring vaccine availability are possible—(1) direct government production and (2) continued reliance on supply by the private sector, domestic and/or foreign. The committee believes that, at present, solutions to vaccine supply problems should employ the facilities and expertise already existing in the domestic commercial vaccine

industry; however, the committee's analysis identified a variety of deterrents to commercial interest in vaccines that could endanger the viability of this approach.

Paramount among current concerns is the pressing need for a consistent and just approach to the issues of liability for vaccine-related injury and of compensation for those who are injured. The committee's investigation showed that the handling of vaccine-related injury liability by the courts has left manufacturers apprehensive and uncertain about the extent of their responsibilities beyond proper manufacturing and labeling. These apprehensions act as a deterrent to vaccine production and thereby threaten the public's health, particularly because the nation is dependent on sole distributors for many of its most-used vaccines.

Action is urgently needed to reduce the uncertainty faced by manufacturers with regard to liability for vaccine-related injury; however, such action should not shield those who may be suspected of misconduct.

The committee believes that the goal of controlling infectious diseases by immunization should be pursued in as just and fair a manner as possible. Persons who respond to government promotion of or legal requirement for vaccination often benefit others in society, as well as themselves, because of reduced disease transmission. Those who are injured as an unfortunate consequence of immunization programs should be provided reasonable compensation in a rapid and equitable manner. The common law tort system does not satisfy these requirements.

The general objectives of providing equitable, rapid compensation in a consistent fashion and reducing uncertainty for manufacturers can be achieved by a wide range of approaches. The committee concluded, therefore, that its most useful contribution would be to define a range of possible options and to identify factors that should be considered in the design of workable solutions. It urges political decision makers to consider these options and to act as rapidly as possible on these questions and the establishment of the proposed national vaccine commission.

Only with action on all of these fronts will the current threat to the public's health be permanently relieved, and the potential of new technologies be fully realized.

OVERVIEW

The committee examined the history of vaccine production and regulation in this country and the manner in which today's products progress from research, through development and production, to utilization. The first vaccines were developed solely on the basis of empirical evidence. Scientists in the nineteenth century knew little or nothing about microbiology, mechanisms of infection, or immunity; yet their observations led to major advances in the control of smallpox, diphtheria, and other important diseases.

Newer vaccines, generally based on greater knowledge of pathogens

and host responses, have contributed to the near eradication of paralytic poliomyelitis in the United States and have reduced dramatically the incidence of measles, mumps, and rubella. The safety and efficacy of existing vaccines could be improved, however, and vaccines are not yet available to combat many pathogens.

Early in the history of vaccine development, physicians and others recognized that vaccine administration, like most medical procedures, carried risks as well as benefits. To reduce these risks, first local and then federal regulatory bodies established safety standards. The current generation of standards and vaccine licensure requirements, which specify production and testing procedures, are administered by the Office of Biologics Research and Review (OBRR) of the Food and Drug Administration.

The availability of vaccines depends almost entirely on the willingness of commercial manufacturers to produce them. The process of vaccine innovation (from basic research to commercial availability) rarely begins in industry, however. The basic research necessary to identify pertinent characteristics of the pathogen and host response, often extremely time-consuming and expensive, usually is conducted in federally funded academic or government laboratories, such as those of the National Institute of Allergy and Infectious Diseases and the Department of Defense (for vaccines required by the military).

If the evidence indicates that available techniques might produce a safe and effective immunizing agent, manufacturers begin to consider other aspects of the decision to develop a vaccine. These are based on assessments of the impact of the infectious disease; of the estimated cost of the disease and the projected costs of development, production, and administration of the vaccine; and of the vaccine's ranking among other health care priorities. Potential utilization, which is dependent both on acceptance of the vaccine by the public and the enthusiasm of physicians and other health care providers, is of major importance to commercial manufacturers.

After the extensive and complex background work has been completed and it appears that the proposed vaccine offers promise of safety and efficacy, permission may be sought from the OBRR for studies in humans. By regulation, this involves filing a permit referred to as an IND (Notice of Claimed Exemption for Investigational New Drug). The investigators must complete three sequential phases in the evaluation of the vaccine.

If the IND sponsor decides that the product is marketable, it files a license application. The OBRR reviews this document, conducts testing of the product, and may convene one or more meetings of the Vaccines and Related Biological Products Advisory Committee to provide advice regarding licensure. If the OBRR is satisfied that the product is safe and effective and that the directions for use developed by the manufacturer are adequate, a license can be granted. Each marketed vaccine requires a license, as does each vaccine manufacturer.

Although hundreds or thousands of individuals may have received a vaccine prior to full licensure, these numbers are insufficient to identify rare untoward events resulting from the vaccine. Therefore, the OBRR encourages continuing surveillance of vaccine recipients.

Any reports of untoward events must be made available by the manufacturer for review by the OBRR.

Recommendations for vaccine use in the United States are made by several advisory groups, most notably the Immunization Practices Advisory Committee of the U.S. Public Health Service, the Committee on Infectious Diseases of the American Academy of Pediatrics, and the Committee on Immunization of the Council of Medical Societies, American College of Physicians.

The Department of the Army oversees efforts to develop vaccines needed to protect military personnel (and others at risk) from a range of pathogens not generally encountered by the U.S. civilian population. These include tropical disease pathogens and potential biological warfare agents. Recommendations for the use of these vaccines are developed by the Armed Forces Epidemiological Board. As with vaccines for general public use, the ultimate availability of these vaccines depends on the willingness of a commercial manufacturer to undertake final development and production.

Recent advances in all aspects of biotechnology, and particularly gene manipulation, offer powerful new approaches to many previously intractable problems. These technologies, combined with a better understanding of the immune process, have opened a new era in vaccine development. Effective vaccines for meningitis, diarrheal diseases, malaria, and other parasitic diseases (responsible for enormous morbidity and mortality) may be technically feasible within a decade.

Full utilization of these new techniques may be forestalled, however, by the same problems that deter the development of vaccines by traditional methods. These include technical problems, high research and development costs, the expense and logistics of clinical testing and surveillance of reactions, the risk of litigation over untoward events associated with vaccine use (whether causally related or not), and limited sales. These problems must be resolved before the full public health benefits of new approaches to vaccine development can be achieved.

VACCINE AVAILABILITY: MAJOR BARRIERS AND IMPEDIMENTS

Concerns about the supply of vaccines and the factors that affect it are not new. The National Immunization Work Groups, convened by the Office of the Assistant Secretary of Health, made recommendations to resolve problems in these areas in 1977. Two years later, the congressional Office of Technology Assessment also studied these issues and presented a series of options, but no significant actions resulted from either effort.

The manufacture of vaccines can be interrupted by a variety of technical problems that arise with biological products and the processes by which they are produced. These include potency variations; stability problems; quantitative imbalance of microbial components in combination vaccines; variations in responses to

inactivation processes; excessive undesirable biological activity, e.g., neurovirulence; and inadvertent contamination.

Vaccine manufacturing requires major investment in a technologically advanced production plant and the establishment of teams with multidisciplinary expertise in the large-scale production of biological products. The decision by vaccine manufacturers to cease production of a particular product results in the dispersion of these teams and, perhaps, the disassembly of the production facilities. Reversal of this process cannot be achieved cheaply or rapidly, as might be necessary in the case of a vaccine shortage or a vaccine needed for military personnel.

The United States is heavily dependent on sole suppliers (either sole manufacturers or distributors). Two commercial companies (who do not compete with each other) dominate the markets for the major pediatric vaccines. The withdrawal, during 1984, of two manufacturers from the distribution of DTP vaccine and technical problems encountered by the one remaining producer resulted in a shortage of it in early 1985, and in a recommendation by the Centers for Disease Control to delay the usual fourth and fifth doses of the vaccine until supplies returned to normal. One of the manufacturers later decided to resume distribution, but this series of events highlights the dangers inherent in the current U.S. vaccine supply situation.

Stockpiling of vaccines has begun to a very limited extent and can provide some protection against brief interruption in the supply of a vaccine. It does not provide protection against the possibility that a single supplier will cease production or distribution of a vaccine.

The committee is not aware of any contingency plan for dealing with a situation in which no U.S. commercial manufacturer is willing to produce a major childhood vaccine. It regards this possibility with grave concern because of the threat of resurgence of these infectious diseases should vaccines become unavailable.

Sole reliance on foreign manufacturers for vaccines does not offer a practicable solution: problems could arise from geographic distance, with related communications and distribution delays; from possible language barriers, which could hamper the resolution of highly technical issues; from political considerations; and from differences in regulatory requirements. Reliance on foreign manufacturers also is not practicable because few firms abroad will compete in the U.S. market—the liability situation is cited as a factor in such decisions.

The supply of vaccines could be ensured if the federal government were willing to become the manufacturer of last resort or to enter into guaranteed contracts with manufacturers for needed vaccines. The possibility of federal vaccine production raises many complex policy questions, however, including the issues of how vaccine injuries from federally produced vaccines would be compensated and whether the facility would compete with commercial manufacturers. The committee did not consider itself an appropriate forum to resolve these issues, but did review other aspects of potential federal production. For example, a government production bureaucracy in the role of a sole

supplier might not be subject to the market pressures that often lead to innovation and the application of new technologies.

The committee believes that, at present, solutions to the problem of ensuring vaccine supply should employ the facilities and expertise already existing in the commercial vaccine industry. It recommends, however, that the national vaccine commission proposed in Chapter 7 should develop contingency plans and recommendations, on a case-by-case basis, for ensuring vaccine availability. These plans should include the possibility of direct federal involvement in vaccine supply if commercial manufacturers find continued "open market" operation no longer viable.

Impediments to Vaccine Innovation

The success achieved by immunization may appear to diminish the need for continuing vaccine innovation. However, vaccines are not yet available for many diseases of importance in the United States and abroad. The attack on many tropical diseases has barely begun. Also, some existing vaccines are not optimal and should be improved.

Modern vaccine development requires a firm scientific foundation, based on an understanding of the pathogen and the host (human) response to it. Limitations of funding for basic research and training, especially in disease pathogenesis, may contribute to delays in acquiring the necessary knowledge. Vaccine improvement also may be impeded by lack of basic knowledge, because if an empirically derived but effective vaccine exists there is a tendency to direct resources to the control of other pressing disease problems. Hence, basic research on the pathogenesis of the preventable disease may be neglected.

The fact that much of the acquisition of basic knowledge required for vaccine development is federally funded previously may have limited commercial interest in collaborations during this phase, because of subsequent problems in clarifying property rights, but changes in government funding policies (with respect to patents) may be reducing this deterrent.

The willingness of manufacturers to produce a new or improved vaccine also depends on evidence of an appropriate market. The achievable market for a vaccine may not reflect its true public health benefits because certain features of the health care system and of vaccine providers and recipients contribute to vaccine underutilization. One possible cause of inadequate market size may be the systematic undervaluation of preventive care in the United States. Vaccines also may be underutilized when viewed from a societal perspective because the total benefits that accrue to society at large (including reduced disease transmission) are greater than the sum of benefits to vaccinated individuals.

Behavioral research indicates that the widespread diffusion of new technologies depends on their successful adoption by "opinion leaders" in the relevant medical communities. This suggests that spreading

scarce resources across all providers to increase awareness of new approaches (including the use of new vaccines) may not be as successful as concentrating on those who exercise opinion leadership.

Considerable empirical evidence supports the usefulness of the "health belief model" in accounting for individuals' health-related decisions. Efforts to maximize public participation in immunization programs should begin with a survey of intended vaccine recipients to obtain information on their perceptions of the disease and the vaccine. Those promoting the vaccine can then develop and implement a campaign that addresses and modifies the (mis) perceptions most likely to act as obstacles.

ECONOMIC CHARACTERISTICS OF THE VACCINE INDUSTRY

Although the available data are incomplete, certain conclusions can be drawn about the current economic situation of the United States vaccine industry.

The number of manufacturers has declined steadily. During the 1970s and early 1980s, the proportion of the total pharmaceutical industry R&D investment in biologics also declined (data are not yet available to determine whether this trend continued after 1982). In addition, the pattern of new vaccine introductions has been considerably different from that of drug introductions in recent decades. Manufacturing of vaccines is highly concentrated and competition is very limited. Also, the sole-supplier situation poses a threat to the continued supply of some vaccines.

Typically, a decline in the growth of an industry and in the number of manufacturers signifies one of two events in its life cycle: either it has matured or it is experiencing problems. If the decline is the result of natural changes in demand patterns, efficiency is enhanced. Alternatively, a decline may reflect distorted incentives.

Economic disincentives to vaccine innovation and production include:

- the complexity of development, production, and quality control
- the cost of research and development in relation to anticipated sales
- a perception that vaccines historically have received less effective patent protection than drugs
- apprehension over the liability situation

The effects of recent changes in the patent law and in government funding policies (related to patents) are difficult to predict, but should generally enhance protection of innovations. The liability situation is discussed in detail in Chapter 6.

Additional disincentives exist on the marketing side: the need for a vaccine to deliver lifelong or long-lasting immunity is at odds with the prospect of multiple or repeat sales, and prospects for export sales are poor. The impact on profits of bulk purchases by government agencies (at prices lower than those paid by private purchasers) is uncertain.

VACCINE INJURY

The committee reviewed scientific data on major adverse reactions to commonly used domestic vaccines for children and adults. It then examined the factors that impede efforts to establish clear cause-and-effect relationships in cases of vaccine-related injury and the problem of determining the frequency of adverse effects among vaccines. Temporal associations between the administration of vaccines and the onset of many conditions similar to vaccine-related events further complicate these efforts.

The vaccines that are currently licensed provide excellent protection to society against their target diseases and are safe for an overwhelming proportion of recipients. They are not, however, universally effective or completely safe. The judgment as to what is adequately safe is difficult; decisions on the urgency with which improvement of vaccines needs to be pursued depends on the undesirability of the risks of vaccination in relation to the risks of the disease, and on other health needs.

Adverse events following immunization are reported to the Food and Drug Administration by manufacturers, pharmacists, physicians, and the military, and to the Centers for Disease Control by the parents or guardians of children who receive federally funded vaccines. Although these reporting systems are useful, neither of them provides an adequate basis for estimation of the total number of events that occur, in part because reporting is voluntary. Even if reporting were mandatory, however, the data would not allow determination of the number of events actually caused by, rather than coincidental to, the administration of vaccines because information on similar events in unvaccinated individuals is not collected. Conclusions about cause and effect and rates of adverse reactions to vaccines should be drawn only from carefully designed and controlled epidemiological studies.

Knowledge about the reasons for adverse reactions to vaccination and how to identify individuals who will respond atypically is incomplete. Hence, there is no way totally to avoid injuries caused by current vaccines manufactured according to approved procedures and administered in accordance with recommended medical practices short of the total suspension of vaccine use, which is unacceptable because of the increased risk of morbidity and mortality. Maintaining and extending awareness of contraindications to specific vaccinations among health care providers and the public are important in minimizing the potential for vaccine-related injuries. Every effort should be made to promote the availability to potential vaccine recipients (or their parents) of information on the risks and benefits of vaccination.

Responsibilities for identifying vaccine-associated risks, promoting awareness of contraindications to vaccination, and completing all of the steps required for vaccine improvement are now poorly defined and coordinated.

THE LEGAL SITUATION AND ITS CONSEQUENCES

Under well-established legal principles, a vaccine manufacturer is

not liable for injuries caused by a properly manufactured and labeled vaccine. In recent years, however, a few courts have acted contrary to these principles and found manufacturers liable for such injuries, possibly because the injured individual had been urged (or required) by the government to participate in the immunization program and appeared to have no other recourse for compensation.

In general, these vaccine injury claims have been decided on the basis of the doctrine of the duty to warn. This doctrine provides that prior to the use of an unavoidably unsafe product, the user must be warned of the risks associated with it. In the case of medicines administered by health professionals, the courts generally have placed this responsibility on the health care provider. For vaccines, however, some courts have ruled that the duty to warn resides with the manufacturer, even though the manufacturer is not involved in administration. It is unclear whether the courts that have ruled in this fashion would permit the manufacturer to avoid such responsibility by obtaining a formal agreement from the purchaser stating that a warning would be given prior to administration.

In two very recent cases (now on appeal), the plaintiffs prevailed by advancing theories of liability that went beyond the adequacy of the warning and asked juries to rule on issues of social benefit and harm, and on the underlying scientific factors that contribute to the basic public policy decision to use a particular vaccine. In one of these cases, punitive damages were awarded; however, punitive damages generally have not been a significant factor in vaccine-related injury litigation.

The committee is not aware of any cases holding health care providers liable for vaccine injury, except in situations involving failure to follow accepted medical procedures. The committee does not presently recommend any change in the rules applicable to health professionals because liability for improper administration is appropriate;[*] it recognizes, however, that if any proposal limiting recovery against manufacturers were adopted without provision for reasonable compensation, lawsuits might be redirected from the manufacturer to the administering professional. This could have deleterious effects on the willingness of health care providers to participate in immunization programs. Such a situation would require careful monitoring. Tracking shifts in litigation and recommending remedial action would be one of the functions of the proposed vaccine commission (Chapter 7).

CONSEQUENCES OF THE STATE OF VACCINE INJURY LIABILITY LAW FOR VACCINE PRODUCTION AND INNOVATION

Clear legal rules notwithstanding, the manner in which claims against manufacturers alleging liability for suspected vaccine-related

[*] The committee recognized that malpractice claims, in general, represent a major concern of the medical profession, but it did not feel that the malpractice issue was within the scope of its charge.

injuries have been handled by the courts does not provide reliable guidelines for predicting the limits and magnitude of their liability. This combines with other organizational and scientific factors to create a situation in which vaccine supply may be threatened. Causation is difficult, if not impossible, to determine with certainty in specific cases, and there is usually no other recourse to compensation for injured individuals. In the committee's judgment, this has led to a situation in which jurors and courts may be inclined to view tort awards as a means of providing compensation, irrespective of misconduct or scientific considerations.

These circumstances require the manufacturer of a vaccine known to have certain adverse effects to engage in a gamble with very large financial stakes. If an increasing number of courts impose liability, the costs will be enormous, because claims average several million dollars per case. The only way to eliminate the risk is to stop manufacturing the vaccine. If the manufacturer chooses to continue to market the vaccine, its only options are to attempt to settle claims, a strategy that could produce a general expectation of liability, or to resist claims in litigation, with the risk that unfavorable outcomes could establish liability. The cost of either strategy will be high (even if claims are defended successfully) and will have to be passed on to consumers in price increases.

To determine the exact nature of concerns over potential liability for vaccine-related injury, the committee conducted an informal survey of vaccine manufacturers. The goal was to solicit information (much of which was commercially sensitive) on the number and size of vaccine injury claims and settlements over the past decade, and on the provisions made by manufacturers for dealing with such eventualities (e.g., insurance). The committee received information from most major companies actively involved in vaccine production. The manner in which the information on these issues was available did not always permit comparisons or aggregation for publication (which was an agreed upon condition of providing such data). For these reasons, the information summarized below should not be taken as a totally comprehensive picture of the situation.

At the time of the initial survey (spring 1984), 166 suits were pending against the four responding manufacturers. The total amount paid in settlements in the previous decade for completed cases (settled or finished with the appeal process) had been $2 million, and about another $1.8 million had been spent on legal defense, not in all cases including salary and expenses of "in-house" counsel.

The information gathered in a follow-up effort (spring 1985) revealed that about 65 additional suits had been filed in the intervening year (only a few of the previous total had been settled, some for amounts averaging $1 million; some trial verdicts were on appeal). Legal costs for the 1-year period ranged up to "several million dollars" for some manufacturers. Time series information supplied by two manufacturers indicated a sharp increase in the number of claims filed: their experiences varied considerably, but the total number of reported claims filed against them in 1983 was more than twice that filed in 1980.

Over the past two decades, pharmaceutical companies have been withdrawing from vaccine manufacturing and marketing. Increasingly, the liability situation and its consequences (i.e., litigation costs or difficulty in obtaining insurance coverage) have been cited as major factors in the decision to withdraw. These decisions seem to indicate that present or anticipated vaccine-related injury liability expenses are seen as an unreasonable burden (or an unacceptably risky gamble) in relation to the costs of product development and the income from sales.

Manufacturers are apprehensive that without some means of compensation for unavoidable vaccine injury and temporally related conditions, the present unclear state of the law will continue to allow them to be held liable for such conditions and penalized financially.

The future behavior of the courts and the responses of the manufacturers cannot be predicted with certainty, but the committee is concerned that the apprehensions themselves might have a negative effect. Earlier withdrawals from the market have created a situation in which the United States is almost totally reliant on one manufacturer for polio and DTP vaccines (Lederle), and on another for measles, mumps, and rubella vaccines (Merck Sharp & Dohme). If apprehensions about the current unclear state of the law caused these manufacturers to withdraw, the vaccine supply and immunization programs could be jeopardized, leading to possible resurgence of these diseases. Also, the apprehensions discussed above are a disincentive to investment in the development of new (or improved) immunizing agents and to competition from new or foreign firms.

Proposals to remedy the compensation and liability problems connected with vaccine injury are discussed below.

A NATIONAL VACCINE COMMISSION

The lack of a formal mechanism to promote cooperation in the innovation, production, and use of vaccines limits the benefits obtainable from existing immunization programs and hampers the development of new programs. The problems associated with the absence of such a mechanism are primarily those of omission rather than commission: they include delay or inefficiency in achieving desired outcomes and failure to tackle problems for which no existing group has direct responsibility.

To overcome these difficulties, the committee recommends the establishment of a national vaccine commission. This commission would monitor all aspects of immunization efforts in the United States. One of its primary responsibilities would be early identification of potential problems affecting vaccine supply. It also would help to educate and inform the public, physicians, and government decision makers about the effects of various immunization actions and policies. When necessary, the commission would become an impartial broker to promote the availability of needed vaccines and to coordinate collaborative activities for which no suitable mechanism exists.

Based on its analysis of the options and its knowledge of the fate of previous recommendations, the committee favors establishment of the commission as a congressionally chartered, nonprofit corporation. However, certain other loci for its operations are not altogether incompatible with the purposes of the commission.

The committee suggests that the vaccine commission should be supported at least in part by federal appropriations. It should report at least annually to the Congress and the President, and on other occasions if immediate action is required to avert threats to the public health. Recommendations for membership on the commission's board of directors should be sought from groups representing health care providers, lawyers, pharmaceutical manufacturers, the insurance industry, public interest organizations, universities, and the international health community. Representatives of relevant government agencies would be appointed as liaison members.

The mode of operation of the commission should be determined by the commission itself. Possible activities include monitoring the availability of existing vaccines; monitoring the need for improvement of existing vaccines and setting priorities in this area; monitoring vaccine innovation activities in the public and private sectors; monitoring the vaccine needs of developing countries and promoting efforts to meet those needs; evaluating the potential applications of advances in basic biotechnology to vaccine development; evaluating the application of knowledge from the behavioral sciences in the design of campaigns to promote vaccines; reviewing the effectiveness of promotional campaigns; monitoring and evaluating patterns of infectious disease as an aid to determining priorities; monitoring the training of personnel needed to ensure continued vaccine innovation; and monitoring and evaluating legal issues related to vaccine development and use.

COMPENSATION AND LIABILITY FOR VACCINE-RELATED INJURY

A variety of methods exist for dealing with the problems arising from vaccine-related injury, the most serious of which are the need to compensate injured individuals and the need to reduce deterrents to vaccine manufacturing. The committee evaluated eight individual options and two combined approaches from the range of possible actions—some address only one aspect of this complex situation and others address a broader range of issues. The 10 alternatives are:

- a supplementary (nonexclusive) compensation system
- a compensation system with restricted tort options
- mandatory claim review by a compensation board with tort option
- a vaccine supply public insurance program
- promotion of no-fault insurance for vaccine-related injury
- a supplementary compensation system and a vaccine supply public insurance program
- a vaccine supply public insurance program and promotion of no-fault insurance for vaccine-related injury

- changes in the tort law relating to liability for vaccine-related injury (two examples are described)
- federal assumption of liability for all vaccine-related injury
- acceptance of vaccine price increases to cover liability costs

The committee believes that the goal of advancing the control of infectious diseases with vaccines should be pursued in as just and fair a manner as possible. Those who respond to the government's promotion of or legal requirement for vaccination confer benefits on other members of society because they reduce the risk of disease in the community. If vaccination results in an injury, the injured individual should be certain of receiving rapid and adequate compensation. The common law tort system cannot be relied on to provide such compensation because each claim requires an extended, costly, and complex adjudicative procedure to establish liability. The results of these procedures are erratic and unpredictable, and therefore inequitable.

The committee urges political decision makers to develop a compensation system for vaccine-related injury with the features outlined in this report. It also recommends that action be taken to reduce the serious deterrents to vaccine manufacturing and innovation that arise from the unpredictable nature of the current liability situation (such action should not shield those suspected of possible misconduct). The information and analysis presented in this report should help guide policymakers in the choice of appropriate solutions.

2

Vaccines: Past, Present, and Future

TYPES OF IMMUNIZATION

Immunization involves the induction (or administration) of antibodies and other natural defense mechanisms to protect against specific pathogens. There are two types of immunization, active and passive.

Active immunization is the major focus of this report. It involves the administration of a modified pathogenic agent, or a component of a pathogen, to stimulate the recipient's immune mechanisms to produce long-lasting protection without causing the clinical manifestations or other consequences of disease.

Three major types of preparations are employed to produce active immunity. The first consists of vaccines made from whole, inactivated (killed) pathogens or components of a pathogen.[1] Examples of whole, inactivated vaccines include currently licensed pertussis vaccines, influenza vaccines, and the Salk poliovirus vaccine. The pneumococcal, meningococcal, and hepatitis B vaccines are among those that contain the immunity-producing fraction of the pathogen.

Toxoids are the second type of active immunogen. The diphtheria and tetanus vaccines are good examples. Toxoids are toxins that have been treated by physical or chemical means until they no longer produce clinical disease, but retain the capacity to induce immunity.

Attenuated infectious vaccines are the third type. Virus vaccines in this group are derived from the offending organism after it has undergone repeated passages in the laboratory in culture; it remains infectious for man but loses the ability to induce clinical disease. Examples include the oral (Sabin) poliovirus vaccine, and the measles, mumps, rubella, and yellow fever vaccines. Other examples of this type of vaccine contain live organisms or agents that are related to but different from the species that causes the disease. These vaccines produce "cross-reacting" immunity. Examples include the vaccinia virus vaccine used to prevent smallpox and BCG (Bacillus Calmette-Guerin), which is used in some countries for immunization against tuberculosis, but only rarely administered for this purpose in the United States.

Passive immunization is accomplished by transferring antibodies against a given disease from an immune person or animal to a nonimmune

individual, usually by injection of serum (antisera) or some partially purified serum extract. Examples are diphtheria and tetanus antitoxins, and immune serum globulin for the prevention of hepatitis. In some diseases, such as diphtheria, passive immunization is effective not only as a preventive measure, but also as a treatment. Immunity acquired in this way is transient, however; it usually requires recognition or anticipation of exposure, and is not infrequently associated with untoward side effects such as serum sickness, manifested by transient fever and arthritis resulting from hypersensitivity to animal sera.

HISTORY OF IMMUNIZATION

Active immunization began with smallpox and was based on the observation that immunity could be conferred by rubbing smallpox scabs against the skin, which usually resulted in a mild case of the disease.[2] Inoculation of susceptibles with infectious material from individuals with mild smallpox was practiced in China and Africa many centuries ago. It was introduced in Britain and the American colonies early in the eighteenth century. It is interesting to note that these inoculations caused an occasional death, resulting even then in controversy about the benefits and risks of the procedure. These concerns led to the search for a "better vaccine."

This search eventually focused on the fact that a vesicular eruption of cow udders, known as cowpox, often led to the development of small blisters or "milkers' nodes" on the hands of milkmaids.[2] By the middle of the eighteenth century, physicians recognized that persons infected with cowpox appeared to be protected from later exposure to smallpox, resulting in Edward Jenner's classic experiment in 1796.

Use of the smallpox vaccine spread quickly in the united States. In fact, the vaccine was the subject of the nation's first law regulating the distribution of drugs, the Vaccine Act of 1813.[3] This act authorized the President to appoint a federal agent to "preserve the genuine vaccine matter, and to furnish the same to any citizen" who requested it. It was repealed in 1822, after Congress decided that vaccine regulation should be left to local authorities.

The apparent success of early smallpox vaccination efforts and the developing science of microbiology led to other attempts to control feared infectious diseases in the late nineteenth century. Among these was the Pasteur method of active immunization against rabies, first tested in a child in 1885.[4]

Serum therapy, later called antitoxin therapy, began in the early 1890s with the discovery that animals inoculated with heat-killed broth cultures of diphtheria or tetanus bacilli were able to survive subsequent (otherwise fatal) inoculations with those organisms. Early researchers did not realize at first that the (cell-free) supernatant of the broth culture, not the killed bacteria, was responsible for the development of immunity.[5] It also was shown that protection derived

from immunization could be transferred to other animals by inoculating them with body fluids, such as serum, obtained from those that had been immunized. The first child with diphtheria treated with antitoxin was in Berlin in 1891.[5] By the mid-1890s, diphtheria antitoxin was produced for widespread use in both Britain and Germany.[6] The antitoxin was first produced and tested in the United States in 1895 by the Mulford Company of Philadelphia, later absorbed by Merck Sharp & Dohme.

The effectiveness of diphtheria antitoxin in the prevention and treatment of diphtheria (although not 100 percent) led a number of competing companies, both in the United States and abroad, to begin to manufacture it for commercial purposes. In the absence of regulations for testing and certification, substandard, ineffective, or dangerous preparations were sometimes produced and sold, occasionally by charlatans. At first, warnings by responsible authorities went essentially unheeded.[6]

Concerns about uncontrolled production of smallpox vaccine and diphtheria antitoxin were expressed in editorials in the Journal of the American Medical Association late in 1894.[7,8] The potential role of state governments in supervising the propagation of vaccine virus was discussed at the National Conference of State Boards of Health held that December.[7] The recognized variability in the efficacy of different smallpox vaccines was attributed, at least in part, to defective preparations.

On December 5, 1894, the New York City Board of Health instructed the Health Department to develop a plan that would assure the potency and purity of diphtheria antitoxin preparations sold in New York City.[8] Although antitoxin shipped in small amounts from two German manufacturers appeared to exhibit acceptable purity and efficacy, some antitoxins from the United States were never subjected to testing and at least one that was tested was inert. Profiteering by manufacturers of presumably effective antitoxins also was lamented by the authorities.

When the concern reached the Congress, an Illinois member recommended that Congress create a national commission for the investigation of the antitoxin treatment of diphtheria.[8] Unfortunately, no definitive action was taken until 1902. This action followed the deaths from tetanus of 13 children in St. Louis who received diphtheria antitoxin prepared from a horse that shortly thereafter died of tetanus.[6] (The antitoxin, incidentally, was prepared by the St. Louis City Health Department, not by a commercial firm.)

This tragedy and the furor it caused in the public press resulted in the passage of the virus-toxin act by Congress in 1902.[6] This act established a board under the Department of the Treasury to develop licensing regulations for the producers of vaccines and antitoxins for interstate or foreign commerce. Under the direction of this board, the Hygienic Laboratory of the Public Health Service was authorized to inspect manufacturing establishments, issue and revoke licenses, and in other ways ensure, insofar as possible, the safety

and efficacy of these biologics. By 1904, licenses had been issued to 13 manufacturers of biologics, primarily smallpox vaccine and diphtheria antitoxin. The number of producers licensed reached 41 by 1921. Standards for potency were developed at the Hygienic Laboratory. Manufacturers failing to meet acceptable standards had their licenses revoked or refused.

These responsibilities were later transferred to the National Microbiological Institute of the National Institutes of Health (NIH) The 1902 act subsequently was incorporated into the Public Health Service Act of 1944. In the 1950s, the Public Health Service Hygienic Laboratory was reconstituted as the Division of Biologics Standards at the NIH, and in 1972 these responsibilities were transferred to the Food and Drug Administration (FDA) with the establishment of the Bureau of Biologics. By 1971, regulations had been established for more than 80 generic biological products employed for passive and active immunization. More recently, the Bureau of Biologics (as the Office of Biologics Research and Review [OBRR]) was combined with the Bureau of Drugs in the FDA to form the Center for Drugs and Biologics.

Following the transfer of the Division of Biologics Standards to the FDA in 1972, procedures were developed for the review of safety, effectiveness, and labeling of biologics. The Bureau of Biologics established outside consultant panels, three of which were concerned with vaccines and antitoxins. These panels reviewed vaccines, toxoids, and products used for passive immunization against bacterial diseases; viral and rickettsial vaccines and products used for passive immunization against viral diseases; and bacterial preparations "without U.S. standards of potency" (e.g., older products such as "mixed respiratory vaccines"). The panels were charged with evaluating the generic safety and efficacy of all vaccines, immunoglobulins, and antitoxins, and with assessing the individual products. After evaluating the safety and efficacy of a manufacturer's preparation, the panels' options were to recommend maintenance of licensure, maintenance of licensure for a limited number of years until further evidence of efficacy could be obtained (only for products deemed to be safe), or revocation of licensure. The final reports of these panels were submitted to the Commissioner of the FDA by 1979.

In creasing evidence in the early 1900s of the effectiveness of diphtheria antitoxin and smallpox vaccination led to the idea that many or all infectious diseases might be amenable to immunologic prevention and therapy. Tetanus antitoxin, prepared in horses, came into general use in the military during World War I. For the first few months of the war, antitoxin was not employed by the British, and monthly rates of tetanus per 1,000 wounded reached the extraordinary figure of 32.[9] With the advent of antitoxin, the British rate was reduced to 1.2. For U.S. wounded during World War I, to whom tetanus antitoxin was given universally, the rate was 0.16 per 1,000.[9] Between the two world wars, tetanus toxoid was developed; by 1940, it was obligatory in the French army,[9] and its mandated use for U.S. military during World War II kept the number of cases of tetanus in the U.S. Armed Forces to 12.[10] By the late 1940s, tetanus toxoid

was recommended as a routine public health measure for all children in the United States and usually was administered in combination with diphtheria toxoid and pertussis vaccine.

The ability to induce immunity to diphtheria in animals with diphtheria toxin suggested that the same could be applied to man. The first preparation for active immunization against diphtheria was a mixture of toxin and antitoxin, and was introduced in 1913.[11] Although effective, this product was not entirely satisfactory because of instability of the mixture and allergic reaction of some recipients to horse serum. Diphtheria toxoid (toxin inactivated by formalin) was developed in the early 1920s, and it has been used, with minor modifications, since the mid 1930s.

The first definitive experiments with pertussis vaccine were conducted in the 1920s.[12] Because the portions of the pertussis organism responsible for clinical immunity to whooping cough had not been identified, the vaccine was composed of whole, killed organisms. Progress in improving the vaccine was slow, and it was still considered experimental in the early 1940s;[13] by the late 1940s, however, several studies had demonstrated its efficacy.[14,15] The pertussis bacterium has been unusually slow in yielding its biological secrets, and as a consequence current U.S. vaccines, though better standardized, still contain the whole, killed organism. Some progress has been made recently, however, in improving our understanding of this organism and its relationship to human disease and immunity.[16]

After World War II, remarkable advances were made in the development of vaccines for other diseases. Such developments were made possible by better understanding of the microorganisms involved, advances in immunology, and the use of cell culture techniques for the propagation of viruses. In rapid succession, viral vaccines were developed for the control of poliomyelitis, measles, rubella, and mumps. Safe, effective vaccines were developed for use under special circumstances in individuals in jeopardy from rabies (replacing older vaccines made from central nervous system tissues of animals), adenovirus infections, meningococcal disease, and others.

It is clear that vaccines widely employed as public health measures in the United States and other industrialized countries have had an enormous impact on morbidity and mortality. Major achievements include the following:[17,18]

- The last confirmed cases of smallpox were reported in 1977; in May 1980, the World Health Organization announced global eradication of smallpox.[17]
- Reported U.S. rubella cases dropped from 57,686 cases with 29 deaths in 1969 to 2,325 cases and 4 deaths in 1982.
- The incidence of measles in the United States decreased from 894,134 reported cases with more than 2,250 deaths in 1941 to 1,497 reported cases and 2 deaths in 1983.
- The incidence of mumps in the United States dropped from 150,000 reported cases in 1968 to fewer than 3,500 reported cases in 1983.
- The average incidence of diphtheria in the United States between 1980 and 1984 was 3 cases per year with 1 or no deaths. In contrast,

in the late 1950s the number of reported cases averaged more than 1,000 per year with about 75 deaths per year.

- Reported U.S. tetanus cases and deaths dropped steadily from a high of 601 cases in 1948 to fewer than 95 cases in 1983.
- Paralytic poliomyelitis, which afflicted more than 57,000 persons in the U.S. in 1952, is now a rarity; fewer than 4 cases were reported in 1984.
- The incidence of pertussis in the United States dropped from a high of 265,269 reported cases with more than 7,500 deaths in 1934, to fewer than 2,000 cases with only 4 deaths in 1982.[18]

Much of the success in the United States can be attributed to the high levels of vaccination among young children that result from the school immunization laws. In the developing world, only about 30 percent of children are vaccinated.

THE PRESENT

Twelve commercial manufacturers (five of which only produce vaccines abroad), two state laboratories, and one university are licensed to produce one or more vaccines for use in the United States. Vaccines against 20 different infectious diseases are marketed, several in various combinations. Three are licensed for use in the military only. Seven vaccines (pertussis; poliomyelitis viruses 1, 2, and 3; measles virus; mumps virus; and rubella virus; and the diphtheria and tetanus toxoids) are recommended for routine administration to all children. The other vaccines are intended primarily for use in groups of individuals who are at special risk because of circumstances such as age, exposure, life-style, or underlying health problems. Often, these vaccines have very limited use; an example is anthrax vaccine, which is recommended only for persons who work with animal hides and a few laboratory personnel who come into contact with the organism.

Many other infections should be amenable to control by immunization, and a variety of potential vaccines are in different stages of development.[19] Vaccines for varicella (chicken pox) and rotavirus diarrhea are being evaluated and probably will be licensed soon.* Studies of vaccines for hepatitis A, both types of herpes simplex infections, cytomegalovirus, gonorrhea, and group B streptococci are in progress. Prospects for vaccines against various vital respiratory and intestinal illnesses are good. The whole field of immunization against parasitic scourges, such as malaria and schistosomiasis, is only beginning to develop.

In contrast to the trial-and-error fashion in which the earliest vaccines, such as those for smallpox and diphtheria, were developed, most current vaccine innovation is based on increasing knowledge of

* A vaccine against Hemophilus influenzae type b, the most frequent cause of meningitis in young children, was licensed April 12, 1985.

microbiology, mechanisms of infection and immunity, and the cellular biology of the infecting organisms, including basic biochemical structures and molecular genetics. These developments offer promise of immunologic prevention of many widespread infectious diseases that hitherto have not been amenable to control, and will help meet new needs for vaccines. Changes in life-style, hygiene, and the environment cause shifts in the patterns of infectious diseases. Advances in medicine also produce new target populations, e.g., transplant patients and others whose immune systems have been suppressed for therapeutic reasons.

Development of Vaccines and Recommendations for Vaccine Use

The development of a new vaccine to the point of application for licensure is a complex, arduous, and expensive process involving both public-and private-sector participants. The initial steps in the process include assessments of the impact of the infectious disease (measured by rates of mortality, acute morbidity, and permanent sequelae in the population); of the estimated cost of the disease and the projected costs of development, production, and administration of the vaccine; and of the vaccine's ranking among other health care priorities. Of major importance to commercial manufacturers is the likely utilization, i.e., the market, which is dependent both on acceptance of the vaccine by the public and the enthusiasm of physicians and other health care providers. Assuming that the health and economic impacts of the disease appear to warrant pursuit of a vaccine, many problems of a technical and practical nature must be identified and solved.

Identification of the causative organism is only the first step. The pathogenesis of the infection (how the organism produces the disease), what components of the organism are responsible for the manifestations of the disease (infectivity, virulence, pathogenicity) and which determine subsequent immunity, and whether current techniques can be anticipated to produce a safe and effective immunizing agent all represent crucial questions. The basic research necessary to answer these questions, which is often extremely time-consuming and expensive, usually is performed by investigators exploring the natural history of the disease. Commercial manufacturers rarely consider the possibility of a specific vaccine until the groundwork has been laid, typically by academic or government researchers.

The most basic technical requirement is the ability to consistently produce the organism (maintaining its immunogenicity) in the laboratory in sufficient quantities for study and, ultimately, for vaccine production. A reliable means must be found to measure immunity without exposure to disease. Researchers also must determine if the organism exists as more than one immunologically distinct type. For example, there are more than 80 immunologically distinct types of pneumococci, and infection or immunization with one type generally produces strong immunity only to that specific type.

Many questions depend on the nature of the organism. For example,

in the case of an anticipated bacterial vaccine, can the immunity-producing component(s) be separated from irrelevant, potentially toxic moieties? Can the immunogenic antigen of a virus be extracted or, employing techniques of genetic engineering, be incorporated into another organism? In the case of a potential live vaccine, can the virulence of the pathogen be attenuated in the laboratory, and can reversion to the more virulent form be avoided with certainty?

The development of an animal model to evaluate toxicity, potency, and, if possible, clinical protection usually is desired. In addition, laboratory tests must be established, insofar as possible, to assess the toxicity and potency of the vaccine in a manner that correlates with test results in man.

These steps to understanding an infectious disease and developing preventive measures such as vaccines are conducted with continuing formal and informal consultations among agencies of the federal government, concerned scientists, and manufacturers. Conferences, often sponsored by federal agencies and professional societies and sometimes by manufacturers, provide useful opportunities to exchange advice, counsel, and ideas, and to coordinate efforts in the development of a vaccine.

After the extensive and complex background work outlined above has been completed and it appears that the proposed vaccine offers promise of safety and efficacy, permission may be sought from the OBRR for studies in humans.[20] By regulation, this involves filing a permit referred to as an IND (Notice of Claimed Exemption for Investigational New Drug). To obtain an IND, the responsible investigators must meet appropriate specifications that cover everything from evidence of sterility of the product to the qualifications of the investigators and the approaches to testing in humans. Full background data in support of the proposed vaccine and its use must be provided.

Three sequential phases of evaluation must be described in an IND. Phase 1 constitutes initial testing of the vaccine in a small number of persons to determine first its safety and then its immunogenicity at various dose levels and for different routes of administration. Phase 2 studies include administration of the vaccine to a larger number of persons to obtain further data on adverse effects and the immune response, and, perhaps, limited evidence of disease prevention.

Phase 1 and 2 studies often overlap, and the results provide the basis for Phase 3 studies, which are controlled field trials with sufficient study subjects to develop reasonable estimates of safety and efficacy. Efficacy usually is measured in terms of protection against clinical disease. Situations in which controlled field trials are not possible or ethical include the testing of an improved, presumably more efficacious vaccine for an otherwise fatal disease, such as rabies, for which there is already a vaccine that protects many or most persons. In these and other cases, it may be necessary to employ serologic or other methods to ascertain the development of immunity. The use of such surrogate methods requires firm evidence of a direct correlation between the results of the method and clinical protection in humans.

By federal regulation, any Phase 1, 2, or 3 study conducted on a population by an institution, such as a university, must be approved by that institution's review committee for protection of human subjects. Strict regulations exist for the institutional review mechanism, and include monitoring of all studies at least once a year. Progress reports by the investigator also must be submitted at least annually to the FDA.

It is generally desirable for Phase 3 studies to be conducted at more than one institution and by different investigators. The number of study subjects required varies with the disease and the vaccine, but usually is in the hundreds or thousands. It is important to ensure that there is adequate representation of all population groups for whom the vaccine may be recommended. The license application process includes review of all records of production, testing, and clinical evaluation by the OBRR. The product itself is submitted to laboratory testing by appropriate scientists at the OBRR, who also conduct on-site inspection of the production facilities. Customarily, although not by regulation, the OBRR convenes one or more meetings of the Vaccines and Related Biological Products Advisory Committee for full discussion and review of the product, its projected uses, and its labeling. When the OBRR is satisfied that the product is safe and effective, a license may be granted. Each marketed vaccine requires such a license, as does each vaccine manufacturer.

Although hundreds or thousands of individuals may have received a vaccine prior to licensure, these numbers are insufficient to identify rare untoward events resulting from the vaccine. (A classic example of an unexpected, rare reaction was the Guillain-Barré syndrome that occurred at a very low rate in persons who received the swine flu vaccine in 1976 [Chapter 5].) Therefore, the OBRR encourages continuing surveillance of recipients as a vaccine becomes widely used. Any reports of untoward events must be made available by the manufacturer for review by the OBRR.

After licensure, the manufacturer must submit data on each new production lot and samples of vaccine to the OBRR for testing. The OBRR also periodically reinspects manufacturing facilities.

Recommendations for vaccine use in the United States are made by a number of advisory groups, most notably the Immunization Practices Advisory Committee (ACIP) of the U.S. Public Health Service, the American Academy of Pediatrics, through its Committee on Infectious Diseases, and the Committee on Immunization of the Council of Medical Societies, American College of Physicians (ACP). These committees maintain close liaison with each other and with the OBRR, thus assuring reasonable consistency between manufacturers' labeling and recommendations by the advisory bodies.

The Department of the Army oversees efforts to develop vaccines needed to protect military personnel (and others at risk) from a range of pathogens not generally encountered by the U.S. civilian population.[21] These include tropical disease pathogens and potential biological warfare agents. Research conducted for these purposes is often valuable in a broader context, e.g., contributions to the development of a vaccine for malaria. Recommendations for the use of

these vaccines for military personnel are developed by the Armed Forces Epidemiological Board. As with vaccines for general public use, the ultimate availability of these vaccines depends on the willingness of a commercial manufacturer to undertake final development and production.

These mechanisms for developing new vaccines, for pursuing licensure, and for establishing recommendations for use are complex and time-consuming, but are clearly necessary to ensure to the extent possible that marketed vaccines are acceptably safe and effective. Further, it is to be expected that the nascent technology for the production of vaccines by genetic engineering will increase the responsibilities and activities of the OBRR and public advisory groups concerned with recommendations for vaccine use.

THE FUTURE

New technologies and better understanding of the immune process have launched a new era in the field of immunization. On the horizon are effective vaccines for a wide spectrum of human ailments, the vital diarrheal diseases, malaria, and other parasitic diseases responsible for enormous morbidity and mortality. Many current vaccines (especially the killed viral and bacterial vaccines) contain superfluous materials (some derived from the production substrates) that could contribute to reactivity and that are irrelevant to the production of immunity. Through further research, we may soon have the capability to replace existing vaccines with specific antigens that are more efficacious, safer, and possibly less expensive.

It is hoped that these vaccines with improved immunogenicity and stability will lead to greater utilization of immunization throughout the world. Millions of children in less-developed countries are disabled or die from diseases that are preventable. Also, no country can be considered safe from a disease as long as it persists in other populations—geographic isolation from disease threats is an unrealistic concept in the current age of extensive travel.

Prospects for new vaccines stem primarily from advances in genetic engineering and the ability to define the antigens responsible for inducing clinical immunity. Current laboratory goals are to determine the precise biochemical structures of these antigens and to synthesize them.

The greatest advances have occurred in the area of vital vaccines, but it is expected that these techniques also will be applicable to the production of bacterial vaccines and, ultimately, parasitic vaccines. Among the approaches available are:[22]

Recombinant DNA Techniques In this approach, the genetic material responsible for production of the immunity-inducing antigen is incorporated into the genetic apparatus of another replicating virus, bacterium, yeast, or animal cell. The result is a hybrid organism that replicates and produces the antigen desired, often in large amounts. A vaccine is made from the purified antigen. The production

of a potential new hepatitis B vaccine illustrates this process: the DNA sequence coding for hepatitis B surface antigen is incorporated into yeast and activated to synthesize the antigen, which is then purified. Preliminary tests indicate that the product is effective in humans.[23] A variant of the same approach that shows promise involves incorporation of the gene for a desired immunizing antigen into a virus that produces a generally benign infection in man, such as the vaccinia virus (smallpox vaccine). Preliminary experiments in nonhuman primates indicate that this approach may be efficacious. These recombinant DNA vaccines offer promise of effective products that are less reactive and less expensive.

Polypeptide Synthesis The ability to define the amino acid sequence of protein subunits (peptides) has allowed researchers to characterize the structures of some immunogenic peptides. Based on this knowledge, several viral antigens have been synthesized. These early man-made antigens are less immunogenic than natural viral antigens, but researchers believe that this situation will improve with further study. In some cases, adjuvants may be required to boost immunogenicity. The synthetic antigens, because of their purity, are expected to be less reactogenic and safer than their natural counterparts. Also, the cost of large-scale production of these antigens probably will be relatively low.

Specific Attenuation of Pathogens The third type consists of modified or attenuated live pathogens, usually viruses. The live, attenuated oral poliovirus vaccine is one example of how this approach can be used. The principal disadvantage of these vaccines is that they contain viruses that have the potential to revert to a virulent, disease-producing form. Fortunately, increasing knowledge of molecular biology is providing a better understanding of many of the changes or mutations that occur in the process of attenuation. Comparing the nucleotide sequences of fully attenuated viruses with those of partially attenuated or fully virulent forms ultimately may provide a mechanism for early recognition of potential mutation of a live vaccine to the more virulent, disease-producing form. Methods of manipulation that result in an attenuated virus incapable of reversion would be even more desirable. Two possible approaches are being studied. One involves gene reassortment, segregation of genes responsible for protection from those responsible for disease manifestations, to produce a nonvirulent but still infectious variant of the same virus. The second approach is "deletion mutation," which would result in the production of a mutant that is incapable of reversion to virulence because it lacks a specific gene.

Anti-Idiotype Antibodies Most remarkable are prospects for the development of anti-idiotype antibodies. The idiotype of an antibody molecule is a recognition site located at or near its antigen-binding site;[22] the idiotype acts as an antigenic site when the body makes anti-antibody molecules (a natural immune system mechanism used to control the level of antibodies in the blood). In some cases, the anti-idiotype antibody appears to resemble the antigenic site of the original antigen and can induce a similar immune response. For example, anti-idiotype antibodies directed against antibody to the

hepatitis antigen HBsAg may induce protection against hepatitis. Theoretically, this approach could produce a vaccine that contained no vital components whatsoever, but a variety of technical and safety questions must be resolved before its full potential is known.

Based on these and possibly other techniques, prospects for new and better vaccines are considerable. Their development, however, may be impeded by the same problems (discussed in subsequent chapters) that deter development of vaccines by traditional methods. These problems must be resolved before the full public health benefits of new approaches to vaccine development can be achieved.

REFERENCES AND NOTES

1. Mortimer, E.A., Jr. 1978. Immunization against infectious disease: active immunization programs are endangered by complacency and litigation. Science 200:902-907.
2. Dixon, C.W. 1962. Smallpox. Boston: Little, Brown.
3. Hutt, P.B. 1983. Investigations and reports respecting FDA regulations of new drugs (Part 1). Clin. Pharmacol. Ther. 33:537-548; 674-687.
4. Pasteur, L. 1884. Méthodé pour prévenir la rage après morsure. C.R. Acad. Sci. 98:457-464.
5. Andrewes, F.W., Bulloch, W., Douglas, S.R., Dreyer, G., Gardner, A.D., Fildes, P., and Ledingham, J.C.G. 1923. Diphtheria: Bacteriology, Pathology, and Immunology. London: His Majesty's Stationary Office.
6. Kondratas, R.A. 1982. Death helped write the biologics law. FDA Consum. 16:23-25.
7. Editorial. 1894. A timely topic. JAMA 23:919-920.
8. JAMA. 1894. Public health. JAMA 23:923-924.
9. Holmes, W.H. 1940. Pp. 351-382 in Bacillary and Rickettsial Infections. New York: MacMillan.
10. Edsall, G. 1959. Report to the council on drugs. Specific prophylaxis of tetanus. JAMA 71:417-427.
11. Dick, G.F., and Dick, G.H. 1929. Immunization against diphtheria. Comparative value of toxoid and toxin-antitoxin mixtures. JAMA 92:1901-1903.
12. Miller, D.L., Alverslade, R., and Ross, E.M. 1982. Whooping cough and whooping cough vaccine: the risks and benefits debate. Epidemiol. Rev. 4:1-24.
13. Holmes, W.H. 1940. Whooping-cough or pertussis. Pp. 394-414 in Bacillary and Rickettsial Infections, W.H. Holmes, ed. New York: MacMillan.
14. Kendrick, P., and Eldering, G. 1939. A study in active immunization against pertussis. Am. J. Hyg. 29:133-153.
15. Sako, W. 1947. Studies on pertussis immunization. J. Pediatr. 30:29-40.
16. Manclark, C.R. 1981. Pertussis vaccine research. Bull. WHO 59:9-15.

17. WHO Chronicle. 1980. Decisions of the health assembly. Declaration of global smallpox eradication. WHO Chron. 34:258.
18. Eddins, D. 1985. Personal communication, Centers for Disease Control, Atlanta, Ga.
19. Institute of Medicine. 1985. New Vaccine Development: Establishing Priorities, Volume 1. Diseases of Importance in the United States. Washington, D.C.: National Academy Press. This report presents the findings of the Institute of Medicine's Committee on Issues and Priorities for New Vaccine Development, which was asked by the National Institute of Allergy and Infectious Diseases, NIH, to design a comprehensive approach to setting priorities for accelerated vaccine development. The method developed by the committee is based on a quantitative model in which vaccine candidates are ranked according to two principal characteristics: expected health benefits (reduction of morbidity and mortality) and expected net costs of achieving the benefits (which are sometimes negative, i.e., savings). Volume 1 of this study describes application of the model to diseases of importance in the United States. Volume 2 will evaluate the usefulness of the model in setting priorities for vaccines needed by technologically less developed nations.
20. Food and Drug Administration. 1966. New drug regulations. Amendment to part 130. Fed. Regist., March 24, 1966, 31 F.R. 4891.
21. Walter Reed Army Institute of Research. 1981. Proceedings of the Workshop on Infectious Disease Threats to the Rapid Deployment Force: Preventive Strategies, July 14-15, 1981. Washington, D.C.: Walter Reed Army Institute of Research.
22. Chanock, R.M. 1984. Summary. Pp. 439-446 in Modern Approaches to Vaccines. Molecular and Chemical Basis of Virus Virulence and Immunogenicity, R.M. Chanock and R.A. Lerner, eds. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory.
23. Jilg, W., Schmidt, M., Zoulek, G., Lorbeer, B., Wilkse, B., and Deinhardt, F. 1984. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 11:1174-1175.

3

Vaccine Availability: Concerns, Barriers, and Impediments

Concerns about the nation's vaccine supply and the factors that affect it are not new. In 1976, the Assistant Secretary for Health convened the National Immunization Work Groups to identify problems associated with immunization programs, including maintaining vaccine supply and continuing innovation.[1] Three years later, the congressional Office of Technology Assessment studied similar issues and produced A Review of Selected Federal Vaccine and Immunization Policies.[2] To date, no significant actions have been taken to implement the solutions offered by either group.

Many of the problems studied by the Work Groups and OTA have worsened. In this chapter, the committee examines the current situation, including concerns over the present supply, and evaluates some alternatives to existing supply mechanisms. It also identifies specific barriers to vaccine innovation and improvement. The decision to pursue vaccine development usually depends, in part, on assessments of the potential market; the final portion of this chapter explores the determinants of vaccine utilization.

CONCERNS ABOUT THE CURRENT SITUATION

Supply

Each of the major pediatric vaccines (or vaccine combinations) used in the United States is now supplied by only one or at most two distributors (Chapter 4). The situation regarding the supply of the combined diphtheria-tetanus-pertussis (DTP) vaccine is disconcertingly unstable. Two of the three commercial firms marketing DTP at the outset of the study in May 1983 (Lederle Laboratories, Squibb-Connaught, and Wyeth Laboratories), have ceased distribution in 1984. Wyeth Laboratories announced on June 13, 1984, that it intended to discontinue the sale and distribution of pertussis vaccine because of extreme liability exposure, the high cost of litigation, and the difficulty of obtaining adequate insurance at premiums considered acceptable by its managers. Wyeth subsequently agreed to supply

Lederle with vaccine for distribution under the latter's label for an unspecified period.[3] In June 1984, Squibb-Connaught Laboratories informed the Centers for Disease Control (CDC) that it would fill only existing contracts, because it was unable to obtain insurance at acceptable premiums to cover its liability risks.[4] (Immediately prior to the printing of this report, Connaught Laboratories obtained insurance that allowed it to resume distribution of DTP vaccine.) Spot shortages of vaccine were reported to the American Academy of Pediatrics during the fall of 1984.[5]

These events demonstrate that the United States is precariously dependent on an extremely small number of companies for the major pediatric vaccines. (Polio, measles, mumps, and rubella vaccines are supplied by only a single manufacturer.) State laboratories in Massachusetts and Michigan produce some vaccines, primarily for intrastate use, but their production facilities are very limited.

More recent events provide a good example of the problems associated with reliance on sole suppliers. Hopps noted in 1983, in a background paper for this study, that there had been several instances in which supplies were at least threatened for a limited period of time, but that "there is no single documented instance of a serious major break in the supply of either bacterial or vital vaccines."[6] Unfortunately, this is no longer true. On December 14, 1984, the U.S. Public Health Service Interagency Group to Monitor Vaccine Development, Production and Usage reported via the Centers for Disease Control that a DTP shortage would occur beginning in January 1985.[7]

Events contributing to this situation included the actions described above by Wyeth and Squibb-Connaught, and the fact that some lots of Lederle DTP did not meet the manufacturer's requirements for release. The shortage originally was anticipated to last through most of 1985.[7] The estimated duration of the shortage was the subject of hearings before the subcommittee on Health and the Environment, Committee on Energy and Commerce, House of Representatives, on December 19, 1984. Testimony at these hearings from Squibb-Connaught indicated that they had continued manufacturing vaccine and would be willing to distribute it if some federal protection were provided from liability risks.[8]

In response to the anticipated shortage, the Interagency Group to Monitor Vaccine Development, Production and Usage recommended that all health care providers postpone administration of the DTP vaccine doses usually given at 18 months and 4 to 6 years (the fourth and fifth doses) until adequate supplies of vaccine became available.[7]

The suspected mode of transmission of pertussis suggests that unvaccinated or partially immunized infants, particularly those who have older siblings, are at greatest risk of complications from pertussis.[9] The CDC stressed its expectation that the recommendation to modify vaccine schedules would protect these infants.[4] (Reductions in immunization levels substantially greater than that expected in this country were associated with increases in the incidences of pertussis cases and deaths in the United Kingdom and

Japan.[10]) This series of events highlights the dangers inherent in a sole-supplier situation.*

The supply of vaccines can be interrupted by a variety of technical problems, as well as by commercial decisions. Potential problems, described by Hopps,[6] include:

- potency variation
- stability problems
- quantitative imbalance of microbial components in polyvalent or combination vaccines
- variations in the response to inactivation processes
- excessive undesirable biological activity, e.g., neurovirulence
- inadvertent contamination (chemical or microbial)

Vaccine manufacturing requires major investment in a sophisticated production plant and the establishment of teams with multidisciplinary expertise in the large-scale production of biological products. Thus, firms that have experience in vaccine production represent a unique combination of resources that would be extremely difficult to duplicate.

The decision by vaccine manufacturers to cease production of a particular product results in the dispersion of these teams and, perhaps, the disassembly of the production facilities. Reversal of this process cannot be achieved cheaply or rapidly—as might be desired in the case of a vaccine needed for military personnel. Hence, the committee believes that there are serious dangers (in addition to possible vaccine supply problems) in permitting the continued decline of the number of vaccine manufacturers.

The long-term prospects for an adequate supply of personnel with vaccine-related technological skills are reasonably good, because of the increasing use of biotechnology and bioengineering for other purposes. However, only a healthy industry can attract scientists and technicians of the desired caliber.

Stockpiling of Vaccines

In 1982, the CDC requested funds to establish a rotating stockpile of vaccines sufficient to meet national needs for 6 months in case of an interruption in supply. The following year, $4.57 million was allotted for this purpose and stockpiling began. In 1984, the CDC requested $20.5 million for stockpiling. The Public Health Service reduced this request to $8 million, and the Office of Management and Budget reduced it further to $4 million. The amount of funds received for stockpiling totaled $4,572,000 for 1983, $4,000,000 for 1984, and

* The decision by Connaught to resume distribution of DTP vaccine, announced immediately prior to the printing of this report, led the CDC to recommend reinstatement of regular vaccination schedules.

$4,000,000 for 1985.[11] It is estimated that several years will be required to build up the 6-month stockpile with this level of funding.

Because only single U.S. suppliers existed for oral polio vaccine and for the measles, mumps, and rubella vaccine combined in 1983, it was decided to use all fiscal year 1983 funds for these vaccines—the threat of an interruption in the supply of DTP vaccine with three manufacturers was not considered as great. A solicitation by the CDC for supply of DTP vaccine for stockpiling was issued in April 1984. Squibb-Connaught, Inc., was the only supplier to respond to this solicitation. On June 15, 1984, Squibb-Connaught, Inc., wrote to the CDC requesting that its offer on the contract solicitation be placed on hold pending clarification of its insurance coverage; later that month, the company withdrew all offers on solicitations from the CDC and state and local health departments.[4]

In December 1984, stockpiles of major childhood vaccines were estimated to be 15 weeks for oral poliomyelitis vaccine and 12 weeks for measles, mumps, and rubella vaccine combined. Stockpiles of inactivated poliomyelitis vaccine (8 weeks) and diphtheria and tetanus toxoids (DT, 11 weeks; Td, 5 weeks) also had been established. No stockpile of pertussis vaccine (marketed only as DTP) had been started.[12]

Stockpiling provides a highly desirable protection against the possibility of a temporary, brief interruption in the production of a vaccine, especially one produced by a single supplier. Its capacity to protect against repeated interruptions in supply depends on the magnitude of the stockpile. Recent price increases mean that the cost of establishing 6-month stockpiles will be considerably greater than when originally proposed. Vaccines have a finite shelf life; hence, stockpiles must be rotated (older vaccines are released from the stockpile to purchasers at prevailing prices and are replaced with fresh supplies).

The stockpiling approach, as currently envisaged and implemented, does not (and is not intended to) provide protection against the possibility that a single supplier will cease production and distribution of a vaccine. If a manufacturer is already producing a vaccine, increasing output requires approximately 6 to 8 months.[13] The addition of a new vaccine to the product line of an existing manufacturer probably would take even longer, although not as long as construction and staffing of a totally new production facility (2 to 4 years). These time periods are considerably beyond the scope of any existing or projected stockpile, and possibly beyond any stockpiling approach that is financially realistic.

The committee is not aware of any contingency plan for dealing with a situation in which no U.S. commercial manufacturer is willing to produce a major childhood vaccine. The committee believes that it is unlikely that foreign manufacturers would be willing to distribute such vaccines in the United States because of the liability situation.[4,14] Even if such a source could be found, there are problems inherent in relying on foreign sole-source suppliers.

Problems with Sole Reliance on Foreign Manufacturers

The withdrawal of current U.S. vaccine manufacturers could lead to reliance for supply on foreign manufacturers, if they were willing to distribute their products in the United States. A variety of factors could cause problems in this situation.[6]

Geographical distance could result in delays in licensing submissions and other communications, and lengthen the chain of supply. Vaccine stability problems could occur if the distribution were particularly slow. Language barriers also could produce problems, especially in the resolution of highly technical issues.

Political considerations might arise during a shortage if a foreign manufacturer felt a primary obligation to meet the needs of its home country before exporting vaccine. Differences in regulatory requirements might require manufacturers abroad to add laboratory and regulatory staff, because U.S. standards are often more stringent. This increased cost might be reflected in vaccine prices, although it could be offset by lower foreign labor costs.

These factors provide added support for the committee's presumption that a healthy U.S. vaccine industry is a necessity. Reliance on foreign manufacturers as sole-source suppliers is not a desirable situation, although they could provide beneficial competition in a stronger U.S. market. In any case, few foreign firms have shown any desire to distribute vaccine products in this country. The considerations that deter their entry have not been examined in detail, but liability issues and low profitability have been cited as major apprehensions.[14]

Federal Action to Ensure Vaccine Supply

The supply of vaccines could be ensured by the federal government. The Office of Technology Assessment addressed this issue, especially with regard to the production of "orphan" vaccines.[2] Supplies could be maintained by direct federal production or by guaranteed contracts with manufacturers, such as those used by the Army to obtain needed vaccines. Employment of these options may become necessary if current sole suppliers find continued "open market" commercial operation no longer viable. The willingness of manufacturers to supply vaccines for public use under guaranteed contracts probably would depend on prior agreements on liability responsibilities.

The possibility of federal vaccine production raises a number of policy questions. These include the range of vaccines that might be produced, whether the facility would compete with commercial manufacturers, and the question of liability for injury from federally produced vaccines. The committee did not consider itself an appropriate forum to resolve these issues, but did review other aspects of potential federal production. For example, a government production bureaucracy in the role of a sole supplier might not be subject to the market pressures that often lead to innovation and the application of new technologies.

The committee recognizes that existing state production laboratories have excellent safety and production records, but believes that federal production on the scale required to meet national needs might not prove a totally satisfactory solution.

Thus, the committee believes that, at present, solutions to the problem of ensuring vaccine supply should employ the facilities and expertise already existing in the private sector. It suggests that a national vaccine commission, proposed in Chapter 7, be charged with developing contingency plans and making recommendations, on a case-by-case basis, for ensuring vaccine availability. These plans should include the possibility of direct federal involvement in vaccine supply if commercial manufacturers continue to withdraw from marketing.

BARRIERS AND IMPEDIMENTS TO VACCINE INNOVATION

One of the goals of this study was to define the barriers and impediments to vaccine innovation, including vaccine improvement. The issues discussed below were identified in the course of the committee's work as the primary factors in the debate on what, if anything, needs to be done to ensure the desirable level of vaccine innovation.

For the lay public, the successes achieved by immunization may appear to diminish the need for ongoing vaccine innovation. Many existing vaccines are not optimal, however, and should be replaced by safer, more effective preparations. Also, vaccines are not available for many diseases of importance in the united States, including varicella-zoster, cytomegalovirus, hepatitis A, Herpes simplex, rotavirus, gonorrhea, and others.[15] The list is even longer for countries in the tropics where parasitic diseases are an additional major problem.

Identification of Need and Establishing Priorities

Federal resources for basic research on infectious diseases and for vaccine development are limited. Hence, some rational method is needed to identify priorities for these health-related investments. A disease must be defined as clinically important relative to others to warrant the efforts required to understand the etiologic agent (s), host responses to the agent(s), and the pathobiology in human beings. The Institute of Medicine report New Vaccine Development: Establishing Priorities provides a quantifiable approach for comparing the health impact of diseases and for setting priorities among vaccine development projects.[15]

Establishing the Technical Feasibility of Vaccine Development

Modern vaccine development requires a firm scientific foundation. Among the factors that must be understood are the nature of the

etiologic agent, including the number of serotypes and the identity of important immunogenic antigens; the nature of the host response to the antigen(s); the clinical manifestations of the disease; and the epidemiology of the disease.

Impediments at this crucial stage begin with the inability to recognize and isolate an etiologic agent(s). For example, Legionnaires' disease was not recognized as a definable entity until 1976, although in retrospect evidence of infection and disease had existed since the mid-1940s. "Serum hepatitis" was described as early as 1833,[16] but it was not clearly distinguished from infectious hepatitis until the 1940s.[17] The discovery of Australia antigen (now designated as hepatitis B surface antigen) in 1965 and its subsequent association with serum hepatitis were essential elements in the development and use of a hepatitis B vaccine.[18,19,20] The identification of a retrovirus as the probable etiologic agent of acquired immune deficiency syndrome (AIDS) removes one barrier to the development of a vaccine for that disease.

For some pathogens, the knowledge may be lacking to say which antigens should be incorporated into a vaccine to provide the desired immunity (gonorrhea is a current example). Delays in acquiring the necessary information may be exacerbated by constraints on funding for basic research and training, especially in disease pathogenesis.

Vaccine Improvement Lack of basic knowledge also may impose barriers to the improvement of vaccines. As noted in Chapter 2, some vaccines that were developed empirically have contributed to drastic reductions in their target diseases, especially after standardization of the vaccine preparation. Pertussis vaccine is an example. In these cases, an understandable tendency exists to divert resources to the control of other pressing disease problems. Unfortunately, when the need for an improved vaccine is recognized, the knowledge base may be inadequate because basic research on the pathogenesis of the disease and the mode of action of the vaccine has not been afforded a high priority.

Economic Disincentives to Innovation and Production

Pharmaceutical manufacturers may be unwilling to undertake development of a vaccine even if the need and potential technical feasibility have been established. (The capacity of the public sector to undertake vaccine development is limited, primarily by financial considerations, but also by other resource limitations, e.g., lack of expertise and facilities for production.)

The potential disincentives or impediments at the development stage are primarily economic and are examined more fully elsewhere in this report. They include:

- complexity of development, production, and quality control; lengthy vaccine production processes may adversely affect inventory and cash flow

- cost of research and development in relation to anticipated sales (Chapter 4)
- perception that vaccines historically have received less effective patent protection than drugs
- apprehension over the liability situation (Chapter 6)

Factors Influencing the Market for Vaccines

Factors that influence anticipated vaccine sales or profitability are described below (precise information on the profitability of vaccines is regarded as proprietary information and was not available to the committee):

- The basic requirement that a vaccine deliver long-lasting or lifelong immunity is at odds with the prospect of multiple/repeated sales. This reflects the fact that vaccines represent a higher level of technology than drugs, but makes them less attractive as commercial products. If a vaccine eradicates a disease, as in the case of smallpox, the market no longer exists. Also, the success of a vaccine in reducing the apparent threat of a disease, e.g., pertussis, tetanus, or measles, reduces the perceived need for it.
- Export sales are usually small (compared with drug sales).[21] United States manufacturers are often at a disadvantage competing in foreign markets because U.S. regulatory requirements are more stringent and many foreign governments actively promote or underwrite vaccine production (Appendix G).
- A large proportion of the doses of many pediatric vaccines (about 40 to 50 percent) are purchased by federal or state governments at reduced prices.[4] The effect of these purchases on profits is uncertain.
- Experience has shown that the achievable market for a vaccine may be considerably less than would be expected on the basis of its potential economic and health benefits because of misperceptions among health care providers and the public.

VACCINE UTILIZATION

The decision to develop and manufacture new vaccines undoubtedly is affected by the pharmaceutical firms' estimates of subsequent utilization. As noted above, the actual market size for a particular vaccine (especially for adult vaccines) often is substantially smaller than the population whose health it could protect or for whom it would be cost-effective.[22,23,24,25] Various features of the care delivery system, and of clients and health professionals, contribute to vaccine underutilization.*

* The following sections were prepared originally for the report of the Committee on Issues and Priorities for New Vaccine Development, Institute of Medicine.[15]

System Factors

Characteristics of the medical care system and payment practices influence patterns of vaccine use and market size. In general, the system slights preventive technologies, such as vaccines, and overemphasizes diagnostic and therapeutic technologies. Medical education and the attitudes of medical professionals encourage the use of sophisticated technologies for acute care. With the exception of pediatricians, medical specialists generally are not attuned to prevention and do little to encourage the use of preventive technologies by patients.

Lack of information also may contribute to lower use of vaccines. The system does not emphasize provision of information to clients or to health professionals about the risks of certain diseases or the benefits and risks of vaccines. Underutilization of vaccines for communicable diseases is especially likely because benefits to society as a whole (through reduced transmission) often exceed the benefits to individuals.

Insurance coverage and payment practices reflect and reinforce these patterns of technology use. Health insurance routinely covers diagnostic and therapeutic procedures for acute care, and new methods based on expensive, sophisticated technologies.[26] In contrast, few insurance policies cover preventive procedures (including vaccination). The Medicare program covers only pneumococcal vaccine and hepatitis vaccine for patients with end-stage renal disease, despite several bills that have been introduced in Congress over the years to cover other vaccines, such as influenza. Medicare does cover vaccines used for treatment, however, including tetanus toxoid administered in the course of treating an injury.

Client Factors

Utilization is determined, in part, by characteristics of the target population, including its access to health care providers and the ease with which its members can be identified by the health care system (in turn, dependent on size, composition, age, and socioeconomic status of the target population). Also important are target population attitudes toward the vaccine, particularly those related to perceptions of the likelihood of contracting the disease, its severity if contracted, and the vaccine's efficacy and safety.

Many investigations examining lay attitudes toward vaccines and the relationship between these attitudes and utilization have employed a Health Belief Model (HBM), depicted in Figure 3.1. This model is based on the hypothesis that willingness to undertake a recommended preventive health measure depends on (1) the individual's subjective state of readiness to take action, which is determined both by perceptions of the likelihood of susceptibility to the particular illness and perceptions of the probable severity of the consequences (organic and social) of contracting the disease; (2) the individual's evaluation of the feasibility and efficacy of the advocated health

behavior (i.e., an estimate of the action's potential benefits in reducing susceptibility, severity, or both), weighed against perceptions of physical, psychological, financial, and other barrier s involved in the proposed action; and (3) the occurrence of one or more cues to action to stimulate conscious or semiconscious feelings about the disease threat or about the recommended action.[27]

Cues to action may be either internal (e.g., symptoms) or external (e.g., mass media or interpersonal communications). Although it is assumed that diverse demographic and sociopsychological variables may, in any given instance, influence an individual' s health-related attitudes and beliefs, these variables are not thought to be direct causes of health action.[28]

The literature provides considerable empirical support for the usefulness of the HBM in accounting for an individual's health-related decisions.[29] Table 3.1 summarizes findings from studies that have examined one or more of the HBM elements as determinants of vaccine-acceptance behavior. These findings indicate that factors included in the HBM play a significant role in decisions about vaccination. They suggest that efforts to maximize public participation in immunization programs should begin with a survey of the intended vaccine recipients to obtain information about their HBM-related perceptions. If a problem is noted, those promoting the vaccine can develop and implement a campaign that addresses and modifies the perceptions most likely to act as obstacles.

In some cases, lay perception of a vaccine's safety may be the most important obstacle to its acceptance (e.g., concern about the occurrence of Gulllain-Barré syndrome interfered with the influenza vaccination programs after the swine flu episode). In other instances, the difficulty may be a low perception of the severity of the disease. This has occurred with measles and influenza. There is also evidence supporting the important role played by the provider's recommendation.[30]

Provider Factors

The question of whether or not a provider will "accept" a new vaccine fits logically within the framework provided by literature on the adoption and diffusion of medical innovations in the health profession.[32] Researchers in this area generally have posited that three classes of variables are important: (1) characteristics of the adopters (in this case, both the providers and their patients); (2) characteristics of the innovation (the vaccine); and (3) characteristics of the "setting" into which the innovation is introduced (e.g., the norms and values of a population or population subgroup or the norms and policies of a health care delivery organization).[33]

Investigations show that the diffusion of many new medical technologies depends on their successful adoption by "opinion leaders" in the relevant medical community. Compared with their colleagues, opinion leaders tend to be younger, to hold more advanced degrees, to be more active in national health and medical organizations, to be

more interested in publishing in scientific journals, to be more likely to read and be influenced by research reports in scientific journals (they rate them as their primary source of reliable information), and to be more aware of the latest advances in their areas of specialization. These opinion leaders influence their colleagues, who use them as a primary source of credible information and advice—this process then continues as a cascade of influence.

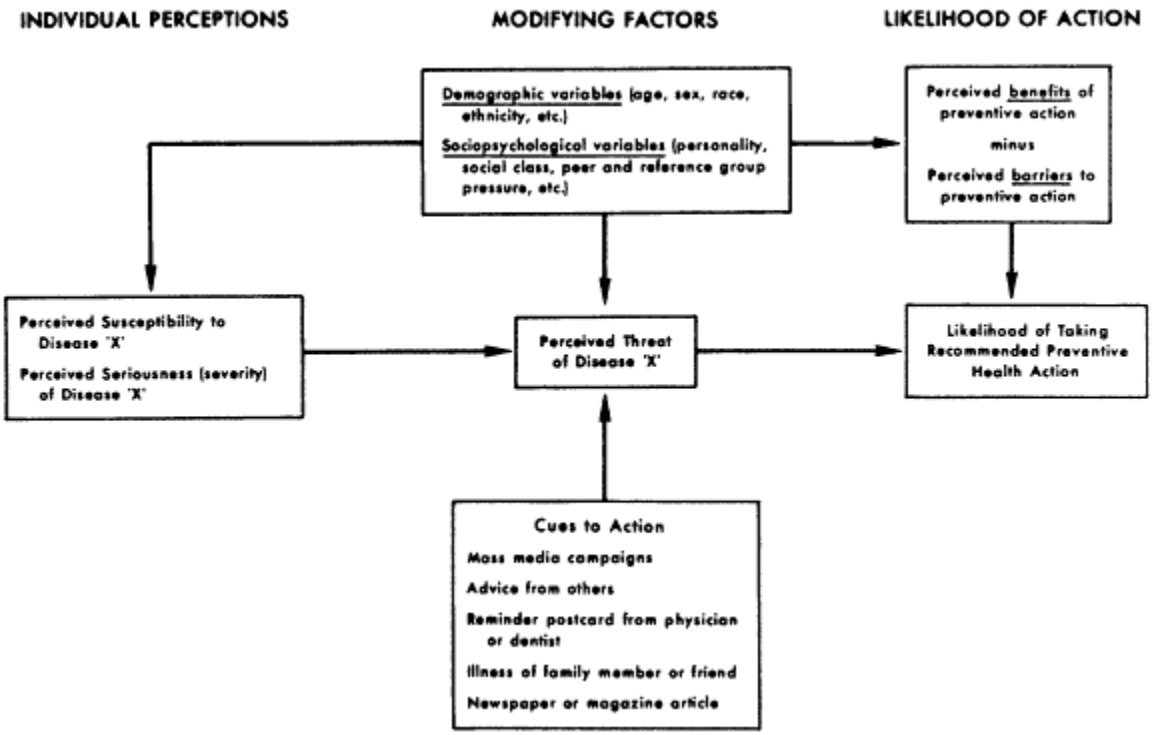

Figure 3.1
Variables and relationships in the health belief model.
Reprinted, with permission, from Becker, M.H., Haefner, D.P., Kasl, J.P., Kirscht, J.P., Maiman, L.A., and Rosenstock, I.M. 1977. Selected psychosocial models and correlates of individual health-related behaviors, Medical Care (supplement), 15(5):27-46.

These findings suggest that if one wishes to increase the likelihood or rate of acceptance of a new vaccine by health care providers, efforts at persuasion should be concentrated on those physicians and other providers who exercise the relevant opinion leadership. Scarce influence resources should not be spread evenly across all providers.[33]

Innovations themselves possess characteristics that have been shown to influence their potential for adoption by providers.[34] These include:

- relative advantage—the degree to which the innovation is perceived as being better than the idea it supersedes (Is the new vaccine superior to what was previously available to prevent or treat the disease in terms of efficacy, safety, costs, ease of administration, and other factors?)

TABLE 3.1 Summary of Studies Using One or More Health Belief Model Variables to Explain Degree of Public Acceptance of Recommendations to Obtain Vaccination

Investigators	Recommended Vaccination	Susceptibility	Severity	Benefits	Barriers
Rosenstock et al. (1959)	Polio	+	+	+	+
Leventhal et al. (1960)	Influenza	+	+	n.m.[a]	n.m.[a]
Becker et al. (1977)	Well-child clinic visits (immunizations)	+	+	+	+
Opinion Research Corporation (1978)	7-13 diseases (vaccines)	+	+	+	+
Aho (1979)	Swine flu	?[b]	?[b]	+	+
Rundall and Wheeler (1979)	Swine flu	+	+	+	+
Cummings et al. (1979)	Swine flu	+	+	+	n.s.[c]
Larson et al. (1982)	Influenza	+	+	+	+

NOTE: Complete references for this table are presented in References and Notes, no. 31.
[a] Not measured.
[b] Assessment unclear.
[c] Not significant.

- compatibility—the degree to which the innovation "fits in" with existing values, procedures, past experiences, etc. (Does the vaccine require new techniques of administration, new personnel, or interactions with groups of clients not familiar with vaccination processes?)
- complexity—the degree to which the innovation is seen as relatively difficult to understand and use (Is the new vaccine's mode of operation, mode of administration, or follow-up schedule simple or complex?)
- suitability for pilot studies—the degree to which the innovation can be implemented and assessed on a limited basis (Does the new vaccine require large commitments of resources?)
- observability—the degree to which the results of adopting the innovation are visible to others (How much time must elapse before the provider is able to estimate the benefits and adverse effects associated with prescription of the new vaccine in a group of patients?)
- risk—the degree to which adopting the innovation poses danger to the adopter (Can the new vaccine cause serious injury to some recipients? Is the provider who prescribes the vaccine earlier than his peers likely to be admired or scorned? Will the provider be protected against possible litigation?) Riddiough et al.[35] list several factors that may influence physicians' vaccine-prescribing behavior and that seem to fit within one or more of the innovation characteristics described above:

- attitudes and knowledge about the targeted disease
- attitudes and knowledge about the safety and efficacy of vaccines
- perceptions about a patient's need for vaccination
- consideration of revenue generated by administering vaccines
- consideration of the potential liability for vaccine-related injury

They suggest that concern about possible adverse reactions and concomitant legal action are the greatest obstacles to physician acceptance. They add that:

> [I]n assessing a patient's need for a particular vaccine, physicians may consider (a) the likelihood of the patient's being exposed to a given disease-producing organism; (b) the patient's vulnerability to the disease after being exposed to the organism; and (c) the extent to which contracting the disease will disrupt the patient's life.[35]

In other words, it is possible to describe a "health belief model" for physicians with dimensions parallel to those for the patient (although the physician's perceptions may be quite different from those of the patient).

When attempting to influence the adoption and diffusion of a new vaccine, it is extremely important to obtain information from the

potential adopters about how they rate the innovation.[34] If these ratings indicate that one or more of the vaccine's characteristics present obstacles, at least two courses of action are possible: (1) attempt to persuade the potential adopters that their perceptions about those characteristics are wrong or (2) attempt to alter the real or perceived characteristics of the vaccine to overcome the adopters' objections.[33]

Provider prescribing behavior is influenced by the setting in which the behavior takes place (e.g., the structure of the health care delivery organization, or group versus solo practice).[36] Some communities or population subgroups hold beliefs, attitudes, and norms that oppose vaccination in general or that oppose a particular vaccine. Any campaign to introduce a new vaccine should be based on a prior assessment of the relevant setting, taking into account important sources of opposition.

CONCLUSIONS

The committee's assessment of the current vaccine situation leads to the following conclusions.

There is cause for grave concern over the nation's vaccine supply. Many factors contribute to this concern: most major pediatric vaccines and many other vaccines are available only from sole suppliers; the manufacture of vaccines can be interrupted by a variety of technical problems; stockpiling cannot be expected to guard against the withdrawal of a sole manufacturer; there are no contingency plans to prepare for such a possibility; and sole reliance on foreign manufacturers does not offer a practicable solution.

The supply of vaccines could be ensured if the federal government were willing to become the manufacturer of last resort or to enter into guaranteed contracts with manufacturers for needed vaccines. The possibility of federal vaccine production raises many complex policy questions, including the question of liability for injury from such vaccines.

The committee believes that, at present, solutions to the problem of ensuring vaccine supply should employ the facilities, resources, and expertise already existing in the commercial vaccine industry. It recommends, however, that a national vaccine commission, proposed in Chapter 7, should develop contingency plans and recommendations, on a case-by-case basis, for ensuring vaccine availability. These plans should include the possibility of direct federal involvement in vaccine supply, if commercial manufacturers find continued "open market" operation no longer viable.

Barriers and Impediments to Vaccine Innovation

Modern vaccine development requires a firm scientific foundation, based on an understanding of the pathogen and the host (human) response to it. Limitations of funding for basic research and training,

especially in disease pathogenesis, may contribute to delays in acquiring the necessary knowledge to develop new vaccines or improve existing ones.

Specific economic deterrents to vaccine innovation and production include:

- the complexity of development, production, and quality control
- the cost of research and development in relation to anticipated sales
- a perception that vaccines historically have received less effective patent protection than drugs
- apprehension over the liability situation

In addition, the need for a vaccine to deliver lifelong or long-lasting immunity is at odds with the prospect of multiple or repeat sales, and the prospects for export sales are poor. Finally, the achievable market may not reflect the true public health benefits of a vaccine because certain features of the health care delivery system and of clients and health care providers contribute to vaccine underutilization.

The widespread, timely adoption and diffusion of new technologies depends on their successful adoption by "opinion leaders" in the relevant medical community. This suggests that spreading scarce resources across all providers to increase awareness of new approaches (such as the use of new vaccines) may not be as successful as concentrating on those who exercise opinion leadership.

Considerable empirical evidence supports the usefulness of the "health belief model" in accounting for individuals' health-related decisions. Efforts to maximize public participation in immunization programs should begin with a survey of intended vaccine recipients to obtain information on their perceptions of the disease and the vaccine. Those promoting the vaccine can then develop and implement a campaign that addresses and modifies the (mis)perceptions most likely to act as obstacles.

REFERENCES AND NOTES

1. National Immunization Work Group. 1977. Report and Recommendations of the National Immunization Work Group. McLean, Va.: J.R.B. Associates.
2. United States Congress, Office of Technology Assessment. 1979. A Review of Selected Federal Vaccine and Immunization Policies. Washington, D.C.: U.S. Government Printing Office.
3. Shaw, D. 1984. Testimony for Wyeth Laboratories on H.R. 5810 before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, December 19, 1984, Washington, D.C.
4. Mason, J. 1984. Testimony on H.R. 5810 before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, December 19, 1984, Washington, D.C.

5. Smith, M. 1984. Testimony on H.R. 5810 before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, December 19, 1984, Washington, D.C.
6. Hopps, H. 1983. Unpublished paper prepared for the Committee on Public-Private Sector Relations in Vaccine Innovation, Institute of Medicine, National Academy of Sciences, Washington, D.C.
7. Centers for Disease Control. 1984. Diphtheria-tetanus-pertussis vaccine shortage—United States. Morbid. Mortal. Weekly Rept. 33:695-696.
8. Williams, D. 1984. Testimony for Connaught Laboratories, Inc. on H.R. 5810 before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, December 19, 1984, Washington, D.C.
9. Centers for Disease Control. 1984. Pertussis transmission. Morbid. Mortal. Weekly Rept. 33:2-5.
10. Fulginiti, V.A. 1984. Editorial. Pertussis disease, vaccine and controversy. JAMA 251:251.
11. Pickelsimer, C.F. 1984. Personal communication, Office of Financial Management, Centers for Disease Control, Atlanta, Ga.
12. Teske, R. 1984. Personal communication, Division of Immunization, Centers for Disease Control, Atlanta, Ga.
13. Johnson, R.B. 1984. Testimony for Lederle Laboratories on H.R. 5810 before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, December 19, 1984, Washington, D.C.
14. Beale, A.J. 1985. Modern approaches to the development of vaccines: perspective of a traditional manufacturer. Pp. 377-381 in Vaccines 85. Molecular and Chemical Basis of Resistance to Parasitic, Bacterial, and Viral Diseases, R.A. Lerner, R.M. Chanock, and F. Brown, eds. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory.
15. Institute of Medicine. 1985. New Vaccine Development: Establishing Priorities, Volume 1. Diseases of Importance in the United States. Washington, D.C.: National Academy Press.
16. Lurmann, A. 1855. Eine icterus epidemic. Berl. Klin. Wochenschr. 22:20.
17. Paul, J., Havens, W.P., Sabin, A.B., and Philip, C.B. 1945. Transmission experiments in serum jaundice and infectious hepatitis. JAMA 128:911-915.
18. Blumberg, B.S., Alter, H.J., Visnich, S. 1965. A "new" antigen in leukemia sera. JAMA 191:541-546.
19. Krugman, S., Giles, J.P., and Hammon, J. 1967. Infectious hepatitis: evidence for two distinctive clinical, epidemiological and immunological types of infection. JAMA 200:365-373.
20. Prince, A.M. 1968. An antigen detected in blood during the incubation period of serum hepatitis. Proc. Natl. Acad. Sci. USA 60:814-821.
21. Pharmaceutical Manufacturers Association. 1984. Statistical Fact Book. Washington, D.C.: Pharmaceutical Manufacturers Association.
22. U.S. Congress, Office of Technology Assessment. 1979. A Review of Selected Federal Vaccine and Immunization Policies. Washington, D.C.: U.S. Government Printing Office.

23. U.S. Congress, Office of Technology Assessment. 1981. Cost Effectiveness of Influenza Vaccination . Washington, D.C.: U.S. Government Printing Office.
24. U.S. Congress, Office of Technology Assessment. 1984. update of Federal Activities Regarding the Use of Pneumococcal Vaccine. Washington, D.C.: U.S. Government Printing Office.
25. Willems, J.S., and Sanders, C.R. 1981. Cost-effectiveness and cost-benefit analyses of vaccines. J. Infect. Dis. 144:486-493.
26. Schroeder, S., and Showstack, J. 1979. Financial incentives to perform medical procedures and laboratory tests: illustrative models of office practice. Med. Care 16:289-298.
27. Becker, M.H., ed. 1974. The Health Belief Model and Personal Health Behavior. Thorofare, N.J.: Charles B. Slack.
28. Becker, M.H., and Maiman, L.A. 1980. Strategies for enhancing patient compliance. J. Community Health 6:113-135.
29. Janz, N.K., and Becker, M.H. 1984. The health belief model: A decade later. Health Educ. Quarterly 11:1-47.
30. Cummings, K.M., Jette, A.M., Brock, B.M., and Haefner, D.P. 1979. Psychosocial determinants of immunization behavior in a swine influenza campaign. Med. Care 17:639-649.
31. Rosenstock, I.M., Derryberry, M., and Carriger, B.K. 1959. Why people fail to seek poliomyelitis vaccination. Public Health Rep. 74:98-103. Leventhal, H., Rosenstock, I.M., Hochbaum, G.M., and Carriger, B.K. 1960. Epidemic impact on the general population in two cities. Pp. 53-77 in The Impact of Asian Influenza on Community Life: A Study in Five Cities. Washington, D.C.: U.S. Government Printing Office. DHEW, PHS, Pub. No. 766. Becker, M.H., Nathanson, C.A., Drachman, R.H., and Kirscht, J.P. 1977. Mothers' health beliefs and children's clinic visits: a prospective study. J. Community Health 3:125-135. Opinion Research Corporation. 1978. Public attitudes toward immunization: August 1977 through February 1978. A study for the Centers for Disease Control, Atlanta, Georgia. Princeton, N.J.: Opinion Research Corporation. Aho, W.R. 1979. Participation of senior citizens in the swine flu inoculation program: an analysis of health belief model variables in preventive health behavior. J. Gerontol. 34:201-208. Rundall, T.G., and Wheeler, J.R.C. 1979. Factors associated with utilization of the swine flu vaccination program among senior citizens in Tompkins County. Med. Care 17:191-200. Cummings et al., see note 30. Larson, E.B., Bergman, J., Heidrich, F., Alvin, B.L., and Schneeweiss, R. 1982. Do postcard reminders improve influenza vaccination compliance? A prospective trial of different postcard "cues." Med. Care 20:639-648.
32. Greer, A.L. 1977. Advances in the study of diffusion of innovation in health care organizations. Milbank Memorial Fund Quarterly: Health and Society 505-532.
33. Becker, M.H. 1970. Factors affecting diffusion of innovations among health professionals. Am. J. Public Health 60:294-304.
34. Becker, M.H. 1970. Sociometric location and innovativeness: Reformulation and extension of the diffusion model. Am. Sociol. Rev. 35:267-282.

35. Riddiough, M.A., Willems, J.S., Sanders, C.R., and Kemp, K. 1981. Factors affecting the use of vaccines: considerations for immunization program planners. Public Health Rept. 96:528-535.
36. Becker, M.H., Stolley, P.D., Lasagna, L., McEvilla, J.D., and Sloane, L.M. 1972. Differential education concerning therapeutics and resultant physician prescribing patterns. J. Med. Educ. 47:118-127.

4

Economic Aspects of Vaccine Innovation and Manufacturing

This chapter explores economic aspects of vaccine manufacturing and development to determine whether a public policy based on market incentives provides the desirable levels of vaccine supply and innovation. The committee identified factors that tend to distort market incentives in the vaccine industry and evaluated specific policy options that could counteract their effects.*

In his testimony before a congressional hearing in 1982, Jack Bowman, then president of Lederle Laboratories, estimated that the total cost of developing a vaccine for Hemophilus influenzae type b (a cause of meningitis) would be in excess of $50 million. At the same hearing, he said that the approximate cost to Lederle of a program to develop a herpes vaccine would be about $30 million.[1] Estimates by the Institute of Medicine Committee on Issues and Priorities for New Vaccine Development indicate that these figures are not extraordinary. The expected average future cost of development for a variety of vaccine candidates evaluated by that committee was between $20 million and $30 million.[2] These figures are within the range of the estimated $12 million spent to develop the pneumococcal vaccine, when the latter figure is adjusted for inflation.[3] A large proportion of development costs (such as those incurred in field trials) usually are met by industry. Estimates indicate that industry was responsible for about 50 percent of the costs of development of the pneumococcal vaccine.[3,4]

Estimation of the total cost of developing a vaccine is difficult, in part because some expenditures, e.g., funds for basic research, result in information that could have several different applications. Nonetheless, the above amounts demonstrate the approximate range of development costs.

To put these costs in perspective, note that total sales for the

* Further analysis of many of the issues discussed in this chapter will take place at a symposium on "Preventive Biomedical Technologies" projected for 1986. This symposium will focus on vaccines and is part of the "Technology and Society" series organized by the National Academy of Engineering.

entire vaccine industry amounted to only $170 million in 1982. The costs and delays to fruition of research and development (R&D) projects for vaccines are similar to those associated with the development of other new pharmaceutical products, but the total revenue stream is substantially lower for vaccines. Occasionally, the annual earnings of one successful drug may be greater than several years of revenue for the entire vaccine industry.[5]

Two current trends in the vaccine industry are noteworthy. The first relates to the problem of assuring adequate and continuous supplies of vaccines. Between 1968 and 1977, more than half of the vaccine producers in the United States ceased production,[4] and withdrawals have continued to the present.[6] In many cases, this has meant that a particular vaccine is produced by only one supplier. Table 4.1 demonstrates the extent of the sole-supplier problem as of early 1984. (Appendix A lists all current vaccine licenses, irrespective of whether the vaccine is produced or distributed.)

Events surrounding the decision by several vaccine manufacturers to stop marketing pertussis vaccine (described in Chapter 3) reflect the precarious nature of the current situation. Polio, measles, mumps, and rubella vaccines are each supplied by a single manufacturer. Lederle Laboratories was for a period the only commercial distributor of DTP vaccine. The public health implications of this sole-supplier situation, for pertussis and other vaccines, also are explored fully in Chapter 3.

The second important trend and the focus of this chapter is the apparent drop in some indirect measures of vaccine innovation activity by manufacturers. Precise documentation of the extent of this suspected decline in research and development (R&D) is difficult, in part because figures on vaccine R&D expenditures by specific companies are rarely available. Table 4.2 indicates that the percentage of total R&D devoted to biologics research (which includes vaccines) by the major pharmaceutical firms generally declined during the 1970s and early 1980s. The ratio of biologics R&D to biologics sales dropped, while the ratio of total R&D to sales for all pharmaceutical products increased slightly. Biologics R&D did not rise proportionally with biologics sales, but the increase in total pharmaceutical R&D has outstripped the rise in total sales.

Between 1979 and 1982, expenditures for biologics R&D rose proportionally at nearly the same rate as those for total pharmaceutical R&D. Unfortunately, data are not yet available for 1983 and 1984. Anecdotal information indicates that both small and large companies may have begun investing in the application of promising new technologies for vaccine development (Chapter 2); however, the lack of post-1982 data makes it difficult to determine the extent of these activities or if they will affect the trends noted above.

Table 4.3 suggests that the historical pattern of new product introductions for vaccines is very different from that of pharmaceuticals. The latter exhibited a sharp downward trend in the early 1960s (after FDA regulations became more stringent), while

TABLE 4.1 Vaccine Groups and Firms Producing Them in Early 1984

Vaccine	Firms
Adenovirus, live, oral, types 4 and 7	Wyeth Laboratories, Inc. (for Defense Dept.)
Anthrax	Michigan Dept. Public Health
BCG	Connaught Laboratories Ltd.
	Glaxo Operations U.K. Ltd.
	University of Illinois
Cholera vaccine	ISVTS[a]
	Wyeth Laboratories, Inc.
	Lederle Laboratories[b]
Diphtheria and tetanus toxoids and pertussis vaccine adsorbed[c]	Connaught Laboratories, Inc.
	Michigan Dept. Public Health
	Lederle Laboratories
	Wyeth Laboratories, Inc.
	Mass. Public Health Labs
Diphtheria toxoid	Connaught Laboratories, Inc.
	Lederle Laboratories
Hepatitis B vaccine	Merck Sharp & Dohme[d]
Influenza virus vaccine	Connaught Laboratories Inc.
	Wyeth Laboratories, Inc.
	Parke-Davis[e]
Measles virus vaccine, live, attenuated	Merck Sharp & Dohme
Measles and mumps virus vaccine, live	Merck Sharp & Dohme
Measles and rubella virus vaccine, live	Merck Sharp & Dohme
Measles, mumps and rubella virus vaccine, live	Merck Sharp & Dohme
Meningococcal polysaccharide vaccine, Groups A, C, A/C combined	Connaught Laboratories, Inc.
	Merck Sharp & Dohme
Meningococcal polysaccharide vaccine, Groups A, C, Y, W135 combined	Connaught Laboratories, Inc.
Mumps virus vaccine, live	Merck Sharp & Dohme
Pertussis adsorbed	Michigan Dept. Public Health
Plague vaccine	Cutter Laboratories, Inc.
Pneumococcal vaccine, polyvalent	Merck Sharp & Dohme
	Lederle Laboratories
Poliomyelitis (inactivated vaccine, trivalent)	Connaught Laboratories Ltd.
Poliomyelitis, oral vaccine, trivalent	Lederle Laboratories
Rabies	Institut Merieux
	Wyeth Laboratories, Inc.
Rubella virus vaccine, live	Merck Sharp & Dohme
Rubella and mumps virus vaccine, live	Merck Sharp & Dohme

vaccine introductions were stable over that period but have shown a gradual cumulative decline since the mid-1970s.*

Vaccine	Firms
Smallpox	Wyeth Laboratories, Inc. (for Defense Dept.)
Tetanus	Michigan Dept. Public Health
	Mass. Public Health Labs.
	Connaught Laboratories, Inc.
	ISVTS
Typhoid vaccine	Wyeth Laboratories, Inc.
Yellow fever	Connaught Laboratories, Inc.

[a] Istituto Sieroterapico Vaccinogeno Toscano Sclavo.
[b] Division of American Cyanamid Corporation.
[c] See text for recent changes.
[d] Division of Merck and Co., Inc.
[e] Division of Warner-Lambert Co.
SOURCE: Food and Drug Administration, and Institute of Medicine survey of producers.

Typically, a decline in the growth of an industry and in the number of manufacturers signifies one of two events in its life cycle: either it has matured, or it is experiencing problems. If the decline is the result of natural changes in demand patterns, as in the much discussed "smokestack" industries, efficiency is enhanced. Alternatively, a decline may indicate distorted incentives, e.g., a demand pattern that does not reflect the true benefit of the product. If such problems are causing an undesirable decline in the vaccine industry, government policymakers must decide whether and how to intervene.

The remainder of this chapter provides a general overview of the economic structure of the vaccine industry, possible causes of unsatisfactory market incentives, and relevant descriptive statistics.

* Data collection procedures for the two types of products are different. Pharmaceutical data are based on introduction dates; vaccine data are based on approval dates.

TABLE 4.2 R&D Expenditures and Sales (Human Use) of All U.S. Pharmaceuticals and of the Biologics Component, 1973-1982

	R&D Expenditures			Sales				
Year	Total Pharmaceuticals ($ millions)	Biologics ($ millions)	Biologics/ Total (percent)	Total Pharmaceuticals ($ millions)	Biologics ($ millions)	Biologics/ Total (percent)	Total Pharmaceutical R&D/Total Sales	Biologics R&D/ Biologics Sales
1973	643.8 (100%)[a]	25.7 (100%)[a]	4.0	5,122 (100%)[a]	138.3 (100%)[a]	2.7	0.126	0.186
1974	726.0 (113%)	32.7 (127%)	4.5	5,657 (110%)	152.7 (110%)	2.7	0.128	0.214
1975	828.6 (129%)	24.9 (97%)	3.0	6,412 (125%)	160.3 (116%)	2.5	0.129	0.155
1976	902.9 (140%)	28.0 (109%)	3.1	7,117 (139%)	121.0 (87%)	1.7	0.127	0.231
1977	984.1 (153%)	30.5 (119%)	3.1	7,705 (150%)	169.5 (123%)	2.2	0.128	0.180
1978	1,089.2 (169%)	34.9 (136%)	3.2	8,424 (164%)	235.9 (171%)	2.8	0.129	0.148
1979	1,243.1 (193%)	31.0 (121%)	2.5	9,240 (180%)	240.2 (174%)	2.6	0.134	0.129
1980	1,454.9 (226%)	45.1 (175%)	3.1	11,091 (217%)	244.0 (176%)	2.2	0.131	0.167
1981	1,764.9 (274%)	42.3 (165%)	2.4	11,926 (233%)	429.3 (310%)	3.6	0.148	0.123
1982	2,157.6 (335%)	49.6 (193%)	2.3	13,991 (273%)	489.7 (354%)	3.5	0.154	0.127

NOTES: All data are for members of the Pharmaceutical Manufacturers Association (PMA). R&D expenditures are company-financed R&D for ethical pharmaceuticals and biologics. Dosage sales are domestic sales only. Dosage sales for 1980-1982 represented 95 to 99.5 percent of total sales. Biologics are bacterial and viral vaccines, antigens, antitoxins, toxoids, and analagous products (such as allogenic extracts) as well as serums, plasmas, and other blood derivatives for human use. On certain biologics (e.g., blood products) there is probably very little R&D, hence vaccine R&D dominates the general category. Vaccine sales are likely to be a less dominant portion of total biologics sales.

[a] For ease of comparison, 1973 is set as the base year. Numbers in parentheses show percentage of 1973 values.

SOURCE: PMA Survey of Members; 1979-1980 Annual Survey Report, U.S. Pharmaceutical Industry; Faith Harbeck, personal communication, 1985, PMA.

TABLE 4.3 New Product Introductions for Vaccines and Pharmaceuticals and Average Annual Rates Over 10-Year Periods

Dates	Vaccines	Average Annual Rate	Pharmaceuticals	Average Annual Rate
1975-1983		0.77		18.0
1980-1983	4		80	
1975-1979	3		83	
1965-1974		1.50		15.9
1970-1974	11		75	
1965-1969	4		84	
1955-1964		0.60		40.0
1960-1964	6		152	
1955-1959	0		248	
1945-1954		0.30		33.3
1950-1954	2		205	
1945-1949	1		125	
1940-1944	3		67	

NOTE: Comparisons are qualified by the fact that the vaccine data include only licenses still valid in December 1984, and thus overlook an introduction if the vaccine is no longer licensed. However, any bias introduced should be in the direction of overstating the relative introductions of later time periods.
SOURCE: Committee interpretation of data supplied by Division of Product Certification, Food and Drug Administration, 1985; Pharmaceutical Manufacturers Association, 1984.

POTENTIAL CAUSES OF INDUSTRY DECLINE

Several factors may be responsible for the symptoms of decline observed in the vaccine industry. These relate to issues of property rights, regulation, market size, and liability.

Property Rights and Innovation

The issue of property rights arises with any invention or innovation. Generation of the product may be expensive and time-consuming, while imitation, diffusion, and competition may be very rapid. In response to this problem, the government awards patent protection to inventors. The promise of a period of protection to

recoup costs and earn a reasonable rate of return has led to an increased willingness to invest in innovation in many fields. In the vaccine industry, however, patent protection has been rare, and process patents are more common than the more effective product patents. A survey conducted by the committee of the manufacturers of 27 vaccine products found that they hold only 2 product patents, 1 product-by-process patent, and 7 process patents.

The patent question is especially important in relation to optimism generated by the recent emergence of the biotechnology industry. Research on innovation in the economics literature has demonstrated that small firms can be a powerful force for technological change in an industry if they can foresee the patentability of their ideas. [7] With patents, even firms without marketing channels or distribution sales forces can gain substantial returns from innovations via licensing. In the vaccine industry, this is quite important. While small biotechnology firms may not have the ability to reach a market large enough to recoup their investments in R&D, they can license their patents to large firms able to take advantage of economies of scale in marketing.

Several recent developments may alter the patent prospects of future vaccines. The first relates to the fact that most vaccines are processed from or made from components of living organisms (unlike pharmaceuticals, which are usually synthesized from chemicals). In the past, the patentability of living organisms and their derivatives was not clear; however, in 1980, the Supreme Court in Diamond v. Chakrabarty, 447 U.S. 303 (1980), held that a living thing is patentable subject matter.

Second, much vaccine-related research is conducted under government grants and in universities. Until recently, this situation often threatened the patentability of practical applications of the research because the research results were regarded as public knowledge; subsequent work could not satisfy the patent requirement of "non-obviousness." Significant changes in government funding policies (in not automatically retaining patent rights) and in the internal practices of many universities (in actively pursuing patents for faculty inventions) may be reducing these problems.

The third development that could affect investments in vaccine innovation was passage in 1984 of the Drug Price Competition and Patent Restoration Act (P.L. 98-417). This act restores, for drugs and biologics, some of the time lost on patent life while the product is awaiting pre-market approval. It also provides that the first drug of its kind to win FDA approval immediately gets a 5-year period of protection from the marketing of a generic copy licensed on the basis of the first regulatory clearance. Biologics and antibiotics are not presently eligible for this 5-year protection period. If this situation is changed, the protection could provide an incentive to increase vaccine innovation; however, it also might mean that some new vaccines would be available only from sole suppliers for the 5-year period. These developments are too recent to further assess their effects on the vaccine industry.

Regulation

Current federal safety regulations, prompted by several tragedies in the pharmaceutical industry, represent a nonmarket barrier to innovation. These regulations provide significant benefits to society, but they also increase R&D costs and manufacturers' administrative costs for all pharmaceuticals. The magnitude of the disincentive posed by regulatory clearance costs depends at least in part on the anticipated product revenues.

Safety and efficacy regulations force innovators to incur the heaviest expenses early in the development process. During several years of testing, the company is paying out "high-value" dollars in expectation of returns that are years down the road. These future returns are significantly lower in real, present value terms than their nominal size may indicate.

Market Size

A particular product may be desirable to some potential customers and yet not commercially viable because its market is too small. One possible cause of inadequate market size in the vaccine industry is the systematic undervaluation of preventive treatment in the United States, discussed in Chapter 3. Also, vaccines may be undervalued because many individuals do not have access to adequate, balanced information on the benefits of preventive care.* Media coverage of vaccines often focuses on adverse reactions,[8] hence, individuals may be more concerned about the risk of an adverse reaction than about the risk of contracting the disease.

Another factor relevant to vaccine utilization is that vaccination of an individual conveys a benefit to other members of society by protecting them against disease. Thus, total benefits from immunization programs may be greater than the sum of benefits to each recipient. Even when the consumer correctly perceives the personal benefits, the service may be underutilized when viewed from a societal perspective. As the percentage of the population that is immunized increases, an individual's chance of contracting a particular disease lessens, but the risk of adverse reactions remains unchanged. Many individuals in this situation will be tempted to be "free riders," hoping that others will choose to be inoculated but concluding that it is not in their own best interest to do so.

* Seat belts present an analogous phenomenon. Surveys of automobile drivers indicate that individuals consistently underestimate the risk of being in a serious accident; this apparently is one of the explanations for low seat-belt usage.[9]

Liability and Risk

All vaccines, even when properly produced and administered, have the potential to cause adverse reactions in some percentage of the population. Among the current problems faced by our legal system is whether and how to compensate those who incur these adverse reactions. In legal theory, vaccines are recognized as being "unavoidably unsafe," but recently some courts have moved toward a strict liability standard, i.e., one in which the manufacturer is liable for all injuries caused by the product (see Chapter 6). This has left manufacturers uncertain and apprehensive about their future liability.

Concerns over liability exposure appear to act as a disincentive to the manufacture and distribution of vaccines, and may be affecting the willingness of some companies to undertake vaccine R&D (see Chapter 6). The liability situation also may engender a lack of support by manufacturers for large-scale immunization programs sponsored by the government, such as the swine flu program.

In a survey of major vaccine producers undertaken by the committee, the manufacturers reported liability judgments to date. The respondents indicated that numerous suits and claims were pending. (These are discussed further in Chapter 6.) Submissions by the manufacturers indicate that vaccine operations are responsible for a disproportionate number of liability claims (about 40 percent) or related costs (e.g., insurance, about 60 percent) when compared with their pharmaceutical operations, even though the vaccines contribute significantly less to total sales (5 to 15 percent). Respondents reported that total defense costs over the past decade were approximately $500,000 per firm, sometimes not including in-house counsel. Most manufacturers are self-insured for large amounts; outside insurance is used for protection above these amounts. The latter is reported to be increasingly difficult to obtain at acceptable premiums. The precise nature of the disincentives arising from liability is discussed in Chapter 6.

For society at large and for the overwhelming majority of vaccine recipients, vaccination benefits dramatically outweigh the risks. Risks do exist, however, and the private sector may be unwilling to bear the cost of liability for these risks in the absence of some governmental or societal institution for risk-sharing. This could cause withdrawal from the market, i.e., failure of the market (in the broad sense) to ensure the supply of a desirable product. possible approaches to compensation and liability problems are discussed in Chapter 8.

DESCRIPTIVE STATISTICS

Data in this section offer some insights into the status of the vaccine industry at the beginning of 1984. The precise situation at the time of publication (mid-1985) was unclear, especially regarding

the DTP vaccine (Chapter 3). The evidence is difficult to interpret, but there are some indications of a distortion of normal market incentives.

The Market and Participants

Table 4.4 lists the vaccine manufacturers licensed in the United States and presents statistics on the number of product licenses

TABLE 4.4 Vaccine Manufacturers Licensed in the United States as of Early 1984

Institution	Number of Product Licenses	Number of Vaccines Produced
American Corporations		
Connaught Laboratories, Inc.	10	8[a]
Cutter Laboratories, Inc.	1	1
Lederle Laboratories	12	11
Merck Sharp & Dohme	18	10
Parke, Davis and Company	1	1
Wyeth Laboratories	15	12[a]
Foreign Institutions		
Connaught Laboratories Ltd.	3	1
Glaxo Laboratories Ltd.	1	1
Institut Merieux	1	1
Istituto Sieroterapico Vaccinogeno Tuscano Sclavo	8	6
Swiss Serum Vaccine Institute Berne	1	0
Wellcome Foundation	1	1
State Governments		
Bureau of Laboratories, Michigan Dept. of Public Health	8	6
Massachusetts Public Health Biologics Laboratories	7	5
Universities		
University of Illinois	1	1

[a] see text and Chapter 3 for recent changes. Pertussis vaccine still produced but not distributed.
SOURCE: Food and Drug Administration and Institute of Medicine survey of producers.

issued and in use in early 1984.* Fifteen different institutions hold licenses for vaccines. Among the 12 commercial licensees, only 6 are domestic proprietary firms. Of these, two produce only one vaccine. Two of the remaining four (Connaught and Wyeth) suspended distribution of DTP vaccine after the information in Table 4.4 was assembled (Connaught subsequently resumed marketing in early 1985; see Chapter 3). More than one quarter of all licenses held by private firms are unused.

TABLE 4.5 Nominal and Real Sales of Vaccines Produced for Human Use

Year	Nominal Sales (millions of dollars)[a]	Percent Change	Real Sales (millions of dollars)[b]	Percent Change
1967	36.6		36.6	
1968	40.9	11.75	39.3	7.37
1969	74.9	83.13	68.2	73.54
1970	84.7	13.08	72.8	6.74
1971	70.5	-16.77	58.1	-20.19
1972	70.5	0	56.2	-3.27
1973	83.0	17.33	62.4	11.03
1974	79.6	-4.10	53.9	-13.58
1975	76.2	-4.27	47.3	-12.29
1976	91.1	19.55	53.4	13.03
1977	99.4	9.11	54.8	2.50
1978	104.5	5.13	53.5	-2.30
1979	105.2	0.67	48.4	-9.56
1980	95.0	-9.70	38.5	-20.45
1981	130.6	37.47	47.9	24.55
1982	169.6	29.86	58.7	22.47

[a] Value of vaccine products shipped by all manufacturing establishments (vaccine products are vaccines, toxoids, and antigens for human use).
[b] Adjusted for inflation, expressed in 1967 dollars.
SOURCE: U.S. Bureau of the Census.

Table 4.5 presents sales figures for human-use vaccines between 1967 and 1982. In 1982, the total value of shipments of the domestic vaccine producers was $169.6 million. Nominal sales increased 363 percent between 1967 and 1982—a 60 percent increase in real sales (corrected for inflation). Between 1967 and 1982, a number of products were introduced to combat diseases for which vaccines previously had not been available.

Unfortunately, it is difficult to obtain good data on the actual sales by product. The only data available come from the International Marketing Services (IMS, Philadelphia, Pa.) database on hospital and drug store purchases. These data underestimate the size of the market because they do not include federal, state, or direct private physician purchases of vaccines.[10] Despite this shortcoming, they

* A vaccine against H. influenzae type b was licensed in April 1985.

can be used to evaluate percentage growth trends and the relative market power of firms in each product line if one assumes that the statistics generally reflect relative market shares of different vaccines.* Table 4.6 indicates that a few product lines have done quite well. Sales of pediatric vaccines would be expected to decline to correspond to the birth cohort once the backlog of potential recipients had been vaccinated.

TABLE 4.6 Percentage Sales Growth of Selected Vaccines 1977-1982

Product	Percent Nominal Growth	Percent Real Growth	Year Introduced
Rubella	9.9	-30.5	1970
Mumps	-51.4	-69.2	1967
Polio	101.53	27.4	1961
Influenza	75.5	10.1	1945

SOURCE: International Marketing Services, Philadelphia, Pa.

TABLE 4.7 Market Share of Four Leading Firms by Major Vaccine Subgroups

Vaccine	1961	1967	1972	1977	1982
Rubella	[a]	[a]	1.00	1.00	1.00
Polio	0.90	0.885	1.00	1.00	1.00
Mumps	1.00	1.00	1.00	1.00	1.00
Tetanus	[a]	0.658	0.957	0.987	0.996
DTP	[a]	0.603	[a]	0.987	1.00

[a] Data unavailable
SOURCE: International Marketing Services, Philadelphia, Pa.

The concentration ratios presented in Table 4.7 show that between 1962 and 1982 the industry had very few firms in any given product market. The concentration ratio is defined as the ratio of sales of the top four firms to total market sales in a specified market. The four-firm concentration ratios for various subgroups of the vaccine industry were calculated on the basis of data supplied by IMS for domestic vaccine sales. The figures show very high levels of

* Bulk federal purchases, the major potential distortion, are made only if a sole-supplier situation exists.

concentration. Only 12 commercial establishments hold licenses for vaccines in the United States. Even if these institutions were to divide the market equally, the structure would still satisfy the usual criteria for a loose oligopoly. However, the overall vaccine market is even more concentrated because it is fragmented into a variety of separate, noncompeting product lines, each with a relatively small number of producers. It is also clear that the concentration in the industry is increasing over time because of withdrawals.

It is important to note that while the industry appears to be highly concentrated, a relatively high concentration also exists on the demand side. Table 4.8 provides a breakdown of the total doses of selected vaccines, as well as the percentages of the distributions that were administered in the public sector between 1972 and 1982. It is clear that the federal government has significant market power on the buyer's side, accounting for 40 percent or more of the total sales of some vaccines. Such buyer concentration can be a countervailing force against the potential market power on the supply side.

Pricing

Pricing data are available only for a distinct subset of the market: sales to the federal government. These data are sufficient, however, to provide insights into the pricing patterns of some vaccine products during recent years. Table 4.9 presents price data for federal contract purchases of selected vaccines between 1977 and 1983. The data include both absolute dollar amounts and the percentage changes from year to year. The last three rows give the consumer price index and the Bureau of Labor Statistics indexes of price charges in the medical care industry and in the prescription drug market in particular. These data show that the rate of price increases in the market for vaccines has, in general, outstripped the rise in prices for the economy as a whole, including the price indexes for medical care and drugs.

It is significant to note that most of the price increase in the vaccine industry has occurred since 1978; indeed, many vaccines showed price decreases during the 1970s, as indicated in Table 4.10. Vaccines have risen in price relatively faster than drugs since 1978. The price of DTP vaccine, not included in Table 4.10, also rose significantly in the past two years.[11]

Many possible hypotheses could explain this observed pattern of behavior. Such pricing could reflect an industry now facing greater liability exposure. Alternatively, the prices could reflect a general "catching-up" by industry members—greater cost pressures and R&D expenses, as well as liability, forcing firms to increase prices. In either case, the implication is that the preventive care offered through immunization has become a relatively more expensive form of health maintenance.

It is important to remember, however, that none of the indexes in the last three rows take into consideration the change in quality of the products that are used to calculate the index. The effective

TABLE 4.8 Net Distribution from Manufacturers and Percentage Administered in Public Sector

	Measles		Rubella		Mumps		Polio		DPT/Td/DT	
Year	Doses (millions)	Percent	Doses (millions)	Percent	Doses (millions)	Percent	Doses (millions)	Percent	Doses (millions)	Percent
1972	8.28	51.7	7.94	66.2	—	—	24.94	38.1	—	—
1973	7.41	50.2	7.81	48.4	—	—	24.87	40.7	—	—
1974	7.06	50.2	7.59	38.2	—	—	25.24	35.4	—	—
1975	7.38	42.1	7.81	36.9	—	—	24.80	37.0	—	—
1976	7.48	39.8	6.40	39.4	4.42	26.7	19.47	40.0	29.98	26.9
1977	10.68	43.4	7.70	39.5	4.09	39.9	23.21	35.9	27.42	33.5
1978	8.93	47.9	7.55	42.8	4.65	65.6	24.58	39.1	28.01	41.7
1979	8.52	46.8	8.19	40.3	5.29	61.6	24.54	39.2	28.76	38.5
1980	7.96	43.6	7.24	41.3	5.21	58.2	23.75	37.1	32.88	33.6
1981	6.62	46.5	6.23	43.5	4.78	56.5	22.79	35.7	29.88	35.1
1982	5.44	46.7	5.57	44.3	4.36	58.7	20.63	35.4	30.55	30.9

SOURCE: Division of Immunization and Biologics Surveillance Program, Centers for Disease Control.

TABLE 4.9 Pricing Patterns for Selected Markets (Prices Indexed at 1967 = 100)

Year	Polio (dollars)	Measles (dollars)	Mumps (dollars)	Rubella (dollars)	MR[a] (dollars)	MMR[b] (dollars)	CPI[c]	Med[d]	Drugs[e]
1971	—	1.04	—	0.61	1.74	—	121.3	—	—
1972	—	1.08	—	0.57	1.78	—	125.3	—	—
1973	0.108	1.04	—	0.57	1.74	—	133.1	137.7	100.5
1974	0.080	0.98	—	0.55	1.74	—	147.7	150.5	102.9
1975	0.150	0.85	—	0.58	1.17	2.42	161.2	168.6	109.3
1976	0.185	0.71	—	0.60	1.19	2.42	170.5	184.7	115.2
1977	0.295	0.86	—	0.60	1.19	2.42	181.5	202.4	122.1
1978	0.313	0.857	1.40	0.71	1.20	2.35	195.4	219.4	131.6
1979	0.332	1.12	1.60	0.94	1.58	2.62	217.4	239.7	141.8
1980	0.354	1.15	1.63	0.97	1.64	2.71	246.8	265.9	154.8
1981	0.396	1.32	1.87	1.12	1.89	3.12	272.4	294.5	172.5
1982	0.582	1.90	2.70	1.61	2.72	4.50	287.4	323.8	190.4
1983	0.658	2.07	2.94	1.75	2.96	4.91	308.4	—	—

NOTE: Polio in 10-dose units; all other vaccines in single doses.
[a] Measles and rubella.
[b] Measles, mumps, and rubella.
[c] Consumer Price Index.
[d] Index of price charges in the medical care industry.
[e] Index of price charges in the prescription drug market.
SOURCE: Centers for Disease Control; U.S. Bureau of Labor.

TABLE 4.10 Pricing Pattern for Selected Markets (Prices Indexed at 1978 = 100)

Year	Polio	Measles	Mumps	Rubella	MR[a]	MMR[b]	CPI[c]	Med[d]	Drugs[e]
1971	—	119	—	86	145	0	62	—	—
1972	—	124	—	80	148	—	62	—	—
1973	35	119	—	80	145	—	68	63	76
1974	26	113	—	77	145	—	76	69	78
1975	48	98	—	82	98	103	83	77	83
1976	59	82	—	85	99	103	87	84	88
1977	94	99	—	85	99	103	93	92	93
1978	100	100	100	100	100	100	100	100	100
1979	106	129	114	132	132	111	111	109	108
1980	113	132	116	137	137	115	126	121	118
1981	127	152	134	158	158	133	139	134	131
1982	186	218	193	227	227	191	147	148	145
1983	210	238	210	246	247	209	158	—	—

[a] Measles and rubella.
[b] Measles, mumps, and rubella.
[c] Consumer Price Index.
[d] Index of price charges in the medical care industry.
[e] Index of price charges in the prescription drug market.
SOURCE: Centers for Disease Control; U.S. Bureau of Labor.

units of health care provided by a one-unit purchase of the composite bundle of prescription drugs may have changed over the years, while the effective units provided by a unit of measles vaccine, for example, may be virtually unchanged. To properly compare the change in prices, more sophisticated empirical techniques must be employed. Congressional hearings were held in 1982 to examine the pricing of vaccines, but no single factor emerged as solely responsible for price increases.[12]

Research and Development

Table 4.2 suggests that during the 1970s and early 1980s, commercial biologics R&D became a less attractive investment than R&D involving other pharmaceuticals. Whether the availability of new development and production technologies for vaccines (Chapter 2) has altered this trend is unclear.

Unfortunately, available information on the rate of new product introductions (Table 4.3) does not distinguish between those that are totally new and those that are merely copies or minor improvements of an existing vaccine. Table 4.11 provides a detailed examination of the history of several of the more recent vaccine products licensed. The table shows that only 5 out of 18 recent licensures involved major innovations. The remaining licenses were "competitive" or "improvement" licenses.

CONCLUSIONS

While the available data are incomplete, certain conclusions can be drawn about the current economic situation of the U.S. vaccine industry.

The number of manufacturers has declined steadily. During the 1970s and early 1980s, the proportion of total pharmaceutical R&D investment in biologics also declined (data are not yet available to determine whether this trend continued after 1982). In addition, the pattern of new vaccine introductions has been considerably different from that of drug introductions in recent decades. Manufacturing of vaccines is highly concentrated and competition is very limited. Also, the sole-supplier situation poses a threat to the continued supply of some vaccines.

Certain factors adversely affect the commercial attractiveness of vaccine manufacturing. As noted in Chapter 3, the potential market for vaccines is comparatively small because repeat sales to recipients are uncommon. The potential market is economically distorted by undervaluation of preventive services—both by the public and by physicians. Vaccines also are undervalued because the total benefits that accrue to society are greater than the sum of benefits to individual recipients (because of reduced transmission). Consequently, research and development costs are relatively large compared to sales revenues.

TABLE 4.11 Vaccine Development and Licensing

Product and Manufacturer	Application/ Issue Date	Comments
Anthrax vaccine adsorbed		
Michigan Dept. of Health	07-17-67 11-04-70	New manufacturer of old vaccine
Cholera vaccine		
ISVTS[a]	05-29-75 08-19-76	New manufacturer of old vaccine
Hepatitis B vaccine Merck Sharp & Dohme	06-12-79 11-16-81	New vaccine
Measles/mumps virus, live		
Merck Sharp & Dohme	12-13-71 07-18-73	New combination of old vaccines
MMR vaccine, live		
Merck Sharp & Dohme	10-02-69 04-22-71	New combination of old vaccines
Measles and rubella, live		
Merck Sharp & Dohme	05-25-70 04-22-71	New combination of old vaccines
Meningococcal polysaccharide vaccine		
Merck Sharp & Dohme	09-28-72 04-02-74	New vaccine
Connaught	08-12-75 12-13-76	Independent introduction
Mumps virus vaccine, live		
Merck Sharp & Dohme	12-28-66 12-28-67	New vaccine
Pneumococcal vaccine, polyvalent		
Merck Sharp & Dohme	01-23-75 11-21-77	New vaccine
Lederle	07-16-76 08-15-79	Independent production
Merck Sharp & Dohme	08-23-82 07-07-83	Improved vaccine
Lederle	01-26-83	Improved vaccine 07-21-83
Rabies vaccine (human diploid)		
Wyeth	05-23-77 08-11-82	Improved production process
Institut Merieux	08-31-79 06-09-80	Same as above

Product and Manufacturer	Application/ Issue Date	Comment s
Rubella virus vaccine, live		
Merck Sharp & Dohme (duck embryo cells)	08-05-68 06-06-69	New vaccine
Smith, Kline & French (rabbit kidney cells)	12-27-68 03-12-70	Improved production process
Rubella virus vaccine, live		
Merck Sharp & Dohme (human diploid cells)	7-16-76 9-15-78	Improved production process

[a] Istituto Sieroterapico Vaccinogeno Toscano Sclavo.
SOURCE: Committee interpretation of data supplied by the Food and Drug Administration.

Other factors that may adversely affect decisions about vaccine development include the perception that new vaccines will not receive useful protection from patents (perhaps arising from historical experience) and liability risks, particularly in the case of companies already marketing vaccines.

The effects of recent changes in the patent law and in government funding policies on vaccine innovation are difficult to predict. The situation should be monitored (by the vaccine commission suggested in Chapter 7) and further actions should be considered if the available protection of property rights appears insufficient to stimulate the desired level of innovation.

REFERENCES AND NOTES

1. Bowman, J. 1982. Testimony for Lederle Laboratories before the Subcommittee on Investigations and General Oversight, Committee on Labor and Human Resources, U.S. Senate , July 22, 1982, Washington, D.C.
2. Institute of Medicine. 1985. New Vaccine Development: Establishing Priorities, Volume 1. Diseases of Importance in the U.S. Washington, D.C.:National Academy Press.
3. Austrian, R. 1983. Development of Pneumococcal Vaccine.

Prepared for the Institute of Medicine Conference on Barriers to Vaccine Innovation, November 28-29, 1984, Washington, D.C.
4. U.S. Congress, Office of Technology Assessment. 1979. A Review of Selected Federal Vaccine and Immunization Policies. Washington, D.C.: U.S. Government Printing Office.
5. Inderal, the largest selling anti-hypertensive drug, has annual sales of about $350 million. Wall Street Journal. May 25, 1984. Prices of prescription drugs soar after years of moderate increase. A31.
6. Beale, A.J. 1985. Modern approaches to the development of vaccines: perspective of a traditional manufacturer. Pp. 377-381 in Vaccines 85. Molecular and Chemical Basis of Resistance to Parasitic, Bacterial, and Viral Diseases, R.A. Lerner, R.M. Chanock, and F. Brown, eds. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory.
7. Scherer, F.M. 1980. Market structure and technological innovation. Pp. 407-438 in Industrial Market Structure and Economic Performance, 2nd ed. Chicago: Rand McNally.
8. Collins, C., and Hanchette, J. December 1984. The Vaccine Machine, A Special Report. Washington, D.C.: Gannett News Service.
9. Arnould, R., and Grabowski, H. 1981. Auto safety regulations: an analysis of market failure. Bell J. Econ. Manage. Sci. 12:34-35.
10. McCabe, E.F. 1983. Personal communication, Merck Sharp & Dohme, West Point, Pa.
11. Mason, J.O. 1984. Testimony on H.R. 5810 before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, December 19, 1984, Washington, D.C.
12. U.S. Congress, Senate. July 22, 1982. Hearing before the Subcommittee on Investigations and General Oversight, Committee on Labor and Human Resources, Washington, D.C.

5

Vaccine Injury

The occurrence of adverse reactions to vaccines raises numerous questions of the magnitude of risk to the individual compared with overall benefits to the population, of how to protect those at increased risk, of the potential for vaccine improvement, of appropriate compensation for injuries, and of the effects of vaccine-related injury liability on vaccine production and utilization. The first section of this chapter focuses on the factors that impede efforts to establish cause-and-effect relationships in cases of vaccine-related injury, and the problem of determining the true frequencies of adverse effects among vaccinees. The second section consists of a review of scientific data on major adverse reactions to commonly used domestic vaccines for children and adults.

Chapter 6 examines the legal ramifications of vaccine injury and compensation issues, and the effect of the current state of the law on vaccine production and innovation. The mechanisms most likely to ensure rapid identification of vaccine-related injuries and improved coordination of vaccine improvement efforts are discussed more fully in Chapter 7.

Adverse reactions have been attributed to various vaccines for many years, but until recently few scientifically acceptable efforts have been made to determine the frequency of these events. One reason for this situation is that many of the diseases for which effective vaccines have been developed were so feared by the public and the medical community that at first the side effects of immunization were ignored or accepted as a necessary evil. Fifty years ago, when an estimated 2 million or more cases of whooping cough with 7,000 deaths occurred annually in the United States, little attention was paid to the rare infant who displayed severe symptoms following inoculation with the newly developed vaccine.

Similarly, the anxiety created by the specter of more than 20,000 new cases of paralytic poliomyelitis each year weighed heavily when compared with the possibility of an occasional case of vaccine-related poliomyelitis. Furthermore, the actual incidence of vaccine-related poliomyelitis could not be determined until the vaccine had been in use for several years.

As serious vaccine-preventable diseases have become rarities in the United States, the attention focused on adverse reactions has

increased. This situation will continue because the immunization programs must be maintained to prevent resurgence of the diseases.[1,2]

The nation's limited ability to deal with the consequences of vaccine injury derives partly from the lack of a unified approach to the problem. Responsibilities for identifying vaccine-associated risks, stimulating research to improve implicated vaccines, and testing and producing these improved products are diffused among the public and private components of the vaccine production enterprise (Chapter 2).

The Office of Biologics Research and Review (OBRR) of the Food and Drug Administration (FDA) is responsible for ensuring the safety and efficacy of vaccine products for use in clinical trials or by the public. While extensive data are examined before licensing, it is not possible prior to widespread use to detect adverse reactions that occur at very low frequencies. In all approval processes for drugs and biological products, a balance must be established between increasing the stringency of testing requirements to ensure safety and placing much-needed products on the market without unreasonable delay. The committee believes that the quality control testing required by the FDA provides adequate safeguards against the risks of injury from an improperly manufactured vaccine. However, no practical mechanism is available for ensuring before licensing that a vaccine is totally free of possible adverse reactions for all individuals, nor is it reasonable to require this for continued licensing.

Adverse events following immunization are reported to the FDA by manufacturers, pharmacists, physicians, and the military, and to the Centers for Disease Control (CDC) by the parents or guardians of children who receive federally funded vaccines.[3] Although these reporting systems are useful, neither of them provides an adequate basis for estimation of the total number of events that occur, in part because most reporting is voluntary. Even if reporting were mandatory, however, the data would not allow determination of the number of events actually caused by, rather than coincidental to, the administration of vaccines because information on similar events in unvaccinated individuals is not collected.

Use of licensed vaccines is guided by the recommendations of several groups, including the Immunization Practices Advisory Committee of the CDC, the Committee on Infectious Diseases of the American Academy of Pediatrics, and the American College of Physicians. Their recommendations generally attempt to identify two groups: those who would benefit from immunization with a specific vaccine and those for whom vaccination is contraindicated because of increased risk of possible adverse reactions. Increasing the awareness of contraindications to specific vaccines among health care providers and the public is important in minimizing the potential for vaccine-related injury. This would be an important function of the vaccine commission proposed in Chapter 7 and of any entity established to oversee compensation to injured individuals.

Identification of true vaccine-related injuries and the development of strategies to minimize their occurrence are made difficult by many factors:

1. Serious or permanent reactions to vaccines are very rare, occurring once in many thousands or millions of doses administered; thus, inordinately large populations must be studied to identify these reactions and determine their incidence.
2. Many suspected vaccine reactions constitute or resemble disease syndromes that occur for other reasons, known or unknown. This problem was illustrated by the difficulty in determining how many of the cases of the Guillain-Barré syndrome that occurred during the swine flu episode were actually attributable to the vaccine and how many would have occurred anyway (the so-called background cases).
3. Preexisting abnormalities that evolve gradually or that are not yet clinically apparent when the vaccine is given may cause confusion. This problem is of particular importance in relation to vaccines given to young infants, in whom serious underlying neurological abnormalities may not become obvious until later stages of development.
4. Clinically and pathologically, the manifestations of many suspected reactions to vaccines are nonspecific and may be associated with a variety of disease entities. Therefore, the symptoms may be of little or no use in assigning causation.
5. Basic understanding of the pathogenesis of reactions to vaccines often is lacking.
6. Enormous problems exist in the ascertainment of reactions. Vaccines are administered by a wide variety of providers, whose interpretations of events following vaccine administration may vary. Over-reporting of alleged reactions often occurs as a result of publicity, but both over-reporting and under-reporting may occur for a variety of reasons. For example, selective reporting of problems in children who had a prior history of receipt of DTP may have occurred because of widespread publicity about the risks of the vaccine.
7. The costs and logistics necessary to overcome these problems for a prospective study of vaccine reactions may be prohibitive, making such studies of low public priority.
8. Even when studies are conducted on large populations, the number of individuals incurring reactions to a vaccine may be so few that estimates of rates are imprecise. For example, if a study involved 300,000 individuals receiving a given immunization and if it were found that eight developed serious reactions (of a type that did not occur in the unvaccinated control population), the reaction rate would be estimated to be approximately 27 per million doses. However, given the small number of individuals with reactions (eight), the so-called 95 percent confidence limits on that rate would be 12 and 53 per million. This means that there is a 95 percent probability that the true rate of reactions lies somewhere between 12 and 53 per million doses. Furthermore, there is a 5 percent chance that the rate might be either lower than 12 or greater than 53 per million doses. Consequently, the estimate of 27 per million is hardly precise.

The Pertussis Controversy

The controversy surrounding the pertussis component of the DTP (diphtheria-tetanus-pertussis) vaccine provides a good example of the

difficulties in establishing a cause-and-effect relationship based on a temporal association between the vaccine and an untoward event.

An alleged reaction to a vaccine may represent one of four events: (1) the vaccine may have caused the disorder; (2) the vaccine may have triggered or precipitated manifestations of an underlying disease destined to appear in the immediate future with or without the vaccine; (3) concern about minor reactions to a vaccine (such as discomfort and fever) may have prompted recognition of previously existing but unnoticed symptoms; or (4) the timing of administration of the vaccine simply may have coincided with the appearance of an unrelated disease problem.

To provide maximum protection, the administration of vaccines to children customarily begins in the first few months of life, when many inherent developmental and neurological abnormalities, such as cerebral palsy or mental retardation of unknown cause, are not yet manifest. Infants and young children also are particularly susceptible to events that may cause death or future disability, such as the sudden infant death syndrome (SIDS) and infections leading to acquired central nervous system damage.

The appearance of one of these conditions shortly after vaccination may be misinterpreted as a cause-and-effect situation, difficult to prove or disprove in an individual case. Many of the alleged severe injuries from pertussis vaccine, such as infantile spasms, have not been found to be caused by the vaccine, temporal associations notwithstanding.[4,5] This distinction between temporal association and causation may not be grasped readily by lay jurors and others who are unaccustomed to dealing with the concept, and most explanations are based on complex epidemiology that is even more difficult to comprehend. Therefore, juries faced with a seriously damaged child and agonized family, who date the onset of disability from the approximate time of vaccination, are understandably sympathetic to the plaintiffs.

Identifying Individuals at High Risk of Adverse Effects

The effort to prevent adverse reactions by identifying high-risk individuals before immunization also is complicated by the time element. For example, live viral vaccines are contraindicated in children with certain immunodeficiency syndromes, but these hereditary syndromes are rarely recognized before 2 months of age (unless a sibling has been affected), the time at which routine immunization usually begins. Children with unrecognized congenital combined immunodeficiency syndrome may be among those who develop vaccine-induced paralytic poliomyelitis, for example. It is important to note, however, that they constitute a minority of those affected: the majority of the rare cases of vaccine-related paralytic poliomyelitis occur in persons who cannot be distinguished immunologically from normal persons even after the event.

Thus, except for the rare immunodeficient child who is in jeopardy

from any live viral vaccine, identification of individuals at high risk of disabling adverse reactions is not possible at present. Indeed, prior identification may never be possible because some or many of these reactions may be idiosyncratic.

From the foregoing, it is clear that conclusions about cause and effect and rates of adverse reactions to vaccines should be drawn only from carefully designed, well-controlled, epidemiological studies. Until recently, few studies have approached these criteria, and available rate estimates have been characterized by wide confidence limits. Mechanisms dependent on the voluntary reporting of events associated with the administration of vaccines have not provided accurate or useful information about the frequency of vaccine-related adverse reactions.

The following is a review of definitive studies and reports of reactions to commonly used vaccines for children and adults. Only major reactions sufficient to justify medical intervention or posing a risk of death or permanent disability are described in detail. Minor reactions, such as local tenderness at the site of injection, low-grade fever, and malaise, are largely ignored.

VACCINES USED IN CHILDHOOD

Pertussis Vaccine

Pertussis vaccine is assumed to be the most reactive component of the familiar, triple-antigen DTP preparation. It also is the childhood immunizing agent that has caused the greatest concern. Because the immunity-producing antigen(s) of the pertussis organism has eluded identification and purification for many years, the vaccine consists of the whole, killed organism.

Reactions to DTP may be divided into three categories.[6] The first comprises minor local and systemic effects, usually limited to the first 48 hours after inoculation. The second category includes certain responses that traditionally have caused parents and physicians some concern, but that have not been shown to have permanent consequences. These include excessive somnolence and protracted, inconsolable crying. More alarming to parents and providers are an unusual shock-like state with hypotonicity and hyporesponsiveness and short-lived convulsions, usually febrile. The third category includes major neurological reactions, often followed by permanent disability.

Among the minor, expected reactions to DTP is fever (39°C or more), which may occur in up to 7 percent of children. Rarely, fever may exceed 40.5°C, which is considered an indication to replace subsequent doses of DTP with DT. More severe local reactions occur occasionally, with considerable swelling and redness at the site of injection, sometimes followed by a "knot" in the subcutaneous tissue that may persist for weeks. Rarely, a sterile abscess occurs. These more severe local reactions usually are attributed to the aluminum salts

employed as adjuvants in the vaccine, and occur more often with subcutaneous than with intramuscular injections of the material. A vaccine that contained two or three times the usual amount of aluminum adjuvant was withdrawn from the market when it was found to be associated with an excess of sterile abscesses.[7] Rarely, small clusters of septic abscesses have occurred;[8] these usually have been shown to be caused by inadvertent contamination of a single multiple-dose vial of vaccine during use.

Cody et al.[9] have provided the best data on the frequency of the more common reactions to DTP, especially those due to the pertussis component. In their study, symptoms occurring within 48 hours after inoculation in infants and children who received DTP were compared with those in infants and children who received DT. Drowsiness, irritability, and anorexia were observed frequently following both vaccines, though at least twice as often after DTP. vomiting also was more frequent following DTP, occurring in about 6 percent of infants. Persistent crying occurred in about 3 percent of infants receiving DTP, which was more than four times as often as it occurred in recipients of DT. In about a third of the DTP recipients, crying persisted more than 3 hours and in a few it was described as high pitched and unusual. Recovery appeared to be complete in all cases.

The study by Cody et al. involved the administration of almost 16,000 doses of DTP. Among those who received the vaccine, nine infants (0.06 percent) experienced short-lived convulsions within 24 hours after inoculation. In all but two, the episodes were associated with fever; none required hospitalization and all appeared to recover completely. For this and other reasons it is generally believed that a simple, short-lived febrile convulsion following DTP immunization does not produce permanent sequelae. In addition, nine infants exhibited the shock-like or collapse state for several hours following injection; all survived without apparent sequelae.

Most public advisory committees concerned with general immunization recommendations agree that fever of 40.5°C or more, excessive crying for 4 or more hours, a shock-like episode, or a convulsion following an injection of DTP contraindicates further use of preparations containing pertussis vaccine; DT (or Td, depending on the age of the child; see Diphtheria Toxoid below) should be employed.[10,11] Recently, the Surgeon General's Immunization Practices Advisory Committee (ACIP) has recommended delaying the initiation or continuation of DTP immunization in children with symptoms of underlying neurological disease until those symptoms have been clarified.[12]

Severe neurological disease, the third type of alleged untoward event following DTP, has been the subject of many reports, mostly anecdotal and uncontrolled.[13] These reports describe an acute encephalopathy with convulsions and coma, often resulting in severe, permanent intellectual and neurological impairment. No characteristic picture has been recognized to differentiate post-vaccine encephalopathy from other acute central nervous system syndromes, nor has a unique pathology beeh identified. Confusion about the frequency of

such a syndrome, and even whether it can be attributed to pertussis vaccine, has resulted because of difficulties in differentiating true vaccine-related encephalopathy from coincidental or pre-existing evolving neurological syndromes in these infants and children. Some clarification of these issues has been provided, however, by a recent National Childhood Encephalopathy Study (NCES) of acute encephalopathy in infants and children in the United Kingdom.[14,15]

In the study, individuals with otherwise unexplained acute encephalopathy were about twice as likely to have received an injection of DTP in the previous week as normal, matched controls. The results may be interpreted as indicating that DTP is responsible for about two-thirds of all cases of acute encephalopathy (otherwise not explainable) occurring within a week of inoculation, and that the remainder must be ascribed to other causes.

From these data the frequency of encephalopathy with residual brain damage 1 year after DTP is estimated to be 1 per 310,000 doses. The 95 percent confidence limits of this risk are 1 per 54,000 to 1 per 5,310,000 doses. This suggests that 1 in 100,000 infants who receive the three recommended doses in the first year of life incurs brain damage. However, it should be noted that children with encephalopathy were less likely than unaffected controls to have received DTP 8 to 28 days prior to onset. This suggests that some of the observed excess risk of encephalopathy in the 7 days following administration of DTP reflects the accelerated appearance or recognition of underlying disorders that were destined to become manifest within a few weeks.[16]

Because there do not appear to be substantive differences between DTP preparations in the United Kingdom and those in the United States, the results of this study suggest that 36 of the approximately 3,650,000 infants born in the United States in 1982 might have incurred permanent brain damage from DTP, if all infants received three doses in the first year of life. A lower rate is suggested by a study from Sweden, which indicates that encephalopathy with residua occurs in approximately 1 child in 170,000 who receives three doses of the vaccine (i.e., 1 per 510,000 doses).[17] Extrapolation of the Swedish data to the United States population indicates that permanent disability would occur in 22 infants in each annual birth cohort of 3,650,000, assuming all receive three doses in the first year.

Further analysis of the data from the British encephalopathy study has clarified the relationship between DTP and infantile spasms, a syndrome that usually appears in the first 6 months of life and that frequently presages severe, permanent neurological disability. Some cases are caused by congenital or metabolic defects, but for others no cause is found. Occasional temporal associations between the administration of DTP and the appearance of infantile spasms led to the concern that the two might be related. The NCES data clearly indicate that DTP does not cause infantile spasms; instead, overt manifestations of infantile spasms may be recognized 1 to 3 weeks earlier than usual because irritability and other minor symptoms secondary to the DTP attract attention to the child's preexisting neurological condition 4

Another problem of major importance is whether DTP might, in some

cases, induce SIDS. About 5,000 infants succumb to SIDS annually in the United States. Because SIDS occurs most frequently in the first 6 months of life, when primary immunization with DTP is begun, questions have arisen about the possible relationship of DTP to this problem. This concern received added impetus from a cluster of cases of SIDS in Tennessee in 1979, but attribution of this cluster to DTP was confounded by enhanced immunization efforts in Tennessee directed at children of lower socioeconomic status, who are at higher risk of SIDS, and by intensified surveillance.[18]

More recently, a study in Los Angeles of infants who succumbed to SIDS seemed to show a causal connection.[19] On preliminary analysis, the time distribution of DTP vaccinations in the 28 days prior to death suggested a distinct temporal association between DTP and death. This study could have been affected by recall bias, however, because families who incur a tragedy such as SIDS are much more likely to recall events that occurred immediately preceding the unfortunate episode. Further, the authors failed to take into consideration week-by-week age-specific incidence rates of SIDS, which are already declining by the time the first dose of DTP is given (approximately 2 months).[20] Thus, such a temporal relationship would be expected even in the absence of causation. Paradoxically, a similar temporal association, though not as strong, was found between SIDS and a recent physician visit without administration of DTP.

Definitive evidence that DTP is not causally related to SIDS has been provided by a case-control study conducted by the National Institute of Child Health and Human Development.[21] In this study, infants succumbing to SIDS were, if anything, less apt to have been inoculated with DTP in the recent past than matched control infants. These findings have been confirmed by a case-control study from the United Kingdom.[22] Thus, reasonable confidence can be expressed that SIDS is not a consequence of DTP.

Although it is likely that the pertussis component of DTP is responsible for rare instances of encephalopathy, there is no evidence that other untoward, disabling neurological events can be attributed to the vaccine. Conditions such as transverse myelitis, Guillain-Barré syndrome, and peripheral neuropathy have not been reported to result from DTP, although occasionally they have been attributed to other vaccines.

Advisory committees concerned with vaccine recommendations occasionally have alluded to thrombocytopenia and hemolytic anemia as rare sequelae of DTP immunization. Causative relationships have not been established, however, and it is likely that any apparent temporal associations are coincidental and can be explained by background rates of these conditions at the age when vaccinations are initiated.

Diphtheria Toxoid

Active immunization against diphtheria is accomplished with diphtheria toxoid, an inactivated toxin that retains immunizing potential. For primary immunization of children it is almost always

administered in combination with tetanus toxoid and pertussis vaccine as DTP. DT, a combination of diphtheria and tetanus toxoids, is administered to children who should not receive pertussis vaccine. A combination containing less diphtheria toxoid, Td, is administered to children over the age of 7 and adults for primary and booster immunization.

Diphtheria toxoid produces frequent minor local and systemic reactions, but these are transient and of no serious consequence. No doubt, both diphtheria and tetanus toxoids contribute to these types of reactions to DTP. In the past, however, less refined diphtheria toxoid preparations were responsible for more severe local and systemic reactions, presumably hypersensitive in nature. These reactions may have been caused, in part, by extraneous proteins present in the toxoid preparations. They also occurred more frequently in adults and in individuals already shown to be immune to diphtheria by Schick testing, including persons who had received repeated doses of toxoid.[23]

Elimination of these more severe, often temporarily disabling, reactions has been accomplished in two ways. First, better purification procedures probably have removed many of the extraneous proteins. Second, for primary and booster immunization of adults and older children, Td is employed; this preparation contains one-tenth to one-fifth as much diphtheria toxoid as DTP or DT.[24]

There is no evidence that diphtheria toxoid produces fatal or permanently disabling reactions.

Tetanus Toxoid

In a review of reactions to tetanus toxoid, it was stated that they "do not endanger life, do not leave any sequelae, and do not occur in more than about 1 percent of adults, mainly the over-immunized."[25] For these reasons and in light of the remarkable efficacy of tetanus toxoid, the benefit-risk ratio of this preparation is considered to be unusually high.

Local reactions (swelling, redness, pain, and sometimes a more severe Arthus-type response) occur, but these are transient and without sequelae. Similarly, fever and malaise lasting a day or two occasionally occur. Urticarial reactions also have been described. These untoward events appear to occur most often following the administration of toxoid as a booster to individuals who are already well immunized or hyperimmunized, particularly adults.[26]

Very rarely, true anaphylaxis involving tetanus toxoid does occur. In confidential material submitted to the Panel on Review of Bacterial Vaccines and Toxoids, Bureau of Biologics, FDA, by manufacturers, anaphylaxis was reported at a rate of 1 per 1.5 to 2 million doses. No fatal episode has been described.

Single anecdotal reports of temporal associations between tetanus toxoid administration and other sequelae, such as peripheral neuropathy and serum sickness, have been difficult to evaluate and probably involve coincidence.

Poliomyelitis Vaccines

Two types of poliomyelitis vaccines are now available in the United States. The orally administered, live attenuated vaccine (OPV), contains all three types of poliovirus and is generally recommended for routine use.

The inactivated poliovirus vaccine (IPV), which also contains all three strains, was used for routine immunization against poliomyelitis from the mid-1950s until the early 1960s, when OPV became widely available. OPV became the preferred vaccine because it was believed to provide more permanent immunity, to prevent transmission by creating intestinal immunity, and to offer better community protection by person-to-person transmission of vaccine virus.[27]

The only known untoward effect of OPV is the rare appearance of paralytic poliomyelitis in recipients of the vaccine or in nonimmune contacts of vaccinees.[28] Induction of paralytic disease appears to be caused by a change in the vaccine virus to a more virulent form in the recipient or contact. Immunodeficient individuals are at special risk. Poliovirus recovered from affected persons usually can be classified as either vaccine-derived or "wild" type (naturally occurring) by special laboratory techniques.

Between 1969 and 1982, about 320 million doses of OPV were distributed. Vaccine-associated paralytic poliomyelitis was recognized in 94 apparently normal individuals during those 14 years. Twenty-eight were recipients and the remainder were household or community contacts. Thus, for recipients the risk appears to be less than about 1 per 11 million doses. A numerical risk for household and community contacts cannot be determined because of the impossibility of estimating the denominator of individuals exposed. During the 14 years, an additional 15 immunodeficient individuals acquired paralytic poliomyelitis, 14 from vaccine virus as either recipients or contacts, and 1 from the wild virus.[28]

In contrast, the current inactivated poliovirus vaccine (IPV) is without risk of vaccine-related poliomyelitis. For this reason and because a more potent inactivated vaccine has been developed in Europe, the desirability of switching back from OPV to IPV for routine immunization against poliomyelitis in the United States is being examined.[29] The complexity of such a decision has been emphasized by Alexander,[30] including uncertainties about optimum dosage schedules and lingering doubts about the effects of IPV on the circulation of wild poliovirus in the population. Of major importance is the fact that surveillance of untoward events following immunization with the newer IPV has been insufficient to determine the potential incidence of rare but disabling sequelae following its administration.

Measles Vaccine

The measles vaccine contains live, attenuated measles virus and is usually administered in combination with rubella and mumps vaccines (MMR). A single injection at 15 months of age is recommended. Five

to 15 percent of recipients incur a mild, measles-like illness with fever of 39.4°C or more about a week after immunization, and occasional transient rashes also occur.[31] Rarely, a febrile seizure may ensue. These responses do not produce permanent sequelae.

The importance of measles in the past was largely measured by pneumonia, which occurred in approximately 10 percent of cases and was often fatal, especially in malnourished and debilitated children. Even today it is estimated by the World Health Organization that about 1.5 million children worldwide succumb to measles annually, almost all in less technologically developed countries. In the United States and other developed countries, pneumonia secondary to measles became less of a threat, even prior to development of the vaccine.

There are two important central nervous system complications of measles, acute encephalitis and subacute sclerosing panencephalitis (SSPE or Dawson's encephalitis).[31] The former occurs in about 1 in 1,000 cases of measles, and results in death or permanent central nervous system disability in about 40 percent of affected individuals. Subacute sclerosing panencephalitis (SSPE) is a slowly progressive complication of measles, beginning months or years after the disease and associated with progressive central nervous system deterioration and, usually, death. There is convincing evidence that SSPE is a slow virus infection with the measles agent.

Because measles vaccine is live, it is important to consider the possibility that it might produce measles encephalitis. Reports of encephalopathy following this vaccine in the United States are rare and anecdotal, and do not prove cause and effect. However, data from the NCES suggest that encephalitis with or without sequelae occurs in 1 in 87,000 immunizations (95 percent confidence limits 1 per 25,000 to 1 per 830,000 immunizations).[15] Reports of post-vaccination encephalitis submitted to the CDC suggest that the rate in the United States is much lower (less than 1 in a million).

SSPE, which appears to occur at a rate of about 1 per 100,000 cases of measles disease, is more difficult to monitor.[31] In particular, concern has been expressed about SSPE related to measles vaccine because the disease appears to occur more often following milder cases of clinical measles. Rare instances of SSPE following measles vaccine have been reported, but it is possible that these may have resulted from inapparent, mild episodes of measles in infancy.[31] Reported cases in the United States have declined steadily over the years that the vaccine has been used widely.[31] Thus, it appears that the risk of SSPE from the vaccine, if any, is far less than that from the disease.

The measles vaccine virus is grown in chick embryo culture, and traces of egg protein may be present in the vaccine. In the past, these minute amounts of egg protein were considered insufficient to cause allergic reactions, but recent reports have indicated that extremely rare anaphylactic-type reactions do occur, almost always in individuals with a strong history of similar reactions following the ingestion of eggs.[31] A history of such reactions is now considered a contraindication to the administration of measles vaccine.

Measles in pregnancy has been associated with excessive fetal

wastage and, in one report, an excess of congenital anomalies.[31] Although there is no report of problems following the administration of measles vaccine in pregnancy, on theoretical grounds and because of the possibility of confusion about causation if an unrelated fetal defect were to occur, the administration of measles vaccine during pregnancy is inadvisable.

Persons with immunodeficiencies, congenital or acquired through disease or pharmacological agents, should not receive measles vaccine because of the enhanced potential for viral replication.

Rubella Vaccine

Rubella vaccine, usually given in combination with measles and mumps vaccine (MMR), is a live, attenuated vital vaccine. It is also available in combination with measles vaccine and in monovalent form.

Because it is a live vaccine, it is reasonable to consider whether complications of the disease also might follow administration of the vaccine to susceptible individuals. Important disease complications include post-rubella encephalitis, the congenital rubella syndrome, purpura, and arthritis.[32]

Encephalitis following rubella disease is rare, probably occurring in less than 1 per 5,000 cases.[33] Though rubella encephalitis is occasionally fatal, sequelae in survivors appear to be uncommon. Experience over 15 years indicates that encephalitis is not a complication of rubella vaccine.

Of major concern is the theoretical possibility of vaccine-induced congenital rubella syndrome following administration of the vaccine to rubella-susceptible women in the first trimester of pregnancy. This concern was enhanced by the recovery of vaccine virus from the aborted fetuses and placentae of a few rubella-susceptible women who received the vaccine in the first trimester.[34] However, from 1971 to 1983, 213 rubella-susceptible women who received rubella vaccine within 3 months before or after conception have been followed to term. All of these pregnancies resulted in normal infants, including two pairs of twins, without signs of the congenital rubella syndrome.[35] This study indicates that the syndrome, if it ever occurs from the vaccine, does so at a far lower rate than that observed following natural disease. (Estimation of confidence limits indicates 95 percent probability that the rate of the syndrome following immunization is no more than 1.7 percent, if it occurs at all.)

Nonetheless, authorities recommend deferring rubella immunization in pregnant women and the avoidance of pregnancy in nonpregnant women for 3 months following rubella immunization, if only because of possible confusion about cause and effect if an infant is born with a coincident anomaly. Because vaccine recipients rarely, if ever, transmit vaccine virus to susceptible contacts, there is no reason[36] to withhold rubella immunization from a child whose mother or other household contact is pregnant

There is no evidence that the transient purpura observed after natural rubella occurs following rubella immunization.

As with the natural disease, rubella-susceptible individuals who receive the vaccine may exhibit transient joint pains 1 to 3 weeks following immunization.[36] Occasionally, clinical arthritis or transient peripheral neuropathy with pain and paresthesia in the extremities occurs.[36] Higher rates of these reactions appear in women, especially adolescents and young adults, than in children. These joint manifestations are almost always transient.

Recently, however, it has been recognized that rare instances of persistent or recurrent arthropathy occur following rubella vaccine or the natural disease. Although some of these may represent temporal association of other joint conditions with rubella disease or receipt of rubella vaccine, it appears that at least some may be attributable to the infection or vaccine.[37] The vast majority of cases apparently caused by the vaccine or illness have been reported in young adult women, which may be due in part to the fact that adult males may be less likely to receive the vaccine. Vaccine or wild virus has been recovered from lymphocytes and occasionally from joint fluids of such persons long after the original infection or inoculation. Curiously, it appears that this syndrome of persistent arthropathy may be a consequence of a secondary exposure to the rubella virus or vaccine. Whether the mechanism relates to circulating antibody-virus complexes or whether it is attributable to persistent virus in tissues, such as joints, is uncertain.[38]

Since 1979, the United States rubella vaccine has been grown in human cells, rather than in duck embryo cell cultures. Thus, the current rubella vaccine exhibits no risk of egg hypersensitivity, in contrast to measles and mumps vaccines.

Mumps Vaccine

Mumps vaccine, which contains live, attenuated mumps virus, usually is administered in combination with measles and rubella vaccines (MMR). The important complications of mumps disease (meningoencephalitis, permanent nerve deafness, and orchitis) rarely, if ever, occur following mumps immunization.[39] The rare reports of transient neurological sequelae following receipt of mumps vaccine probably represent other coincidental diseases.

Although natural mumps infection during pregnancy does not appear to cause congenital defects, avoidance of administration of mumps vaccine during pregnancy is recommended on theoretical grounds. Similarly, as with all live viruses, it is recommended that mumps vaccine be avoided in individuals with congenital or acquired immunodeficiencies.

Mumps vaccine is propagated in chick embryo culture. It is possible that individuals who exhibit anaphylactic responses to egg products could experience similar episodes following the vaccine.39

Although there are contradictory data relating mumps to diabetes mellitus, there is no evidence that the vaccine is causatively related to the disease.[39,40]

VACCINES FOR ADULTS

The following vaccines are used primarily in adults, but are recommended for children and adolescents under certain circumstances.

Influenza Vaccines

Vaccines for viral influenza, types A and B, contain inactivated preparations produced in embryonated chicken eggs. Given that the antigenic constituents of prevalent influenza viruses vary from year to year, viral strains incorporated into the vaccine must be changed annually.41

Transient local and systemic reactions to influenza vaccines occur at low but predictable rates, but these are usually minor and of no permanent consequence.[41] Two types of reactions of major consequence have been described. The first of these comprises anaphylactic responses to traces of egg protein present in the vaccine.[41] These reactions, though frightening and potentially life-endangering, are usually effectively treated pharmacologically and result in no sequelae.

The second major putative reaction is Guillain-Barré syndrome, approximately 500 cases of which were reported following swine flu vaccine administration to almost 41.5 million people in 1976.[42] This unprecedented experience appears to have been unique to that particular vaccine. No prior association between influenza vaccines and this syndrome had been recognized, and careful monitoring of recipients of influenza vaccine subsequently has demonstrated no excess of this disease in association with other influenza vaccines.[41] Why this sequela was unique to the swine flu vaccine is unknown.

The incidence of Guillain-Barré syndrome peaked 2 to 3 weeks following administration of the swine flu vaccine.[42] The precise incidence rate of the disease following the vaccine has been difficult to determine, however, because the syndrome occurs at low rates for other and unknown reasons throughout the year and, particularly for cases that occurred 6 or more weeks following vaccine administration, attribution of the disease to the vaccine has been difficult.

Pneumococcal Vaccines

Pneumococcal vaccine is used to prevent pneumonia and other severe pneumococcal diseases. It is prepared from the carbohydrate of the organism's capsule, which is the major virulence factor of the pneumococcus and also the antigen responsible for inducing clinical immunity. The vaccine contains capsular antigens from the 23 serotypes of pneumococci that are responsible for the majority of severe pneumococcal disease. Although the vaccine may be responsible for some annoying local reactions and rare systemic responses such as fever and

possibly anaphylaxis, no permanent sequelae have been attributed to this preparation.[43] Booster doses are not recommended, however, because they result in more severe, though transient, local and systemic reactions.[43]

Meningococcal Vaccines

Vaccines against meningococcal infections contain the type-specific capsular carbohydrate of the organism. Ninety-five percent of meningococcal meningitis is caused by types A, B, and C. Type A, the epidemic strain, has been inexplicably rare in the United States for almost 30 years. Thus, current low rates of endemic meningococcal disease in the United States are due almost entirely to types B and C.[44] To date, it has not been possible to produce a protective type B vaccine. Of the two preparations available, one includes types A and C, and the other types A, C, Y, and W-135 (the Y and W-135 strains are infrequently associated with disease). These vaccines are recommended only for use under special circumstances, such as travel to endemic areas and during local outbreaks in the United States.[45]

Minor local and systemic reactions occur at low rates following injections of meningococcal vaccine. One instance of anaphylaxis following a booster dose has been reported but otherwise there is no evidence of major risk from these vaccines.[44]

Rabies Vaccine

Rabies vaccines, containing killed rabies virus, are used for two purposes in the United States: (1) post-exposure prophylaxis against the disease in individuals who have been bitten by an animal shown or suspected to have been rabid and (2) pre-exposure prophylaxis of individuals who are anticipated to be at high risk of exposure because of occupation or travel to areas of high endemicity.[46]

Until about 30 years ago in the United States, rabies vaccines were prepared in neurological tissues of various animals (this remains the practice in many other countries). These vaccines resulted in low but nonetheless unacceptable rates of serious reactions, often involving the nervous system. From the mid-1950s until 1980, killed rabies vaccine was prepared in embryonated duck eggs; this vaccine, though far safer than the former preparation, resulted in undesirable rates of severe allergic reactions.[47] Since 1980, the vaccine of choice in the United States has been an inactivated vaccine prepared in human cell tissue culture; approximately 100,000 persons have received a total of about 400,000 doses.[48] Reactivity is low in most persons. However, approximately 1 per 1,000 vaccinees has exhibited a systemic allergic reaction, usually of the serum sickness type and most often occurring with the fifth (booster) dose. Almost all have occurred in persons immunized electively because of potential occupational exposure, and all reactions have been followed by complete recovery.

Hepatitis B Vaccine

Hepatitis B vaccine, licensed for use in the United States in 1982, is prepared from human plasma that contains the infective antigen (HBsAg). The antigen is extracted from plasma and submitted to a series of procedures known to inactivate hepatitis B virus and representative viruses from all other groups. use of the vaccine is recommended for individuals at high risk of hepatitis B because of occupation, specific medical problems, or life-style.[49]

As of February 1984, 1,400,000 doses of the vaccine had been distributed, and it is estimated that 450,000 individuals have received at least two of the three recommended doses.[50] Although minor local reactions have been observed occasionally following the vaccine, there has been no evidence of severe or life-endangering sequelae. Because the vaccine has been prepared from plasma of individuals at high risk of acquired immune deficiency syndrome (AIDS), careful surveillance has been conducted for this complication. The inactivation processes to which the vaccine is submitted make it highly unlikely that any viral agent could survive.[51] Accumulating epidemiologic evidence further indicates that the vaccine does not serve as a risk factor for AIDS.[51] Thus, there is no evidence that hepatitis B vaccine is associated with permanent or disabling sequelae.

SUMMARY

Vaccines licensed in the United States provide excellent protection to society against their target diseases and are safe for an overwhelming proportion of recipients. They are not, however, universally effective or completely safe. The judgment as to what is adequately safe is difficult, and decisions on the urgency with which improvement of vaccines needs to be pursued depends on the undesirability of the risks of vaccination in relation to the risks of disease, and on other health needs.

Adverse events following immunization are reported to the FDA by manufacturers, pharmacists, physicians, and the military, and to the CDC by the parents or guardians of children who receive federally funded vaccines. Although these reporting systems are useful, neither of them provides an adequate basis for estimation of the total number of events that occur, in part because reporting is voluntary. Even if reporting were mandatory, however, the data would not allow determination of the number of events actually caused by, rather than coincidental to, the administration of vaccines because information on similar events in unvaccinated individuals is not collected. Conclusions about cause and effect and rates of adverse reactions to vaccines should be drawn only from carefully designed, well-controlled epidemiological studies.

Responsibilities for identifying vaccine-associated risks, promoting awareness of contraindications to vaccination, and completing all of the steps required for vaccine improvement are now poorly defined and

coordinated. Proposals outlined elsewhere in this report should ensure greater cooperation among the multiple public and private components of the vaccine innovation and immunization effort.

REFERENCES AND NOTES

1. Centers for Disease Control. 1982. Pertussis-England and Wales. Morbid. Mortal. Weekly Rept. 31:629-631.
2. Kanai, K. 1980. Japan's experience in pertussis epidemiology and vaccination in the past 30 years. Jpn. J. Med. Sci. Biol. 33:107-143.
3. Centers for Disease Control. 1985. Adverse events following immunization. Morbid. Mortal. Weekly Rept. 34:43-47.
4. Bellman, M.H., Ross, E.M., and Miller, D.L. 1983. Infantile spasms and pertussis immunisation. Lancet I:1031-1033.
5. Melchior, J.C. 1977. Infantile spasms and early immunization against whooping cough: Danish survey from 1970 to 1975. Arch. Dis. Child. 52:134-137.
6. Mortimer, E.A., Jr., and Jones, P.K. 1979. An evaluation of pertussis vaccine. Rev. Infect. Dis. 1:927-932.
7. Bernier, R.H., Frank, J.A., Jr., and Nolan, T.F., Jr. 1981. Abscesses complicating DTP vaccination. Am. J. Dis. Child. 135:826-828.
8. Centers for Disease Control. 1982. Group A streptococcal abscesses after DTP immunization-Georgia. Morbid. Mortal. Weekly Rept. 31:519-520, 525-526.
9. Cody, C.L., Baraff, L.J., Cherry, J.D., Marcy, S.M., and Manclark, C.R. 1981. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics 68:650-660.
10. Centers for Disease Control. 1981. Recommendations of the Immunization Practices Advisory Committee (ACIP). Diphtheria, tetanus, and pertussis: guidelines for vaccine prophylaxis and other preventive measures. Morbid. Mortal. Weekly Rept. 30:392-407.
11. American Academy of Pediatrics. 1982. Pertussis. pp. 198-202 in Report of the Committee on Infectious Diseases, J.O. Klein, P.A. Brunell, J.D. Cherry, and V.A. Fulginiti, eds. Evanston, Ill.: American Academy of Pediatrics.
12. Centers for Disease Control. 1984. Supplementary statement of contraindications to receipt of pertussis vaccine. Morbid. Mortal. Weekly Rept. 33:169-171.
13. Griffith, A.H. 1978. Reactions after pertussis vaccine: a manufacturer's experiences and difficulties since 1964. Br. Med. J. 1:809-815.
14. Miller, D.L., Ross, E.M., Alderslade, R., Bellman, N.H., and Rawson, N.S.B. 1981. Pertussis immunisation and serious acute neurological illness in children. Br. Med. J. 282:1595-1599.
15. Department of Health and Social Security. 1981. Whooping cough: reports from the Committee on Safety of Medicines and the

Joint Committee on Vaccination and Immunisation, Department of Health and Social Security. London: Her Majesty's Stationery Office.
16. Committee interpretation of material in reference 15.
17. Strom, J. 1967. Further experience of reactions, especially of a cerebral nature, in conjunction with triple vaccination: a study based on vaccinations in Sweden 1959-1965. Br. Med. J. 4:320-323.
18. Centers for Disease Control. 1979. DTP vaccination and sudden infant deaths-Tennessee. Morbid. Mortal. Weekly Rept. 28:131-132.
19. Baraff, L.J., Ablon, W.J., and Weiss, R.C. 1983. Possible temporal association between diphtheria-tetanus toxoid-pertussis vaccination and sudden infant death syndrome. Pediatr. Infect. Dis. 2:7-11.
20. Mortimer, E.A., Jr., Jones, P.K., and Adelson, L. 1983. DTP and SIDS (letter). Pediatr. Infect. Dis. 2:492.
21. Hoffman, H.S., Hunter, J.C., and Hasselmeyer, E.G. 1982. SIDS and DTP. Pp. 79-88 in 17th Immunization Conference Proceedings, Atlanta, Ga., May 18-19, 1982. Atlanta, Ga.: Centers for Disease Control.
22. Taylor, E.M., and Emery, J.L. 1982. Immunization and cot deaths. Lancet II:721.
23. Edsall, G. 1952. Immunization of adults against diphtheria and tetanus. Am. J. Public Health 42:393-400.
24. Edsall, G., Altman, J.S., and Gaspar, A.J. 1954. combined tetanus-diphtheria immunization of adults: use of small doses of diphtheria toxoid. Am. J. Public Health 44:1537-1545.
25. Editorial. 1974. Reactions to tetanus toxoid. Br. Med. J. 1:48.
26. Edsall, G., Elliott, M.W., Peebles, T.C., Levine, L., and Eldred, M.C. 1967. Excessive use of tetanus toxoid boosters. JAMA 202:17-19.
27. Institute of Medicine. 1977. Evaluation of Poliomyelitis Vaccines. Washington, D.C.: National Academy Press.
28. Kim-Farley, R., Bart, K., Schonberger, L., Orenstein, W., Hinman, A., Kew, O., Hatch, M., and Kaplan, J. 1983. Has indigenous wild paralytic poliomyelitis been eliminated from the United States? Pp. 43-47 in 18th Immunization Conference Proceedings, Atlanta, Ga., May 16-19, 1983. Atlanta, Ga.: Centers for Disease Control.
29. McBean, A.M., Thoms, M.L., Johnson, R.H., Gadless, B.R., MacDonald, B., Nerhood, L., Cummings, P., Hughes, J., Kinnear, J., Watts, C., Kraft, M., Albrecht, P., Boone, E.J., and Bernier, R. 1983. Preliminary results from a comparative trial of live and inactivated polio vaccines. Pp. 49-55 in 18th Immunization Conference Proceedings, Atlanta, Ga, May 16-19, 1983. Atlanta, Ga.: Centers for Disease Control.
30. Alexander, E.R. 1984. Inactivated poliomyelitis vaccination. Issues reconsidered. JAMA 251:2710-2712.
31. Centers for Disease Control. 1982. Recommendations of the Immunization Practices Advisory Committee (ACIP) . Measles prevention. Morbid. Mortal. Weekly Rept. 31:217-231.

32. Krugman, S., and Katz, S.L. 1981. Infectious Diseases of Children. St. Louis: Mosby.
33. Sherman, F.E., Michaels, R.H., and Kenny, F.M. 1965. Acute encephalopathy (encephalitis) complicating rubella. JAMA 192:91-97.
34. Horstmann, D.M. 1982. Rubella. Pp. 519-539 in Viral Infections of Humans, A.S. Evans, ed. New York: Plenum.
35. Centers for Disease Control. 1984. Rubella vaccination during pregnancy-United States, 1971-1983. Morbid. Mortal. Weekly Rept. 33:365-368, 373.
36. Preblud, S.R., Serdula, M.K., Frank, J.A., Jr., Brandling-Bennett, A.D., and Hinman, A.R. 1980. Rubella vaccination in the United States: a ten-year review. Epidemiol. Rev. 2:171-194.
37. Tingle, A.J., Yang, T., Allen, M., Kettyls, G.D., Larke, R.P.B., and Schulze, M. 1983. Prospective immunological assessment of arthritis induced by rubella vaccine. Infect. Immun. 40:22-28.
38. Vergani, D., Morgan-Capner, P., Davies, E.T., Davies, A.W., Tee, D.E.H., and Pattison, J.R. 1980. Joint symptoms, immune complexes and rubella. Lancet II:321-322.
39. Centers for Disease Control. 1982. Recommendations of the Immunization Practices Advisory Committee (ACIP). Mumps vaccine. Morbid. Mortal. Weekly Rept. 31:617-625.
40. Feldman, H.A. 1982. Mumps. Pp. 419-440 in Vital Infections of Humans, A.S. Evans, ed. New York: Plenum.
41. Centers for Disease Control. 1984. Recommendations of the Immunization Practices Advisory Committee (ACIP) . Prevention and control of influenza. Morbid. Mortal. Weekly Rept. 33:253-266.
42. Schonberger, L.B., Bregman, D.J., Sullivan-Bolyai, J.Z., Keenlyside, R.A., Ziegler, D.W., Retailliau, H.F., Eddins, D.L., and Bryan, J.A. 1979. Guillain-Barré syndrome following vaccination in the national influenza immunization program, United States, 1976-1977. Am. J. Epidemiol. 110:105-123.
43. Centers for Disease Control. 1978. Recommendations of the Immunization Practices Advisory Committee (ACIP). Update: pneumococcal polysaccharide vaccine usage-United States. Morbid. Mortal. Weekly Rept. 35:273-281.
44. Gold, R., and Lepow, M.L. 1976. Present status of polysaccharide vaccines in the prevention of meningococcal disease. Adv. Pediatr. 23:71-94.
45. Centers for Disease Control. 1978. Recommendations of the Immunization Practices Advisory Committee (ACIP). Meningococcal polysaccharide vaccines. Morbid. Mortal. Weekly Rept. 35:327-329.
46. Centers for Disease Control. 1980. Recommendations of the Immunization Practices Advisory Committee (ACIP). Rabies prevention. Morbid. Mortal. Weekly Rept. 29:265-280.
47. Plotkin, S.A. 1980. Rabies vaccination in the 1980s. Hosp. Pract. 15:65-72.
48. Centers for Disease Control. 1984. Systemic allergic reactions following immunization with human diploid cell rabies vaccine. Morbid. Mortal. Weekly Rept. 33:185-187.

49. Centers for Disease Control. 1982. Recommendations of the Immunization Practices Advisory Committee (ACIP). Inactivated hepatitis B virus vaccine. Morbid. Mortal. Weekly Rept. 31:317-328.
50. Surveillance, Investigations, and Research Branch, Division of Immunization, Center for Prevention Services, Centers for Disease Control. 1984. Unpublished data presented to the Surgeon General's Immunization Practices Advisory Committee (ACIP), February 7, 1984.
51. Centers for Disease Control. 1984. Hepatitis B vaccine: evidence confirming lack of AIDS transmission. Morbid. Mortal. Weekly Rept. 33:685-687.

6

Liability for the Production and Sale of Vaccines

Potential liability for vaccine-related injuries has received much attention as a deterrent to vaccine manufacturing. A variety of approaches to the issue have been suggested, but there have been few attempts to determine the magnitude of the problem or to analyze basic trends in the interpretation of laws in this area. This chapter provides such an analysis and examines the ways in which the state of the law influences decisions that ultimately affect vaccine availability and innovation.

STATE OF THE LAW

Liability for injury resulting from vaccination is a matter of state law. Thus, there are potentially 51 different sets of rules on this subject in the United States. No vaccine-related product liability litigation resulting in a publicly available opinion has occurred in most jurisdictions, and in many there has been no liability litigation related to drugs. Although it is possible by extrapolation from other product liability cases to predict how these states would handle vaccine cases, any such extrapolation might prove inaccurate.

The subject of product liability has become increasingly controversial over the past few years. Manufacturers have complained about the costs, the unpredictability of the law, and the unavailability and cost of insurance. A majority of states have enacted statutes relating to some aspect of product liability actions.[1] Legislation at the federal level has been considered extensively, but has not been passed.[2]

A manufacturer who produces and sells a defective vaccine that creates a risk of significant injury to the recipient is liable to any person injured by that defect under the principles stated in section 402A of the Restatement of Torts 2d.[3] This is thought to be the law in every American jurisdiction. The key portion of section 402A states:

> One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused to the ultimate user or consumer. . . . [The rule applies although]

the seller has exercised all possible care in the preparation and sale of his product.

Cases holding manufacturers or others liable for allegedly defective vaccines administered to humans are very rare.[4] The reported cases are:

- Griffin v. United States, in which the U.S. government was held liable because the Division of Biologics Standards of the National Institutes of Health released a batch of Sabin polio vaccine that did not conform to its own regulatory standards (the manufacturer settled), 351 F. Supp. 10 (E.D. Pa. 1972), aff'd in part, rev'd in part and remanded, 500 F.2d 1059 (3d Cir. 1974);
- Grinnell v. Charles Pfizer & Co., in which the manufacturer was held liable for virulent particles in Salk killed-virus vaccine, 274 Cal. App. 2d 24, 79 Cal. Rep. 369 (Dist. Ct. App. 1969);
- Four cases in which the manufacturers of quadrivalent vaccine (diphtheria, tetanus, pertussis, and poliomyelitis) were held liable because new preservative activated the pertussis component, Tinnerholm v. Parke-Davis & Co., 285 F. Supp. 432 (S.D.N.Y. 1968), aff'd, 411 F.2d 48 (2d Cir. 1969), Stromsodt v. parke-Davis & Co., 257 F. Supp. 991 (D.N.D. 1966), aff'd, 411 F.2d 1390 (8th Cir. 1969), Vincent v. Thompson, 79 Misc. 2d 1029 (N.Y. 1974), and Ezagui v. Dow Chemical Corp. 598 F.2d 727 (2d Cir. 1979);
- Gottsdanker v. Cutter Laboratories, in which live particles were found in Salk killed-virus vaccine, 182 Cal. App. 2d 602, 6 Cal. Rptr. 320 (Dist. Ct. App. 1960); and
- Sandel v. State, in which pus was found in typhoid vaccine, 115 S.C. 168, 104 S.E. 567 (1920).

A manufacturer is not liable for harm caused by a nondefective product due to its inherent or unavoidable dangerousness. Thus, if a properly manufactured vaccine will cause harmful side effects in some portion of the recipient population, the manufacturer of the vaccine is not liable for those side effects. This principle is the subject of comment k to section 402A.

> k. Unavoidably unsafe products. There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidably high degree of risk which they involve. Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except

> to physicians or under the prescription of a physician. . .. The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.

The qualification "proper warning is given" is critically important and a manufacturer will be liable if he markets a drug or vaccine with known risks and fails to warn of them, and it can be shown that the recipient would not have taken the drug or vaccine had he known of the risks. An example of this situation involving polio vaccine is Davis v. Wyeth Laboratories, Inc., 399 F.2d 121 (9th Cir. 1968). In that case, Sabin polio vaccine had been administered to the plaintiff, a 39-year-old male, in a mass immunization campaign conducted with the assistance of a sales representative of the defendant. The plaintiff had developed polio. The Surgeon General had recommended that mass programs using Sabin Type III be limited to children because of the risk of transmission of the disease to adult recipients. The mass immunization campaign involved in the case, however, included adults. The defendant's promotional materials failed to warn of the risk to adults, although the package insert did. The pharmacist who dispensed the oral vaccine did not read the package insert and did not warn the plaintiff of the risk.

The duty to warn arises from the notion that the failure to inform consumers of dangerous aspects of a product may render the product unreasonably dangerous. For instance, if an electric device operated in a certain way will blow up and cause harm to bystanders, a failure to warn the consumer of this risk so that he can avoid the harm will make the manufacturer liable for the harm. Or in the Davis case, if the plaintiff had been warned of the risk, he could have chosen not to take the vaccine, as was then recommended in the case of adults.

If a product is not sold directly to the public, but is distributed through intermediaries who can be expected to know about the product and its risks and to be responsible for informing the ultimate consumer on its proper use, then the manufacturer does not have a duty to warn the public (although it does have a duty to warn the intermediaries of risks not known to them). Prior to Davis, this exception to the duty to warn was thought to be applicable to drugs and vaccines distributed through health professionals (as contrasted with over-the-counter drugs, for which the manufacturer does have a duty to warn the user).

In Davis, the defendant manufacturer argued that its duty to warn had been satisfied by the fact that it had informed the county medical society sponsoring the mass immunization program of the risk that a vaccinee might develop polio. The court rejected this argument in the context of the mass immunization program:

> Here . . . although the drug was denominated a prescription drug it was not dispensed as such. It was dispensed to all

> comers at mass clinics without an individualized balancing by a physician of the risks involved. In such cases (as in the case of over-the-counter sales of nonprescription drugs) warning by the manufacturer to its immediate purchaser will not suffice. . . . In such cases, then, it is the responsibility of the manufacturer to see that warnings reach the consumer, either by giving warning itself or by obligating the purchaser to give warning. Here . . . [the manufacturer] knew that warnings were not reaching the consumer. Appellee had taken an active part in setting up the mass immunization clinic program for the society and well knew that the program did not make any such provision, either in advertising prior to the clinics or at the clinics themselves. On the contrary, it attempted to assure all members of the community that they should take the vaccine. 399 F.2d 131.

The Missouri Supreme Court reached the same result in Stahlheber v. American Cyanamid Co., 451 S.W. 2d 48 (Mo. 1970), involving another mass administration of oral polio vaccine. Recipients included a 41-year-old adult who contracted polio. The manufacturer had not warned that the vaccine should not be administered to adults other than those facing special risks of contracting the disease.

The law summarized here appears to lead to the conclusion that a vaccine manufacturer need not fear liability from injuries resulting from the administration of the vaccine if (1) the vaccine is correctly manufactured in accordance with regulatory standards and prudent manufacturing practices and (2) the manufacturer has taken reasonable steps to ensure that the recipient of the vaccine will be warned of possible side effects. Merrill's comprehensive 1973 survey of the law of liability for all drugs concludes: "If a manufacturer adequately warns physicians [or, in the case of mass-administered vaccines, the recipient] about a drug's foreseeable adverse effects, he will escape liability unless the plaintiff can show that his injury was caused by some impurity or resulted from an unreasonably dangerous design" [Merrill, "Compensation for Prescription Drug Injuries," 59 Va. L. Rev. 1, 49 (1973)].

In two decisions, the Fifth Circuit Court of Appeals, nominally applying the law first of Texas and then of Florida, imposed liability in circumstances that would not be covered by these rules. Both decisions have been subject to criticism,[5] and it is not clear how many courts would follow them today.

The first and most important of these decisions is Reyes v. Wyeth Laboratories, 498 F.2d 1264 (5th Cir. 1974). That case involved a young girl to whom Sabin oral polio vaccine was administered at a county department of health clinic in Mission, Texas. She developed polio, and her parents sued on her behalf for damages.

The manufacturer's main line of defense at the trial was that the vaccine was not the cause of the disease. Experts testified that virus isolated from a specimen of the child's stool taken on the day after she was admitted to the hospital was "probably wild," i.e., naturally occurring and not the same strain as the vaccine [498 F.2d

1270-1271]. The jury found, however, that the vaccine was the cause of the child's disease, and found for the plaintiff under the district court' s instructions.

The critical issues decided by the court of appeals were two. First, had the manufacturer discharged its duty to warn? And second, was the failure to warn sufficiently connected to the occurrence of the child's disease to support liability? Judge Wisdom wrote a unique opinion strongly affirming the judgment for the plaintiff.

In Reyes, Wyeth had played no role in the vaccination program, perhaps because it had changed procedures after its loss in Davis. It had simply shipped the vaccine in response to an order from the Texas State Department of Health. The package insert warned of the risk, and Wyeth argued that it was all that was required to discharge its responsibility. The procedures, forms, and warnings actually used in the immunization program were the responsibility of the Texas Department of Health, to which it had quite properly shipped the vaccine.

Judge Wisdom answered this argument without really meeting it. Wyeth knew that the vaccine was customarily administered in mass administration programs staffed at least in part by volunteers and nonprofessionals. Knowing that each recipient would not have individualized medical advice, it "was required to warn foreseeable users, or see that the Texas Department of Health warned them" [498 F.2d 1277]. Exactly how Wyeth was to provide these warnings at distant clinics with which it had no connection, or why Wyeth was not entitled to rely upon the Texas Department of Public Health to do its job properly, Judge Wisdom did not clarify. To the argument that Davis was inapplicable because in that case Wyeth had actively participated in the program, Judge Wisdom observed that "the present controversy, however it differs from Davis factually, invites application of the Davis principles, and the conclusion that Wyeth was under a duty to warn . . . [the recipient's parents]" [498 F.2d 1277].

The second issue confronting the court of appeals was whether there was sufficient connection between the failure to warn and the injury to the child. There was no demonstration that had the child's mother been warned of the minute incidence of polio from the vaccine she would have decided not to have her child immunized. This possibility would seem to have been extremely unlikely because polio was occurring in the area. The court first looked to Texas cases for the following rule:

> Where a consumer, whose injury the manufacturer should have reasonably foreseen, is injured by a product sold without a required warning, a rebuttable presumption will arise that the consumer would have read any warning provided by the manufacturer, and acted so as to minimize the risks. In the absence of evidence rebutting the presumption, a jury finding that the defendant's product was the producing cause of the plaintiff's injury would be sufficient to hold him liable [498 F.2d 1281].

In the normal product liability case, this rule makes sense. If the consumer is warned of a danger, he or she can take steps to avoid it.

However, what was the parent confronted with the warning that Sabin polio vaccine might cause polio to do? Forgo vaccination and incur the risk of contracting polio naturally? No, said the court, take Salk killed-virus vaccine first.

> Buttressing the presumption that Mrs. Reyes might have taken preventive steps is the testimony of Reyes's expert, Dr. Ramiro Casson, that some pediatricians in Hidalgo County, at least by the time of trial, had begun administering killed-virus vaccine to infants in order to build up their level of antibodies before feeding them the live-virus drug [498 F.2d 1282].

This aspect of the decision has been vigorously criticized by Franklin and Mais in "Tort Law and Mass Immunization Programs: Lessons from the Polio and Flu Episodes," 65 Calif. L. Rev. 754 (1977):

> First, the court did not discuss the availability of Salk vaccine at the time plaintiffs' child was vaccinated. In fact, manufacturers discontinued making Salk vaccine and concentrated on the Sabin vaccine after the government selected Sabin vaccine for its mass immunization programs in the early 1960s. Indeed, from 1968 to 1975 no Salk vaccine was manufactured in the country, although small amounts were imported. Although the court referred to immunizations in Hidalgo County using Salk vaccine in the early 1970s, it is likely that these units were imported and not generally available. Thus, those who would have chosen Salk vaccine after being warned of the danger of Sabin vaccine would have had a difficult time obtaining the alternative.
> Second, the court did not discuss the significance of the fact that the plaintiffs' child was vaccinated during an outbreak of polio in her area. When quick protection is essential, Sabin vaccine has been preferred despite the risk from the live virus. Therefore, even if Salk vaccine had been available it is unlikely that a well-informed person seeking protection would have chosen it [65 Calif. L. Rev. 761].

The Oklahoma Supreme Court did not follow Reyes in Cunningham v. Pfizer & Co., 532 P.2d 1377 (Okla. 1976), because the evidence in that case showed that at the time of the plaintiff's vaccination in 1963, Oklahoma was in "an epidemic state." The court reversed a verdict for plaintiff and remanded, requiring the plaintiff to show that if the warning had been given, he would not have been vaccinated.

In Reyes, the court imposed liability on the manufacturer for failing to warn the recipient directly of a risk of contracting poliomyelitis from the vaccine even though the warning accompanied the vaccine and would have been very unlikely to change the conduct of the recipient, or to have prevented the child from contracting polio.

Judge Wisdom's opinion closed with an extraordinary section in which, in response to an amicus brief filed by the American Academy of Pediatrics and the Conference of State and Territorial Epidemiologists

opposing liability, he took on both medical practice and the Congress. To the doctors he said:

> Obviously, however, one can choose to be inoculated with killed-virus Salk vaccine, either to provide complete immunity or as a precautionary prelude to ingesting oral vaccine. This position [that no warning should be required] raises a policy consideration scarcely less urgent than the need for mass immunization from disease; the right of the individual to choose and control what risk he will take . . . [498 F.2d 1294].

To the Congress he said:

> 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. . .. [cite] 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.

Givens v. Lederle, 556 F.2d 1341 (5th Cir. 1977), was a further extension of Reyes. Givens, like Reyes, involved Sabin oral polio vaccine. However, unlike Reyes, the vaccine had not been administered in a county health clinic, but by a pediatrician in his office. The victim was not the child but the child's mother, who had apparently contracted the polio from the vaccinated child. The pediatrician had given no warning of this or any other risk, although the risk was disclosed in the package insert.

The case had concluded in a jury verdict for the defendant in the Middle District of Florida (then part of the Fifth Circuit), on the grounds that the vaccine could not have caused the polio [556 F.2d 1343]. Reyes was handed down before the entry of judgment, however, and the trial judge granted a new trial in light of Reyes. On retrial, the verdict was for the plaintiff, and the defendant appealed.

A remarkable aspect of the Givens opinion is that the court did not rely on Florida law to support its judgment. In Reyes, the court had gone to great lengths to highlight a line of Texas cases concerning possible allergic reactions to a drug. In these cases, it was held unnecessary to warn recipients of possible allergic reactions if the number of people affected was not significant. It might appear that because the number of people who get polio from the vaccine is minute, this line of cases would suggest that no warning of the risk was necessary under the controlling Texas law. The court, however, distinguished between the cases on the ground that an allergic reaction affected only a small group of recipients, while all recipients of the polio vaccine were apparently subject to the minute risk of vaccine-induced polio [498 F.2d 1278-1279]. In contrast, the

Givens opinion made no reference to Florida law. It simply followed Reyes—ostensibly applying Texas law—and treated it as Florida law.

"[A] proposed major distinction is that a county health clinic administered the vaccine in Reyes, whereas a private pediatrician did so here," said the court [556 F.2d 1344]. The manufacturer apparently was relying on the long line of authority indicating that the duty to warn in the case of prescription medicines prescribed by doctors belongs to the doctor, not the manufacturer. The pediatrician in Givens had an established doctor-patient relationship, was a trained and licensed professional, and had determined that the patient should receive the vaccine as part of her health care. This was not a case of an unadvised patient responding to the entreaties of a mass vaccination campaign.

The court responded to this argument as follows: "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" [Ibid]. Testimony by the plaintiff's physician that". . . the administration in his office 'really doesn't differ' from that of the Public Health Center; 'not in the administration at all'" emphasized the similarity to the Reyes situation, rather than his role as an informed intermediary [556 F.2d 1345].

The defendant also argued that its warning to the doctor was adequate, and should protect it from liability. The warning stated:

> Paralytic disease following the ingestion of live polio virus vaccines has been reported in individuals receiving the vaccine, and in some instances, in persons who were in close contact with subjects who had been given live oral polio virus vaccine. Fortunately, such occurrences are rare, and it could not be definitely established that any such case was due to the vaccine strain and was not coincidental with infection due to naturally occurring poliomyelitis, or other enteroviruses [556 F.2d 1343].

Of this warning, the plaintiff's doctor testified: "[T]he wording of the inserts states that it is a safe and effective means of immunizing the population and that the risk, if it exists, is no more than 1 in 3 million. I felt this was a very nebulous way of putting it, . . . and I did not feel there was sufficient evidence or warning to warn Mrs. Givens about this" [556 F.2d 1345]. The court held that this was sufficient evidence to sustain a jury verdict that the warning was inadequate.

Thus, the court of appeals in Givens treated as factual questions for the jury whether or not the vaccine caused the polio, and whether or not the warning was adequate in light of the actual degree of risk that the vaccine might cause the polio. This situation, in which a jury confronted with a grievously ill child or adult (who has no other potential source of financial support or redress) is asked to judge retrospectively the actions of the manufacturer, the regulatory authorities, and those responsible for the public health, tends toward a biased outcome in favor of the plaintiff.

Although Reyes and Givens were decided in conformity with the verbal formulas of previous product liability law, the skeptical reader might easily conclude that they really stood for a different and simpler rule: the manufacturer is liable for all damages caused by a vaccine. Just such a rule for all prescription drugs had been advocated in Merrill's "Compensation for Prescription Drug Injuries," 59 Va. L. Rev. 1 (1973), and that article was cited by Judge Wisdom in the policy discussion in the Reyes opinion, 498 F.2d 1294 n. 57. Even though the Fifth Circuit had no power to make law on this point for Florida and Texas (the Texas or Florida courts could repudiate these decisions at any time if they had a case in point and chose to do so), the skeptical lawyer advising a manufacturer could take as the message from the judges: manufacturers are going to pay, one way or the other.

Experience From the Swine Flu Vaccination Program

These issues received highly publicized national attention in the summer of 1976. The discovery of swine flu virus in a human population with resulting illness (and one death) at Fort Dix, New Jersey, in January 1976, led the CDC to recommend a national program to provide immunizations against swine flu for the population.[6] The need for the program was based on the extensive morbidity and mortality experienced during the disastrous pandemic of 1918, caused by an apparently identical strain of influenza virus.

The proposals for such a vaccination program moved through the executive branch and the President to the Congress without a full appreciation of the problems presented by the threat of liability. The program was formulated and advanced on the assumption that the vaccine manufacturers would gladly produce for a fee close to cost the needed vaccine. The public health officials and government lawyers did not realize that Reyes and Givens in the district court represented an entirely new factor in the decision to produce and sell vaccines, particularly a vaccine proposed for administration to nearly the entire population in a short period.

The manufacturers and their insurance carriers, on the other hand, no doubt resented the liability burdens placed upon them by Judge Wisdom, and were perhaps not unhappy about the opportunity to have their concerns addressed in a national forum. In any case, it became clear that the program would not go forward without some legal protection for the manufacturers, who were unable to obtain insurance at a price acceptable to them and refused to carry the risk themselves, in large part because of the limited time available for safety testing.

Rapid congressional action necessitated by the need to manufacture and administer the vaccine before the onset of the flu season resulted in P.L. 94-380, effective August 11, 1976. The act provided for an exclusive remedy against the United States "for personal injury or death arising out of the administration of swine flu vaccine under the swine flu program and based upon the act or omission of a program participant" [P.L. 94-380 sec. 2(k) (2) (A)]. Program participant was defined broadly to include

> . . . the manufacturer or distributor of the swine flu vaccine used in an inoculation under the swine flu program, the public or private agency or organization that provided an inoculation under the swine flu program without charge for such vaccine or its administration and in compliance with the informed consent form and procedures requirements prescribed [in the statute], and the medical and other health personnel who provided or assisted in providing an inoculation under the swine flu program without charge for such vaccine or its administration and in compliance with such informed consent form and procedures requirements.

The statute left open the possibility of the manufacturer's or other participant's liability only in the form of a right of the United States to sue any participant for the amount it had paid and the costs of defending the litigation "resulting from the failure of any program participant to carry out any obligation or responsibility assumed by it under a contract with the United States in connection with the program or from any negligent conduct on the part of any program participant . . ." [Id. sec. 2(k)(7)].

The Swine Flu Act had little to recommend it except that it made it possible to go ahead with swine flu vaccine production. The manufacturers obtained protection for one vaccine under one temporary program, but no attention to the issues on any systematic basis. The law was criticized from many points of view but, in fact, it only changed the defendant and the rules, albeit unclear, remained the same. It also thrust the government into the unfamiliar role of product liability and malpractice defendant. The preamble to section 2 (k) stated that the statute was necessary "in order to be prepared to meet the potential emergency . . . until Congress develops a permanent approach for handling claims arising under programs of the Public Health Service Act." That "permanent approach" subsequently faded as rapidly as the swine flu emergency.

The concern about the liability problems of vaccination programs so visible in the debate over swine flu carried over to the state level. To further the cause of universal vaccination and to protect participants in the process, the manufacturers, the American Academy of Pediatrics, and others sought state legislation limiting liability. In the wake of the swine flu controversy, they were successful in two states: Maryland and California. Since then, no new, relevant state legislation has passed.

The Maryland statute provides for immunity of all "program participants," including manufacturers, if the state Secretary of Health and Mental Hygiene finds that an immunization project conforms to good medical and public health practice and gives written approval. No person is exempted from liability for gross negligence, and a manufacturer is not exempted "from the duty to use ordinary care in preparing and handling a drug or vaccine" [Maryland Code sec. 18-401, revised version of Ch. 238 of the 1977 laws].

The California statute mandated the creation of a special fund to provide for the medical, institutional, supportive, and rehabilitative

care required "because of severe adverse reaction to any immunization required by state law to be administered to children under 18 years of age."[7] The statute also stated that "No person shall be liable for any injury caused by an act or omission in the administration of a vaccine or other immunizing agent to a minor . . . if such immunization is required by state law and the act or omission does not constitute willful misconduct or gross negligence" [California Health and Safety Code secs. 429.35 and 429.36, passed as Ch. 1097, secs. 1 and 2 of the 1977 statutes]. A California trial court has held that this statute protects manufacturers from liability [Flood v. Wyeth Laboratories, Inc., No. SW C 58664 (Superior Court for the County of Los Angeles)].

The swine flu program was not a public health success. The vaccine was successfully manufactured, distributed, and administered to over 45 million people in a relatively short period of time—a considerable administrative and logistical achievement. However, the virus did not reappear the following winter, for reasons that no one understands. Furthermore, it appeared that 1 out of 100,000 of the recipients developed Guillain-Barré syndrome (the most recent study reports a rate of 1 per 200,000)[8], an unexpected and unique occurrence of unknown etiology. As a result of the publicity about side effects and the documentation of the apparent relationship between the vaccine and Guillain-Barré syndrome (GBS), a large number of claims were filed. The special liability provisions of the swine flu statute, which very well might have faded into history, proved to be important.

For the purposes of this study, the main importance of the provisions is that they resulted in a large body of litigation relating to the issue of liability for vaccine manufacture and administration. The claims and suits are summarized in Table 6.1, prepared by the Torts Branch of the Civil Division of the Department of Justice. The government has paid more than $73 million to claimants alleged to have been injured by the swine flu vaccination. Although this amount is large in absolute terms, it is less than $2 per vaccine recipient.

Because there has been so little litigation directly relevant to the liability issue for vaccine manufacture and administration, the numerous swine flu cases provide the best guide to date on the legal rights of injured recipients, the liability risks of manufacturers, and the likely results of court action. It is useful, therefore, to describe this experience at some length and to evaluate the factors that make it relevant to the general question of what vaccine manufacturers need or need not fear.

The most important decision made in connection with the swine flu litigation was a decision by the government to stipulate to liability (accept liability responsibility) for damages caused by the GBS in any case where the plaintiff could show that the GBS was caused by the administration of the vaccine. What was the basis of this stipulation to liability? Was the U.S. government taking the position that the law imposed strict liability, that the warning had been inadequate, or that the vaccine was negligently manufactured or administered?

The court in In re Swine Flu Immunization Products Liability Litigation , 533 F. Supp. 703, 718 (D. Utah 1982), reported the following:

TABLE 6.1 Swine Flu Claims, Suits, and Outcomes (as of December 15, 1983)

	Number	Amount Requested (dollars)	Amount Received (dollars)
Suits			
Filed	1,601	2,178,805,111	
Dismissed	591	704,054,816	
Settled	345	362,559,989	
Judgments (liability stipulated)	47	86,677,815	16,355,551
Judgments for Plaintiff	37	71,346,620	16,733,390
Judgments for Defendant	209	293,463,093	0
Pending	372	660,702,778	
Claims			
Filed	4,152	3,092,856,048	
Denied	2,794	1,960,223,431	
Closed	165	68,617,514	
Settled	277	123,519,475	6,715,519
"Deemed Denied"	496	544,771,161	
Deemed Denied/Settled	386	353,862,546	33,150,825
Pending	34	41,861,921	
Total Settled	663	477,382,021	39,866,344
Total Awarded			72,955,285

NOTE: Some suits include multiple claims.
SOURCE: Torts Branch, Civil Division, U.S. Department of Justice.

During pretrial procedures . . . the controversial but crucial official statement of then-Secretary of Health, Education, and Welfare, Joseph A. Califano, Jr. was made.

Secretary Califano stated that with respect to those alleging GBS, the government was adopting a new policy. Persons who contracted GBS from the swine flu vaccine, in order to receive federal compensation:

> [W] ill not need to prove negligence by Federal workers or others in the Swine Flu Program as required by Federal law and the law in many states. Instead claimants in most cases need only to show that they in fact developed Guillain-Barré as a result of a Swine Flu vaccination and suffered the alleged damage as a result of that condition [Statement of Secretary Califano, June 20, 1978].
>
> Secretary Califano set out two reasons for adoption of this policy:
>
> First, the informed consent form . . . did not warn individuals that there was a one in one hundred thousand risk that a person receiving a flu shot would contract Guillain-Barré and that one in every two million would die from the condition . . . Second, in the Swine Flu program, the Federal Government, in an unprecedented effort, actively urged millions of Americans to get flu vaccination shots and funded the nationwide campaign. Thus we have decided to provide just compensation [emphasis added] for those who contracted Guillain-Barré as a result of the Swine Flu program rather than force many individuals to prove government negligence in protracted proceedings.

The court then added: "The Justice Department had stated that this policy was 'within the intent of the Swine Flu Act and its legislative history and was appropriate under the circumstances.' (Statement of Mr. Califano reiterating the Department of Justice policy statement)" [533 F. Supp. 718].[9] These positions attributed to Secretary Califano are difficult to interpret. The simplest explanation for the decision would have been that the tort claims act (incorporated in the Swine Flu Act by reference) conferred upon the Department of Justice the authority to represent the government in the litigation, that part of the authority to represent a client includes the authority to settle or compromise claims, and that the Department determined in light of the risks and costs of litigation that a stipulation to liability for this class of cases was a prudent litigation stance. That would require a determination, of course, that there was some risk of liability, but in light of Reyes and Givens such a determination would seem to have been quite reasonable.

The explanations attributed to Secretary Califano by the court raise a number of troubling questions. First, the Secretary said that the warning did not warn of the GBS. Does this imply that there is liability if a manufacturer fails to warn of an adverse side effect even when there is little reason to expect the side effect? If, in fact, there was no reason to warn of the side effect because there was no reason to anticipate it, then why is the failure relevant to the stipulation of liability? Second, why wasn't it sufficient to warn, as was done, of "the possibility of severe or potentially fatal reactions?" Does each possible reaction have to be separately named, or named and then described? Third, what is the relevance of the fact

that the government encouraged people to get vaccinated? If that should make the government liable, then surely it should make the manufacturer liable, for the manufacturer is the one that makes the vaccination possible. And if the major point is that Secretary Califano thought there should be what in his view was "just compensation," then why was that a decision for Secretary Califano to make?[10] Congress had specifically decided in the course of considering the statute not to change the liability rules. Hence, Secretary Califano's authority to interpret the law in this fashion remains unclear.[11]

The stipulation was limited to an admission of liability in cases where the plaintiff could prove that the GBS was caused by the vaccination. Given the fact that there is no understood causal path between the vaccination and the syndrome, that was not a trivial burden of proof. However, the suspicion about a connection surfaced early, and the Centers for Disease Control instituted an intensive surveillance system, which resulted in the halt in the program and established an apparent association between vaccination and a higher rate of GBS in the 10 weeks after vaccination. Because of this government study, which provided proof of causal connection, the Department of Justice adopted the policy of admitting liability in all cases where the plaintiff had experienced an onset of GBS within 10 weeks of the vaccination. That left for litigation those cases characterized by issues such as: (1) Did the plaintiff display symptoms of GBS within 10 weeks of vaccination? (2) What were the damages? (3) Did the vaccination cause GBS in cases in which the symptoms were not observed until more than 10 weeks after vaccination? and (4) Did the vaccination have any other adverse effects, and, if so, was there liability for them? The reported results of this litigation are summarized in Table 6.2.[12]

Table 6.2 reflects the fact that the government was successful in maintaining its position in court. Almost all decisions upheld the position that the government had no liability for conditions other than GBS that appeared in the first 10 weeks after vaccination. Table 6.2 also shows the inherent unpredictability of litigation. There are six decisions that depart from this pattern. The government policy was not to settle cases that did not fit within the "GBS in 10 weeks" criterion, so these six cases should represent the only claims of the 1,600 filed that did not meet that criterion but resulted in recovery.

Overall, the cases demonstrate the phenomenon, reported by others, that a few tort plaintiffs receive a large percentage of the total recovery. This same phenomenon is also documented by Table 6.3, which breaks down total payments by size grouping. This occurs, in part, because it is only in cases with the potential for substantial damages that the incentives exist for a lawyer compensated on a contingent fee basis to make the significant investment required to pursue a legally and technologically complex case to trial.

The six cases that fall outside the basic pattern of the swine flu claims resolution are instructive because one of the risks that concerns potential product liability defendants is the risk of the unexpected result, particularly when it may cost millions of dollars.

TABLE 6.2 Reported Swine Flu Vaccine Cases Based Upon Manufacturers' Liability Theory

Guillain-Barré Syndrome Within 10 Weeks	Guillain-Barré Syndrome After 10 Weeks	Other Conditions
McDonald, 555 F. Supp. 935 (M.D. Pa. 1983) $3,971,470	Liability	Liability
Wolfe, No. 81-5528, slip op. (6th Cir. May 4, 1982) $1,989,327.08	Spencer, 569 F. Supp. 325 (W.D. Mo. 1983) $259,881.69	Petty, 536 F. Supp. 860 (N.D. Iowa 1980) $212,807.22; vacated and remanded, 679 F.2d 719 (8th Cir. 1982); damages reinstated, No. C 78-4083, slip op. (N.D. Iowa, March 31, 1984); aff'd, 740 F.2d, 1428 (8th Cir. 1984)
Barnes, 581 F. Supp. 536 (N.D.) $1,577,112.67	Sulesky, 545 F. Supp. 426 (S.D. W.V. 1982) $186,065.80	Gassman, No. 79-314-ORL-CIV-06, slip op. (M.D. Fla. June 27, 1984)[a]
Grubbs, 581 F. Supp. (N.D. Ind. 1984) $721,040	Hockett, 730 F.2d 709 (11th Cir. 1984) $324,275.61	Unthank, 732 F.2d 1517 (10th Cir. 1984)[a]
Pretre, 531 F. Supp. 931 (E.D. Mo. 1981) $658,903.17	No Liability	No Liability
de la Rosa, No. B-78-102, slip op. (S.D. Tex. April 23, 1982) $498,232.33	Lima, 708 F.2d 502 (10th Cir. 1983)	Stich, 730 F.2d 115 (3d Cir. 1984)
Funston, 513 F. Supp. 1000 (M.D. Pa. 1981) $490,009.65	Gates, 707 F.2d 1141 (10th Cir. 1983)	Freeman, 704 F.2d 154 (5th Cir. 1983)
Draisma, 492 F. Supp. 1317 (W.D. Mich. 1980) $329,528	Alvarez, 495 F. Supp. 1188 (D. Colo. 1980)	Hasler, 718 F.2d 202 (6th Cir. 1983)
Fraysier, 566 F. Supp. 1085 (S.D. Fla. 1983) $275,000	Beall, 567 F. Supp. 131 (M.D. Pa. 1983)	Tabaczynski, No. 83-1158, slip op. (6th Cir. May 5, 1983
Hewitt, 550 F. Supp. 589 (D. Mass. 1982) $218,162.08	Cook, 545 F. Supp. 306 (N.D. Cal. 1982)	Smith, 726 F.2d 428 (8th Cir. 1984)
Lawrence, No. 81-5017, slip op. (6th Cir. Dec. 1, 1981); aff'd No. 83-5114, slip op. (6th Cir. Dec. 1, 1982) $179,710.73	Gaul, 582 F. Supp. 1122 (D. Del. 1984)	Zeck, 720 F.2d 534 (8th Cir. 1983)
Leeper, 577 F. Supp. 553 (M.D. Pa. 1983) $115,905.25	Heyman, 506 F. Supp. 1145 (S.D. Fla. 1981)	Gundy, 728 F.2d 484 (10th Cir. 1984)
Overton, 619 F.2d 1299 (8th Cir. 1980) $108,056.35	Iglarsh, No. 79C2148, slip op. (N.D. Ill. Dec. 9, 1983)	Daniels, 704 F.2d 587 (11th Cir. 1983)
Lee, 499 F. Supp. 307 (E.D. Tenn. 1980) $80,000	Latinovich, 537 F. Supp. 671 (E.D. Wis. 1982)	Adleson, 523 F. Supp. 459 (N.D. Cal. 1981)
Barnes, 525 F. Supp. 1065 (M.D. Ala. 1981) $40,000	Migliorini, 521 F. Supp. 1210 (M.D. Fla. 1981)	Azzinaro, No. 79 Civ. 2416 (RWS), slip op. (S.D.N.Y. Nov. 19, 1982)
	O'Gara, 560 F. Supp. 786 (E.D. Pa. 1983)	Baum, 541 F. Supp. 1349 (M.D. Pa. 1982)
	Padgett, 553 F. Supp. 794 (W.D. Tex. 1982)	Bean, 533 F. Supp. 567 (D. Colo. 1980)
	Robinson, 533 F. Supp. 320 (E.D. Mich. 1982)	Cohen, 571 F. Supp. 589 (S.D.N.Y. 1982)
	Thompson, 533 F. Supp. 581 (N.D. Okla. 1981)	Daniskewski, No. 80 C 1923, slip op. (N.D. Ill, March 31, 1983)
	Varga, 566 F. Supp. 987 (N.D. Ohio 1983)	Gicas, 508 F. Supp. 217 (E.D. Wis. 1981)
		Grill, 552 F. Supp. 505 (E.D.N.Y. 1982)

Guillain-Barré Syndrome Within 10 Weeks	Guillain-Barré Syndrome After 10 Weeks	Other Conditions
Brown, 715 F.2d 463 (9th Cir. 1983) $35,000		Hixenbaugh, 506 F. Supp. 461 (N.D. Ohio 1980)
Kynaston, 717 F.2d 506 (10th Cir. 1983)[a]		Hooper, No. CA 79-584-1, slip op. (D. Mass. Aug. 8, 1983)
Clinton, 530 F. Supp. 126 (E.D. Tex. 1982)[a]		Hupp, 563 F. Supp. 25 (S.D. Ohio 1982)
		Kubs, 537 F. Supp. 560 (E.D. Wis. 1982)
		Lung, 535 F. Supp. 100 (E.D.N.Y. 1982)
		MacEwen, 525 F. Supp. 1063 (M.D. Ala. 1981)
		Marneef, 533 F. Supp. 129 (E.D. Mich. 1981)
		May, 572 F. Supp. 725 (W.D. Mo. 1983)
		Montoya, 533 F. Supp. 586 (D. Colo. 1981)
		Parham, 503 F. Supp. 70 (E.D. Tenn. 1980)
		Peterson, 569 F. Supp. 676 (D. Idaho 1983)
		Rankin, 578 F. Supp. 840 (N.D. Ohio 1983)
		Rein, 531 F. Supp. 67 (E.D.N.Y. 1982)
		Sanders, No. 79-1277-S, slip op. (D. Mass. May 10, 1983)
		Saxe, 577 F. Supp. C135 (N.D. Ohio 1983)
		Simonetti, 533 F. Supp 435 (E.D.N.Y. 1982)
		Szczepaniak, No. 80-990-MA, slip op. (D. Mass. March 2, 1983)
		Terrell, 517 F. Supp. 374 (N.D. Tex. 1981)
		Warner, 522 F. Supp. 87 (M.D. Fla. 1981)
		Young, 542 F. Supp. 1306 (S.D.N.Y. 1982)

[a] Amount of damages awarded not reported.
SOURCE: Reference 12.

TABLE 6.3 Analysis of Swine Flu Awards

	Number of Suits				
Amounts Paid Out (dollars)	Judgments	Settlements	Total Suits	Total Claims Settled	Grand Total
1-999	0	1	1	23	24
1,000-9,999	0	36	36	101	137
10,000-49,999	19	99	118	86	204
50,000-99,999	15	86	101	33	134
100,000-149,999	6	39	45	4	49
150,000-299,999	22	35	57	8	65
300,000-499,999	16	17	33	0	33
500,000-999,999	11	5	16	0	16
1,000,000/Over	8	0	8	0	8
Totals	97[a]	362[b]	415	278[c]	670

[a] This figure reflects a discrepancy of three cases; the actual number of swine flu lawsuits resulting in judgment awards to plaintiff is 94: 51 cases wherein the liability was stipulated to by the United states and 43 suits decided on the merits for the plaintiff.
[b] 318 personal injury/wrongful death suits settled with 44 related loss of consortium suits.
[c] 255 personal injury/wrongful death claims settled with 23 related loss of consortium claims.
SOURCE: Torts Branch, Civil Division, U.S. Department of Justice, October 19, 1984.

Also, two of the cases resulted in decisions of precedential importance that have further confounded the law in this area.

Hockett v. United States, 730 F.2d 709 (11th Cir. 1984), affirmed a verdict in favor of the plaintiff of $324,275.61. (The decision below is unreported and unavailable on Lexis™.) The plaintiff received the vaccination in October 1976. She was diagnosed as having GBS six months later, with no evidence of prior onset.

The plaintiff's proof of causation rested upon the testimony of one Dr. Eylar, described as a biochemistry professor. The court of appeals summarized his testimony as follows:

> Dr. Eylar described his work with laboratory animals and experimental allergic neuritis (EAN), a demyelinating disease generally recognized by the scientific community to be an excellent animal model for human GBS. A demyelinating disease attacks myelin, the component of a sheath surrounding the nerve

> that serves a function similar to that of insulation surrounding an electrical wire. Dr. Eylar found that EAN can be produced in animals by injection of a protein designated as P_2, when accompanied by a chemical adjuvant used to heighten the reaction. . . .
> Dr. Eylar tested a sample from the same lot of vaccine given to plaintiff and found that it contained chicken P_2 protein. He also tested plaintiff's blood serum and found that it contained antibodies that reacted with chicken P_2. Dr. Eylar testified that he found P_2 antibodies in the blood sera of approximately 50 percent of 30 people who had been vaccinated and contracted GBS and that no P_2 antibodies had ever been found in the blood sera of "conventional" GBS patients (those who had not received a swine flu vaccination) [730 F.2d 711].

This summary implies that Dr. Eylar did not testify that he himself or anyone else had ever looked for P_2 antibodies in the blood of GBS victims who had not received swine flu vaccine. The government countered the Eylar testimony with the testimony of Dr. Brostoff, who testified that he tested a sample of the same lot of vaccine and that it did not contain any P_2 antibodies [sic, probably did not contain any P_2].

The government also relied upon the CDC statistical study, arguing that because the plaintiff's GBS had begun not 10 weeks but 6 months after the vaccination there was no basis for finding causation. The district court rejected the study on the following grounds:

> [T]he mere fact that the time interval in plaintiff's case was significantly longer is not dispositive. The statistics reveal a skewed bell curve relation between the vaccinations and the onset of GBS; that does not rule out the possibility of a causal relationship between the two. Dr. Daniel Bader pointed out in his deposition that the existence of a bell curve relationship doesn't mean that things that fall outside the middle part of the curve, on either side, are not associated. After ten weeks, the incidence of GBS in the vaccinated population does not fall to zero—it drops to the background incidence rate. . . .
> Dr. Bader's observation that one shouldn't throw away the outside margins of the bell curve just because the majority of things occur in the middle of the bell curve is well taken. We know that the overall risk of GBS in the vaccinated population is approximately four times greater than normal, and that some of those in the vaccinated population do in fact develop GBS more than nine or ten weeks later; we also know that not all of the cases of GBS can even be explained with associations, much less proven causes. If cases such as this were to be decided on the bell curve statistics alone, no plaintiff who contracted GBS more than nine weeks after his vaccination would ever be able to recover [730 F.2d 712] [second emphasis added].

This logic, of course, treats the failure to prove the existence of a relationship as having no bearing on proof of its absence. The district court then placed heavy emphasis on the fact that the government's experts had not tested the plaintiff's blood for P_2 antibodies [730 F.2d 712]. Therefore, they were not in a position to testify that P_2 antibodies were not present in the plaintiff's blood.

The court of appeals affirmed, placing reliance on the fact that the district court had accepted the credibility of Dr. Eylar's testimony. "Had the P2 testimony not been in the case the plaintiff would have proven only a possibility. The P_2 testimony carried plaintiff's burden, and the government's statistics and discredited attack on Dr. Eylar's P_2 testimony did not eliminate that preponderance of the evidence" [730 F.2d 713].

Judge Tjoflat concurred with a separate opinion. His concurrence is revealing about the problems of dealing with issues of scientific fact in the litigation process.

> Counsel for the government did not contemporaneously object to Dr. Eylar's qualifications when he was tendered as an expert; nor did counsel object to his testimony describing the experiments he conducted or the opinion he based on those experiments. See Fed. Rules Evid. 702 and 703. Such objections would not have been frivolous. Dr. Eylar's testimony has not been well received in other district courts. See Carter v. United States, No. G79-369, CA Slip op. (W.D.Mich. Jan. 15, 1984) (court "not persuaded" by Eylar and others); Iglarsh v. united States, No. 79C 2148, Slip op. (N.D.Ill. Dec. 9, 1983) (same); Pancho v. United States, No. C-79-0429, Slip op. (N.D.Cal.1983) (Eylar theory "speculative"); Kirby v. United States, No. 79-1805, Slip op. (D.D.C. July 16, 1982) ("other scientists have not duplicated the testing . . . his latest theories have not been published. . .. Dr. Eylar's testimony . . . has not been accepted by the scientific community"); Anger v. United States, No. 80-F-105, Slip op. (D.Colo. July 31, 1981) (Eylar's theories novel, unsupported, and not sufficiently similar to GBS). As the Middle District of Florida held in Mason v. United States, No. 79-614-Div-Orl-17, Slip op. (M.D.Fla. Jan. 24, 1984):
>
> Were it not for Dr. Eylar's own statements concerning the developing nature of his theories and the obvious unreliability of his testing of the relevant vaccine lot, perhaps his theories would deserve more serious thought and discussion.
>
> Moreover, even accepting all of Dr. Eylar's objective tests and test results as valid, the leap in logic from his findings to his conclusion concerning the causation of GBS in humans remains monumental.

By failing to make timely objection to Dr. Eylar's qualifications and testimony, and the experiments on which his opinions

> were founded, the government's counsel deprived the plaintiff, and the court, from further inquiry which, for all we know, may have cast Eylar in a more credible light. Certainly, justice does not require that we now give the government, having failed in its trial strategy, a second chance to prevail.

In other words, the particular attorney appearing for the government at the Hockett trial failed at the right moment and the right time (in the ex-post view of the court of appeals) to make the point that Dr. Eylar's testimony was very far from the scientific mainstream. The failure of the government attorney conferred upon plaintiff Hockett the benefit of a windfall recovery that no one else in her situation enjoyed.

In Sulesky v. United States, 545 F. Supp. 426 (S.D. W. Va. 1982), the court found that the "onset of the Plaintiff's GBS occurred on approximately February 1, 1977 . . . in the fourteenth week after the administration of her swine flu shot" [Id. at 428]. The court first found that the statistical studies did not disprove that the plaintiff's GBS had been caused by the vaccine because their basic method was to compare the incidence of GBS in the vaccinated population against a background rate, and "the actual background rate for GBS has not yet been established . . ." [Id. at 430], pointing to disagreement about the precise background rate. Then the court found "that the resolution of the causation issue turns on the testimony of the treating and evaluating physicians." Although the physicians had originally diagnosed the plaintiff as suffering from upper-respiratory illness, the treating physician testified at trial that she had GBS. In addition, the court heard "the compelling testimony of Dean Robert Waldman which convinced the Court . . . that this case turns upon the uncontroverted diagnosis which he made based upon his evaluation of all of the medical evidence before him in the individualized case of Kathryn Sulesky."

The court took this approach, although there is nothing in the scientific literature to suggest that there is anything about an individual patient's condition or history that enables anyone to distinguish between GBS caused by a vaccination and GBS caused by something else. A treating doctor can diagnose a condition based upon his examination of the patient at the time of examination. The notion that such a doctor also has the expertise to determine the cause of the condition is one that has been discarded in areas such as proving the efficacy of drugs. In that area of the law, a drug is not approved for use because a doctor is of the opinion that a particular patient that he treated was helped by the drug. Scientific evidence is required.

In Spencer v. United States, 569 F. Supp. 325 (W.D. Mo. 1983), the plaintiff-decedent was vaccinated on November 2, 1976, and first sought medical treatment on February 25, 1977, more than 15 weeks later. That visit to his family physician was inconclusive, and he sought no further medical treatment until his hospitalization in an acute condition the morning of March 31, 1978.

> [I]n comparatively rare instances in which a low-grade, chronic malady develops, and later apparently flares into acute GBS, the courts and the medical profession are divided in their conclusions as to causation. A small number of experts, including Dr. Poser [who testified for numerous plaintiffs in the swine flu cases], have recognized a related phenomenon of 'smoldering' and 'flaring' . . ." [569 F. Supp. 328].

The court then reviewed testimony of family members that the decedent had experienced "early symptoms involving the leg and hands," 569 F. Supp. 329, and concluded:

> Plaintiff's expert, Dr. Poser, is obviously well qualified and familiar with all aspects of both past and current literature on the subject. The government's expert testimony was from less highly qualified witnesses. Dr. Vernon I. Rowe, a local witness, was not unimpressive, but he appeared to testify more from knowledge of orthodox theories and materials published in past decades than from current and thorough familiarity with the applicable field. It may be argued that Dr. Poser is more of an advocate, having been retained in many of the swine flu cases, but the Court found his testimony more persuasive than that of the less-knowledgeable witnesses presented by the government.
> Consideration of the medical issues does not, of course, turn entirely on Dr. Poser's testimony, but a detailed review of the pertinent literature and material presented to the Court would not be worthwhile. This would tax not only the Court's understanding of the details of the medical debate but also its ability to articulate the debated issues in medically correct jargon. . .. The Court does emphasize, however, the usefulness of current expert testimony directed toward the facts of the case [569 F. Supp. 330].

Thus did "knowledge of orthodox theories and materials published" fall to the more speculative theories of Dr. Poser.

Gassman v. United States, No. 79-314-ORL-CIV-06 (M.D. Fla. June 27, 1984) involved a plaintiff who fell ill within 2 weeks after receiving the vaccine. She, however, suffered not from GBS but from what her neurologist diagnosed at the time of her discharge from the hospital as "probable vital encephalitis, probably with secondary transient cerebral ischemic episodes." Again the treating doctors testified that the condition was caused by the vaccination, principally on the ground that they had not been able to figure out what else caused it. The government's expert offered knowledge of the epidemiological literature, but little knowledge of the plaintiff. The court was impressed by the skill of the plaintiff's doctor in treatment, and therefore accepted his testimony on the issue of causation. Even the government's expert, noted the court, conceded that the plaintiff's doctor had done "an excellent job" in treating the plaintiff [Id. n. 10].

Again the court made the point that a failure to prove a statistical association does not prove that the vaccine did not cause the condition. "Although these numbers [of reported cases of neurological syndromes other than GBS] are much lower than the reported cases of Guillain-Barré syndrome (more than 500 [as opposed to 24]), and the overall incidence of encephalitic disorders among those vaccinated may not have risen significantly, clearly one cannot logically exclude the possibility that certain of these reported cases were caused by the swine flu vaccine (just as one cannot logically exclude the possibility that certain reported cases of Guillain-Barré syndrome were not caused by the swine flu vaccine)."

The court then offered a theory of causation derived from the plaintiff's experts.

> It was undisputed that Mrs. Gassman's neurological syndrome included a mild polyradiculitis which produced the generalized aches and pains in her thighs beginning shortly after the vaccination. This finding by Dr. Derbenwick is significant, in the court's view, because polyradiculitis, an inflammation of the nerve roots, is characteristic in cases of Guillain-Barré syndrome. It would seen reasonable to conclude, therefore, in accordance with Dr. Derbenwick's testimony, that Mrs. Gassman most likely experienced an inflammatory response to the swine flu vaccine which, although idiosyncratic in that it occurred mainly in the brain, was pathogenetically related to the sort of inflammatory response, involving predominately the peripheral nervous system, experienced in cases of post-vaccinal Guillain-Barré syndrome.

This passage suggests that the court thought that polyradiculitis was a distinctive feature of post-vaccinal GBS, whereas, in fact, it is a feature of all GBS. There is no demonstrated association between polyradiculitis and the vaccine, only between GBS and the vaccine.

The issue of causation having been resolved in favor of the plaintiff, that left the issue of liability. The court first complained of the "unfairness" of the government's stipulation of liability in the GBS cases. "By rejecting in all other cases the interpretation it has given the swine flu act in Guillain-Barré syndrome cases, the government places an unfair burden, in the court's opinion, upon plaintiffs such as Mrs. Gassman who have proven that the swine flu vaccine caused a related neurological disorder. . .. During a hearing . . . the court inquired as to why the government's Guillain-Barré syndrome policy should not collaterally or equitably estop it from claiming in other cases that, e.g., the informed consent form was adequate" [Id. n. 16]. The court then went on to find liability on the ground that the consent form was inadequate.

The issue of the adequacy of the consent form was crucial in Gassman and the two court of appeals cases yet to be discussed. It was a brief and fairly straightforward document (see Pure Politics and Impure Science by Arthur M. Silverstein6). Under the heading "Possible Vaccine Side Effects," it said (in full): "Most people will

have no side effects from the vaccine. However, tenderness at the site of the shot may occur and last for several days. Some people will also have fever, chills, headache, or muscle aches within the first 48 hours." Then followed a new heading, "Special Precautions." It said, "As with any vaccine or drug, the possibility of severe or potentially fatal reactions exists." If the warning was legally adequate, this was the sentence that made it so.

The court in Gassman found the warning inadequate because it was under the wrong heading and because it did not enumerate the specific complications that constituted the "severe or potentially fatal reactions." A judgment of $90,673.95 was entered.

In Unthank v. United States, 533 F. Supp. 703 (D. Utah 1982), affirmed 732 F.2d 1517 (10th Cir. 1984), the plaintiff was vaccinated on October 18, 1976, and experienced a sudden onset of severe pain in her lower back, followed by tingling and numbness in her legs and torso 4 weeks later. She was hospitalized and diagnosed as suffering from transverse myelitis. The plaintiff's experts (not the treating doctor) testified that the vaccine caused the transverse myelitis, reaching this conclusion "by ruling out other possibilities" [533 F. Supp. 710]. The defendant's expert testified, without conducting an examination of the plaintiff, that her condition was caused by a preexisting multiple sclerosis [see the summary of the expert medical testimony, 533 F. Supp. 709-713]. The court followed the theories of Dr. Poser and found causation. That left the question of liability.

The district court first rejected the argument that the warning was inadequate, relying on its own previous decision, Bean v. United States, 533 F. Supp. 567 (D. Colo. 1980). "[T]he inclusion of potential neurologic disorders resulting from the vaccine adds nothing to the knowledge that the vaccine may lead to 'severe or potentially fatal reactions'" [Id. at 715].

The court then adopted a direct path to liability. It found that the statute required compensation for all conditions caused by the vaccine—a unique construction of the statute. Alternatively, the court based liability upon Secretary Califano's concession of liability in the case of GBS. "The fact that GBS alone was singled out by Secretary Califano does not justify differing treatment for other 'closely related' disorders proven to have been caused by the swine flu vaccine" [533 F. Supp. 722]. The legal principles invoked were not clear. The district court then discussed at length the need for a national compensation program, citing all the authorities who have urged one since 1976. "The field of national immunology cries out for a more expeditious and fairer way of determining legitimate claims and compensating victims of the vaccination" [533 F. Supp. 726-727].

The court of appeals affirmed [732 F.2d 1517 (10th Cir. 1984)]. "We believe the trial court's ultimate conclusion that the federal government was liable must be sustained, not only on the ground which the trial court purported [sic] to give but on at least two additional theories . . ." [732 F.2d at 1519]. The court then threw a few new ideas into the liability debate. First, the Califano concession required liability because it really included transverse myelitis,

because Guillain-Barré syndrome "is a broad, encompassing term which would include the transverse myelitis" [732 F.2d at 1520]. The court went on to reinterpret the trial court conclusion that the warning was adequate:

> [E]ven though the trial court expressly purported to reject a theory of inadequacy of the informed consent in this and a previous case not appealed, we think its findings belie that conclusion. Thus we conclude that the trial court's findings, as a matter of law, support the theory of inadequate informed consent.

The court then set out its own notion of what informed consent requires. "We believe that encompassed in the duty to inform a patient of all material information, substantial and significant risks, is the duty to inform not only of risks that might occur from the particular treatment in question, but also any alternative treatments and the risk of no treatment at all."

The court emphasized the importance of the setting of the swine flu program.

> A barrage of publicity aimed at overcoming the reluctance of citizens to participate included the unprecedented appearance of the President of the United States on national television to plead for a positive response. Against that background, it would be a travesty to suggest that people who hurriedly signed the standardized form presented to them were adequately informed of the risks [732 F.2d at 1521].

Based on this combination of factors, the court concluded that the government was liable under the standard of section 402 of the Restatement .[3]

Petty v. United States resulted in three reported decisions at 536 F. Supp. 860 (N.D. Iowa 1980), 679 F.2d 719 (8th Cir. 1982), and 740 F.2d 1428 (8th Cir. 1984), and one unreported decision, N.D. Iowa, No. C 78-4083, March 31, 1983. The plaintiff experienced severe symptoms resulting in hospitalization 8 days after his vaccination. The treating doctor diagnosed this condition as "serum sickness-like reaction to a foreign protein." The treating doctor testified that this condition was caused by the vaccination. The government presented no live medical expert, relying on depositions and exhibits.

> At trial, Dr. Hyden [the treating doctor] testified that in his medical opinion the swine flu shot caused plaintiff's severe serum sickness, which in turn caused plaintiff's congestive heart failure. Dr. Hyden testified that the vaccine was a foreign protein which caused an immune complex to form, setting up an antibody-antigen reaction, which created an inflammatory condition throughout the body. Dr. Hyden testified that there was no evidence that plaintiff received any other foreign protein besides the swine flu vaccine.

> . . . The Court is of the opinion that because Dr. Hyden was plaintiff's personal physician and examined plaintiff throughout the relevant times involved in this matter, that his testimony is the more convincing in this matter" [536 F. Supp. 871].

The government had not stipulated to liability for "a serum-like sickness," so the problem of liability remained. The court found liability on the ground that the information form failed to meet the standards of the swine flu statute, although there was nothing in the statute to suggest that a failure to meet its requirements would result in liability of the government. Of the form, the court said:

> [B]ecause of the "hard sell" campaign, the Government has a responsibility to protect and help those citizens who volunteer for the vaccination and subsequently become ill as a result thereof. The Government should not hide behind the four corners of a complicated registration form (now argued to be a consent form) and thereby deny and avoid liability [536 F. Supp. 870].

The court of appeals reversed. The district court erred, it said, because the district court found that the liability arose under the swine flu act itself. Rather, said the court of appeals, liability was to be controlled by state law. Judge Bright, writing for the court, reversed and remanded the case to the district court for findings under the standards of Iowa's informed consent law [679 F.2d 727-729].

On remand, the district court found that the information form failed to meet the standards of Iowa law. The court of appeals affirmed. It affirmed because the Iowa statute requires disclosure of the known risks "of death, brain damage, quadriplegia, paraplegia, the loss or loss of function of any organ or limb, or disfiguring scars associated with such procedure or procedures, with the probability of each such risk if reasonably determinable." The swine flu information form had said only "the possibility of severe or potentially fatal reactions exists," failing to enumerate in detail the potential reactions and the risks of each. Because the form had failed to warn Petty of the risk of "serum sickness," the manufacturer would have been liable under Iowa law. The court placed particular emphasis on the government's "unprecedented promotional campaign," and on the Califano statement explaining the stipulation to liability for GBS. The court concluded:

> [T]here is a public policy consideration favoring allocating the risk of loss among the distributors who can then absorb the cost or distribute it more easily. See Reyes v. Wyeth Laboratories, 498 F.2d 1264 n. 57 (recognizing view that burden should be borne by the government because of the societal benefit bestowed by individuals receiving the vaccine).

The court went on to make it clear that its holding was not limited to

the government under the special conditions of the swine flu statute and vaccination program. It was a holding that the manufacturer would have been liable under Iowa law if it had not been for the swine flu act. "Under Iowa law, Merrill-National would have been held strictly liable for its distribution of a defective product which proximately caused Petty's injuries" [740 F.2d 1441].

Judge Bright dissented. His dissent in full [740 F.2d 1441-1442] was as follows:

> I dissent. I believe that the warning Petty received before being vaccinated was adequate. Therefore the United States is not liable under either the negligence or the strict liability theory propounded by the majority.
>
> Even assuming that serum sickness was a foreseeable risk attending swine flu vaccination, I think vaccinees received adequate warning. The information form Petty read stated that, '[A] s with any vaccine or drug, the possibility of severe or potentially fatal reactions exists.' I do not think that a more specific warning, either describing the symptoms of serum sickness or mentioning that condition by name, would have served any useful purpose in the context of this mass inoculation program. Vaccinees were warned that a small risk of severe or fatal reaction accompanied receiving the vaccine. The majority does not dispute the minimal nature of the risk, but maintains that the warning should have itemized the potential adverse reactions from the vaccine. Yet, the warning of the "possibility of severe or potentially fatal reactions" more directly, completely, and graphically describes for the lay person the hazards of receiving the vaccine than a specific itemization of adverse effects. I agree with the government and with most of the courts that have considered the issue, see supra N.6., that a detailed catalogue of every serious complication that might befall a vaccinee would have been counter productive, serving to confuse or needlessly alarm potential vaccinees without giving them any more information necessary to the making of an informed decision. I therefore reject the majority's conclusion that the failure to specify the potential adverse effects of the vaccine makes the warning inadequate when, as here, the warning aptly apprised vaccinees of the overall possibility of harm.
>
> Because the warning was adequate, the government was not negligent. Nor is the government strictly liable under the theory that the unavoidably unsafe vaccine was rendered defective or unreasonably dangerous by the failure to give a more detailed warning.
>
> I think the practical consequence of the court's decision is to impose so stringent a warning requirement as likely to render any future mass inoculation program infeasible, no matter how desirable.
>
> Accordingly, I dissent.

The mixture of liability theories put forward in Petty is comprehensive. Most significantly, the court emphasizes the primary importance of the state informed consent law (as did the district court in Gassman). The informed consent statutes have been passed in many states to provide a clear procedure by which a doctor, in the context of a direct doctor-patient relationship, can obtain consent to a medical procedure that may constitute battery. They set standards for genuine consent, requiring full disclosure. The statutes deal neither with malpractice nor product liability, nor with mass health care procedures such as a public vaccination program in which the vaccinee is not a "patient," in the usual sense, of anyone. The implication in the Petty case is that those statutes now set the standard for vaccination and that failure to meet the standard results in liability for any resulting damages, apparently liability imposed on all participants in the vaccination process. This, combined with the favorable citation of a portion of the Reyes opinion, makes Petty a notable development in the area.

What conclusions can be drawn from the swine flu litigation about the risks of a manufacturer's liability? That question depends upon the extent to which litigation occurred under circumstances similar to those that would be faced by a vaccine manufacturer. There are a number of features of the swine flu litigation that are different.

First, the government approach to the problem of defending tort claims is different from that of private parties. Defendants in tort suits with large claims make use of substantially more lawyers and legal resources than does the government. The government, in accordance with its usual tort claims procedures, assigned defense of these numerous tort claims to a small law office, assisted on an intermittent and erratic basis by generalist lawyers with many other duties from the offices of the various U.S. attorneys. This shows up in many aspects of the government defense, particularly its heavy reliance on documentary submittals and expert witnesses who had not examined the particular plaintiff. Indeed, the most straightforward explanation for the government's stipulation to liability in the "GBS within 10 weeks" cases may be that the stipulation was necessary to make the cases manageable—the stipulation left for litigation only those cases in which the government had a straightforward defense that could be submitted largely on paper.

The second important distinguishing feature is that plaintiffs under the tort claims act (incorporated by reference into the swine flu statute) do not have a right to trial by jury. All swine flu cases were tried in bench trials, in which the judges alone heard the evidence and made the findings of fact. It is widely believed that juries increase the unpredictability of outcomes, and tend to be more sympathetic to plaintiffs.

A third important distinguishing feature is that all claims under the tort claims act must be brought in the federal district courts. Many cases against a vaccine manufacturer would be brought in state courts. The differences among state courts would introduce another source of variance in such litigation. The federal district judges have lifetime tenure and historically have received premium salaries.

Although there are distinguished state judiciaries, in a "worst case" scenario a vaccine manufacturer from a distant state would face trial in a state court located in the hometown of the plaintiff, and controlled by a judge subject to frequent elections before that hometown electorate. The plaintiff's case is likely to be supported by "expert" testimony from the treating doctor, perhaps well known and respected in the community.

Fourth, the swine flu program was accompanied by much more intense publicity and news coverage than regular, ongoing vaccination programs. That news coverage may have made many more people aware of the possible connection between the vaccine and GBS, it may have made more recipients consider filing claims, and it may have made doctors more sensitive to the possibility of a GBS diagnosis in persons who received a vaccination.[13]

Fifth, there is a difference between the swine flu claims and the claims that would confront a manufacturer of pediatric vaccines in an analogous situation. The swine flu vaccination program was focused on adults and particularly on older persons more likely to incur serious complications from the disease. This affected the litigation in two ways. First, older people have shorter life expectancies and any element of damages calculated over life expectancy is reduced. Second, in many states, a statute of limitations does not run against a minor. Thus, a 1-year-old who suffers injuries as the result of a vaccination may have more than 20 years before any claim is cut off by the passage of time. This makes it more difficult for the manufacturer in the pediatric case to estimate the amount of potential outstanding claims.

Sixth, it is hard to overlook the fact that the defendant in the swine flu litigation was the ultimate "deep pocket"—the government of the United States. The judges in the swine flu litigation were not confronted by a vaccine producer whose solvency and future ability to provide vaccines would be critically affected by the outcome of the litigation. The defendant, instead, was the United States, which would hardly notice the difference. This fact affected not only the reactions of the judges, but the decision to stipulate to liability, the resources dedicated by the Department of Justice to the defense of the cases, and the style of argument that could be made to the courts.[14] Indeed, in retrospect it may become clear that the major mistake of the swine flu statute was to place the defense in the hands of a bureaucracy without any long-term stake in the controlling rules.

What can be concluded from the swine flu litigation?

First, the professionals close to the plight of a particular victim find it hard not to support the merits of the claim. The treating doctor, perhaps not unhappy to direct a potential malpractice claim elsewhere, provides supportive testimony. Trial judges, confronted by the hardship the plaintiff has experienced, are tempted to adopt new interpretations of the law.

Second, doctors and lawyers prefer to treat the issues as the other profession's problem. The lawyers and judges involved with a particular case focus their discussion on issues of medical fact, and ostensibly base their decisions on which medical expert's testimony is

more believable. Many doctors, on the other hand, think the law should provide a solution to the problem: some are unwilling to testify, and others fail to differentiate in their testimony between established effects and ideas outside the scientific mainstream.

Third, the reaction of the courts who found liability to Secretary Califano's stipulation vividly illustrates the problem facing the manufacturers. One might argue that the manufacturers have a simple solution to the liability burden and the costs of litigation. Instead of strongly resisting liability, as they have, they could simply concede liability and settle, recovering the costs of their settlements in higher vaccine prices and avoiding all the costs of extended and unproductive disputes over issues of esoteric medical fact. That is what Secretary Califano basically did when he supported the government's stipulation of liability for GBS, but a concession of liability builds upon itself. The pressure to treat like claims alike generates an ever-expanding pool of liability if the original concession of liability is based upon no identifiable theory or principle.

Finally, the Unthank and petty opinions seriously erode any confidence that in the future a defendant faced with substantial claims could duplicate the government's basic success. In spite of the fact that the government won almost all of the cases it contested, Unthank and Petty are court of appeals' opinions strongly favoring liability. If they had been handed down early in the litigation, they might have been viewed as setting a precedent in favor of recovery for the plaintiff.

Recently, a few other cases relating to liability for the manufacture of vaccines have been reported. One is a flu vaccine case, involving an administration during the same fateful fall of 1976, but of a monovalent vaccine (Victoria A strain only) administered in a doctor's office and thus not falling within the swine flu statute [Stanback v. Parke-Davis & Co., 657 F.2d 642 (4th Cir. 1981]. The plaintiff had contracted GBS, and the defendant had not warned of the risk of GBS. The doctor testified that it was his practice not to warn patients of the type of risk, and that, although he was aware of a possible risk of GBS in the fall of 1976, he did not warn the patient and would not have warned the patient even if the package insert had been different. The district court granted a summary judgment to the defendant for failure of the plaintiff to prove a causal connection between the manufacturer's failure to warn and the plaintiff's injury. The court of appeals affirmed.

There also have been additional polio cases. The most notable is Schindler v. Lederle Labs., 725 F.2d 1036 (6th Cir. 1983), which affirmed a judgment in favor of the manufacturer on the grounds that its package insert provided adequate warning of the risk of contracting polio. The doctor had administered the vaccine under conditions that are contraindicated. Dunn v. Lederle Laboratories, 121 Mich. App. 73 (1982), also affirmed a verdict for the defendant. In Loge v. United States, 662 F.2d 1268 (8th Cir. 1981), the district court had dismissed the complaint against the United States. The court of appeals reversed on the grounds that the plaintiff's allegations that the United States had approved the vaccine in violation of its own

regulations were sufficient to state a cause of action. In Fraley v. American Cyanamid Co., 570 F. Supp. 497 (D. Colo. 1983), the court held that the defendant was collaterally estopped from contesting the adequacy of a warning accompanying a dose administered in 1971 and identical to the warning in Givens.

There are two reported decisions relating to DTP. Walton v. Charles Pfizer & Co., Inc., 590 P.2d 1190 (Okla. 1979), affirmed a verdict (of $2,000, a statutory limit) against the City of Tulsa for the 1966 administration of pediatric vaccines (probably DTP, but not clear). Morris v. Parke-Davis & Co., 573 F. Supp. 1324 (C.D. Cal. 1983), an ongoing case, involves a claim based on a DTP vaccination given in 1965. The plaintiff seeks actual and punitive damages. All manufacturers who produced DTP at the time are joined as defendants because the source of the DTP is not known. A motion to strike the claim for punitive damages was denied by the court.

Caron v. United States, 548 F.2d 366 (lst Cir. 1976), affirmed a judgment of $705,606 for immunization of a 4-month-old baby with DTP, oral polio vaccine, and typhoid vaccine leading to convulsions, grand real seizures, and permanent mental retardation. The typhoid given was an adult dose. The claim was brought 10 years after the vaccination on the theory that the typhoid vaccine was administered negligently, both because the dosage was improper and because in the absence of a special risk of typhoid, it should not be given to a baby.

Lemar v. United States, 580 F. Supp. 37 (W.D. Tenn. 1984), dismissed a suit against the government for encouraging pediatric vaccination without warning of possible adverse consequences.

Calabrese v. Trenton State College, 162 N.J. Super. 145 (1978), held the manufacturer, distributor, and seller not liable for damages allegedly caused by rabies vaccine, but denied the physician's motion for summary judgment because a fact issue existed as to whether he had disclosed possible adverse side effects. Hitchcock v. United States, 479 F. Supp. 65 (D.D.C. 1979), awarded $519,051 against the united States to the wife of a foreign service officer who was given anti-rabies vaccine as "pre-exposure prophylaxis" by government doctors prior to a foreign posting. The liability was based on the failure of the government to warn of the benefits and risks of the vaccine.

Recent Trends

As the committee completed its work, it became aware of two recent, substantial verdicts against Lederle Laboratories. It will be impossible to assess the long-term importance of these verdicts until the appeal process has been completed, because they may not, in fact, reflect the current state of the law (although the ability of plaintiffs to obtain substantial verdicts in trial courts itself reflects the present unstable state of the decisional law). In both cases, the plaintiffs advanced theories that went beyond the adequacy of the warning; they asked the juries to rule on issues of social

benefit and harm and on the underlying scientific factors that contribute to the basic public policy decision to use a particular vaccine. Juries making such decisions in the liability context easily could become the de facto regulators of immunization practices in the United States: verdicts unfavorable to the manufacturers could effectively stop production of a vaccine even if a majority of juries decided against liability.

In Toner v. Lederle Laboratories, No. CV 80-1245 (D. Idaho), a jury returned a verdict of $1,131,200 in April 1984, based on the theories that the defendant's DTP preparation caused the plaintiff child's transverse myelitis and that the defendant could have marketed a safer pertussis vaccine. The plaintiff pointed to the pertussis vaccine marketed until 1975 by Eli Lilly and Company. Eli Lilly sold its rights in the vaccine to Wyeth Laboratories after questions were raised about its efficacy by a review panel of the FDA, and Wyeth never obtained a license to manufacture and market it. An appeal to the U.S. Court of Appeals for the Ninth Circuit is pending [No. 84-3906].

In Johnson v. American Cyanamid Co., No. 81 C 2470 (18th Jud. Dist., Sedgwick Co. Kansas), the jury on June 1, 1984 returned a verdict of $2 million for compensatory and $8 million for punitive damages for a parent-contact of a child who received Sabin (attenuated live virus) polio vaccine. The plaintiff argued that marketing the vaccine was negligent because the Salk (inactivated virus) vaccine is safer, and the parent was not informed that this alternative was available and equally efficacious. An appeal to the Kansas Supreme Court is pending.

The Issue of Punitive Damages

If the Johnson punitive damage verdict is affirmed on appeal, it could significantly affect future vaccine litigation. Prior to the Johnson verdict, punitive damages were not a prominent factor in vaccine cases. Most plaintiffs' complaints did not even ask for punitive damages (information supplied to the committee by one manufacturer indicated that only 15 percent of suits involved claims for punitive as well as compensatory damages). If the verdict is affirmed, claims for punitive damages may become more prevalent.

Affirmation of the punitive damage verdict in Johnson could be interpreted as a determination by a powerful regulatory body (the common law court and lay jury) that Sabin vaccine should not be administered in the United States unless preceded by an administration of Salk vaccine to unimmunized contacts, and perhaps to the child as well. However, society generally has deemed it desirable to delegate decisions on such health policy issues to specialist groups, such as those advising the FDA and CDC—an approach viewed as appropriate by the committee.

Punitive damage awards would greatly increase the magnitude of financial risk for manufacturers because such damages can be almost unlimited in amount and can be duplicative. (Each jury, in each case,

could assess an amount measured by the nature of the defendant's total conduct.)

Punitive damages generally are awarded to punish defendants for conduct that could be characterized as outrageous or as showing a reckless disregard for the safety of others. In Johnson, the argument was based on the wording of the package insert. In addition to disclosing the risk of contact polio, should the insert also have described the option of administering Salk vaccine first? The Immunization Practices Advisory Committee did not (and still does not) recommend this procedure. The Kansas court's judgment that Lederle's failure to suggest preimmunization with the Salk vaccine in its package insert meets the criteria for punitive damages is currently being appealed. In a previous case, however, the Kansas Supreme Court affirmed a punitive damage award by a jury that determined retrospectively that a package insert was insufficient [Wooderson Ortho Pharmaceutical Corp., 235 Kan. 387, 681 P.2d 1038 (1984)*].

The Johnson verdict again shows that the manner in which courts rule on questions involving a manufacturer's responsibility is highly unpredictable.

Summary of the Legal Situation

Under well-established legal principles, a vaccine manufacturer is not liable for injuries caused by a properly manufactured and labeled vaccine. In recent years, however, a few courts have acted contrary to these principles and found manufacturers liable for such injuries, possibly because the injured individual had been urged (or required) by the government to participate in the immunization program and appeared to have no other recourse for compensation.

In general, these vaccine injury claims have been decided on the basis of the doctrine of the duty to warn. This doctrine provides that, prior to the use of an unavoidably unsafe product, the user must be warned of the risks associated with it. In the case of medicines administered by health professionals, the courts generally have placed this responsibility on the health care provider. For vaccines, however, some courts have ruled that the duty to warn resides with the manufacturer, even though the manufacturer is not involved in administration. It is unclear whether the courts that have ruled in this fashion would permit the manufacturer to avoid such responsibility by obtaining a formal agreement from the purchaser stating that a warning would be given prior to administration.

In two very recent cases (presently on appeal), the plaintiffs prevailed by advancing theories of liability that went beyond the

* There are numerous differences between the two cases. One that is important for the punitive damage issue is that the package insert for the Sabin polio vaccine did warn of the risk of contact polio, while the insert in Wooderson did not warn of the possibility of the condition that actually beset the plaintiff.

adequacy of the warning and asked juries to rule on the issues of social benefit and harm, and the underlying scientific factors that contribute to decisions to use a particular vaccine. In one of these cases, punitive damages were awarded; however, punitive damages previously have not been a significant factor in vaccine-related injury litigation.

This review demonstrates that the limits of a manufacturer's responsibilities (beyond safe manufacturing and adequate package labeling) are unclear. Some decisions appear to suggest that the manufacturer can be held strictly liable in all cases.

At the time this report was compiled, the committee was not aware of any cases holding health care providers liable for vaccine injury, except for situations involving failure to follow accepted medical procedures. It does not presently recommend any change in the rules applicable to health professionals because liability for improper administration is appropriate;* it recognizes, however, that if any proposal limiting recovery against manufacturers were adopted without provision for reasonable compensation, lawsuits might simply be redirected from the manufacturer to the administering professional. This could have deleterious effects on the willingness of health care providers to participate in immunization programs. Such a situation would require careful monitoring. Tracking shifts in litigation and recommending remedial action would be one of the functions of the proposed vaccine commission (see Chapter 7).

CONSEQUENCES OF THE STATE OF VACCINE INJURY LIABILITY LAW FOR VACCINE PRODUCTION AND INNOVATION

Despite clear legal rules, the manner in which claims against manufacturers alleging liability for suspected vaccine-related injuries have been handled by the courts does not provide reliable guidelines for predicting the limits and magnitude of their liability. This combines with other organizational and scientific factors to create a situation in which vaccine supply may be threatened.[15,16] Causation is difficult, if not impossible, to determine with certainty in specific cases, and there is usually no other recourse to compensation for injured individuals. In the committee's judgment, this has led to a situation in which jurors and courts may be inclined to view tort awards as a means of providing compensation, irrespective of misconduct or scientific considerations.

These circumstances require the manufacturer of a vaccine known to have certain adverse effects to engage in a gamble with very large financial stakes. If an increasing number of courts impose liability, the costs will be enormous because claims average several million dollars per case. The only way to eliminate the risk is to stop

* The committee recognized that malpractice claims, in general, represent a major concern of the medical profession, but it did not feel that the malpractice issue was within the scope of its charge.

manufacturing the vaccine. If the manufacturer chooses to continue to market the vaccine, its only options are to attempt to settle claims, a strategy that could produce a general expectation of liability, or to resist claims in litigation, with the risk that unfavorable outcomes could establish liability. The cost of either strategy will be high (even if claims are defended successfully) and will have to be passed on to consumers via price increases.

To determine the exact nature of concerns over potential liability for vaccine-related injury, the committee conducted an informal survey of vaccine manufacturers. The goal was to solicit information (much of which was commercially sensitive) on the number and size of vaccine injury claims and settlements over the past decade, and on the provisions made by manufacturers for dealing with such eventualities (e.g., insurance). The committee received information from most major companies actively involved in vaccine production. The manner in which the information on these issues was available did not always permit comparisons or aggregation for publication, which was a condition agreed upon for providing such data. For these reasons, the information summarized below should not be taken as a totally comprehensive picture of the situation.

At the time of the initial survey (spring 1984), 166 suits were pending against the four responding manufacturers. The total amount paid in settlements in the previous decade for completed cases (settled or finished with the appeal process) had been $2 million, and about another $1.8 million had been spent on legal defense, not in all cases including "in-house" counsel.

The information gathered in a follow-up effort (spring 1985) revealed that about 65 additional suits had been filed in the intervening year (only a few of the previous total had been settled, some for amounts averaging $1 million; some trial verdicts were on appeal). Legal costs for the 1-year period ranged up to "several million dollars" for some manufacturers. Time series information supplied by two manufacturers indicated a sharp increase in the number of claims filed; their experiences varied considerably, but the total number of reported claims filed against them in 1983 was more than twice that filed in 1980.

Over the past two decades, pharmaceutical companies have been withdrawing from vaccine manufacturing and marketing. Increasingly, the liability situation and its consequences (i.e., litigation costs or difficulty in obtaining insurance coverage) have been cited as major factors in the decision to withdraw.[17,18,19] These decisions seem to indicate that present or anticipated vaccine-related injury liability expenses are seen as an unreasonable burden (or an unacceptably risky gamble) in relation to the costs of product development and the income from sales. Such decisions threaten the nation's supply of vaccine because vaccine production in the united States is overwhelmingly dependent on commercial manufacturers.

From the data and comments submitted by manufacturers and from testimony before congressional committees,[20,21] the committee concluded that the precise nature of the problem arising from vaccine injury liability cannot necessarily be measured solely in terms of

data reflecting past experiences. Litigation over medical injuries in general has increased substantially during the past 10 years. The rate of malpractice claims against physicians during the 5 years between 1978 and 1983 was more than twice that of the preceding 5 years.[22] The swine flu episode and publicity about pertussis vaccine risks have drawn attention to the fact that vaccines may cause injury. Also, in many states, the statute of limitations for alleged injury in childhood does not operate while the individual is a minor, thus vaccine manufacturers may be at risk of claims for many years.

Manufacturers are apprehensive that without some means of compensation for unavoidable vaccine injury and temporally related conditions, the present unclear state of the law will continue to allow them to be held liable for such conditions and penalized financially.

The future behavior of the courts and the responses of the manufacturers cannot be predicted with certainty, but the committee is concerned that the apprehensions themselves might have a negative effect. Earlier withdrawals from the market have created a situation in which the United States is reliant on one manufacturer for polio vaccine and most of its DTP vaccine (Lederle), and on another for measles, mumps, and rubella vaccines (Merck Sharp & Dohme). If apprehensions about the current unclear state of the law caused these manufacturers to withdraw, the vaccine supply and immunization programs could be jeopardized, leading to possible resurgence of these diseases. Also, the apprehensions discussed above are a disincentive to investment in the development of new (or improved) immunizing agents and to competition from new or foreign firms.[23,24]

Proposals to remedy the compensation and liability problems connected with vaccine injury are discussed in Chapter 8.

REFERENCES AND NOTES

1. See, e.g., Prod. Liab. Rep. (CCH) Par. 90,110-195,270 for a listing of state product liability statutes; see, generally, L.R. Frumer and M.I. Freidman, Products Liability (1984).
2. Prod. Liab. Rep. (CCH) Par. 90,000; but see Product Liability Risk Retention Act, P.L. 97-45 (allows groups of companies to form captive insurance companies and exempts such activity from certain state regulations).
3. American Law Institute. 1965. Restatement of Torts 2d. St. Paul, Minn.
4. There are also cases involving animals: Lovington Cattle Feeders Inc. v. Abbott Labs., 97 N.M. 564 (1982); Pearson v. Franklin Labs. Inc., 254 N.W. 2d 133 (S. Dak. 1977); Colorado Serum Co. v. Arp, 504 P.2d 801 (Wyo. 1972); Waller v. Fort Dodge Laboratories, 356 F. Supp. 413 (E.D. Mo. 1972); Alman Bros. Farms & Feed Mill, Inc. v. Diamond Lab., Inc., 437 F.2d 1295 (5th Cir. 1971); and Anderson v. Blackfoot Livestock Commission Co., 375 P.2d 704, 85 Idaho 64 (1962).
5. See Marc A. Franklin and Joseph E. Mais, Jr. "Tort Law and Mass Immunization Programs: Lessons from the Polio and Flu Episodes,"

65 Calif. L. Rev. 754 (1977) (written before Givens); see also Richard A. Epstein, Modern Products Liability Law 107-110 (Westport, Conn.: Richard A. Greenwood Press, 1980)

6. There are two extended accounts of the swine flu episode and the government's reaction to it. The first, Richard Neustadt and Harvey Fineberg, The Swine Flu Affair: Decision-Making on a Slippery Disease (U.S. Department of Health, Education and Welfare, 1978), was written by two Harvard professors for Secretary of Health, Education and Welfare Joseph Califano, the appointee of newly elected President Jimmy Carter. The study is in very much the "how we can learn from the mistakes of the past and do it better" style, and strongly criticizes the officials of the Ford administration for having committed too early and too irrevocably to the manufacture and administration of the vaccine, so that when negative information such as the lack of further confirmations of the disease or problems in its distribution began to develop, it was impossible to reverse course and call off the program. Arthur M. Silverstein, a microbiologist at Johns Hopkins University, who had served as a congressional fellow during the episode, felt the Neustadt-Fineberg study greatly oversimplified the problem and the reasons the government reacted as it did. His study, Pure Politics and Impure Science (Baltimore: Johns Hopkins University Press, 1981) is more thorough. Although Secretary Califano attempted to deal vigorously with the issues created by the swine flu program and its problems, in the end he, too, was unsuccessful in achieving significant gains in the institutional and legal framework within which these questions arise. It remains to be seen whether some future epidemic threat will become a tragic reality because the lesson learned from swine flu will be thought to have been: "Don't act too soon."
7. Esmond S. Smith, M.D., chief of California Children Services, reported in a letter to the committee November 21, 1984 that California's Immunization Adverse Reactions Fund has paid the claims of two children ($1,644.73 and $2,064.59). One claim is pending for an immunization in 1973.
8. The entire Matter was restudied in A.D. Langmuir, D.J. Bregman, L.T. Kurland, N. Nathanson, and M. Victor, "An Epidemiological and Clinical Evaluation of Guillain-Barré Syndrome Reported in Association with the Administration of Swine Influenza Vaccines," 119 Am. J. Epidemiol. 841 (1984). It concluded that the rate was less than previously thought, 1 out of 200,000 (a total of between 211 and 246 cases), and that an incidence rate above the background rate was confined to the first 6 weeks after administration. This study explicitly recognized that these results may have been inflated by the publicity.
9. The document referred to is a press release issued by Secretary Califano's office in connection with the announcement that the government would agree to accept liability for cases of Guillain-Barré syndrome that arose in the first 10 weeks after vaccination. The press release was not in the record of the

case. When, at Secretary Califano's deposition, the plaintiffs attempted to inquire into the reasons for the government's stipulation, counsel for the government successfully objected to the line of questioning.

10. The "just compensation" provided by the stipulation in the swine flu litigation is substantially different from the compensation recommended by this committee because it included all the traditional elements of tort damages.
11. These problems may explain why counsel, as reported in No. 9, desired to prevent deposition testimony by the Secretary on these issues.
12. The information underlying Table 6.2 was assembled by Mary Koelbel, a second-year student at the University of Virginia Law School using Lexis™. There are additional swine flu decisions that are not reported either in print or in the Lexis™ data base. The Torts Section of the Civil Division, Department of Justice (DOJ), has a comprehensive litigation file of all decisions made in the swine flu litigation. Jeffrey Axelrad, director of the Torts Branch, permitted Kitch, a member of the committee, to examine this file on February 6, 1984. To base this report on information that could be easily verified by others, the summaries here are based only on publicly available information. Review of the DOJ files led Professor Kitch to conclude that there were no important differences between the outcomes reflected in the published and unpublished decisions, except that the unpublished decisions tend to be briefer, less notable, and more overwhelmingly in favor of the government. Publicly available decisions relating to procedural matters are not reflected in Table 6.2. Axelrad also prepared Tables 6.1 and 6.3. The committee appreciates the assistance provided by Axelrad.
13. The CDC study attempted to determine the rate of vaccine-induced GBS by comparing rates for the vaccinated and unvaccinated populations. It then attempted to check for the possibility that doctors had been more ready to make a GBS diagnosis of patients who had been vaccinated by comparing objective measures of the severity of the condition in the vaccinated and unvaccinated victims. GBS is not a well-defined disease complex. The study found that these measures were on average the same in the two populations. That check, however, does not rule out the possibility that medical personnel were quicker to consider a possible GBS diagnosis in the vaccinated population after the widespread publicity about the possible connection. Langmuir, Bregman, Kurland, Nathanson, and Victor, "An Epidemiological and Clinical Evaluation of Guillain-Barré Syndrome Reported in Association with the Administration of Swine Influenza Vaccines," 119 Am. J. Epidemiol. 841, 865-866 (1984), explicitly recognizes this problem. "However, it is only reasonable to believe that the history of a swine influenza vaccination in the individual patient may well have influenced his physician to more seriously consider both the diagnosis of Guillain-Barré syndrome and the

reporting of the case if so diagnosed. In addition, patients who had received swine influenza vaccine may well have sought medical care more promptly" [Id. at 865-866].

14. Indeed, it is telling that when the General Accounting Office studied the processing of swine flu claims at the request of Rep. John A. Durkin, no attention was paid to the question of whether the claims being paid were valid claims under the statute, but only to why the Department of Justice was taking so long before it authorized payment [U.S. GAO letter B-199297 (January 14, 1981)] .
15. National Immunization Work Groups. 1977. Reports and Recommendations of the National Immunization Work Groups. McLean, Virginia: JRB Associates.
16. U.S. Congress, Office of Technology Assessment. 1980. Compensation for Vaccine Related Injury. Washington, D.C.: U.S. Government Printing Office.
17. Pettinga, C.W. 1983. Vaccine Innovation in the Private Sector. Paper prepared for an Institute of Medicine Conference on Barriers to Vaccine Innovation, November 28-29, 1983, Washington, D.C.
18. Mason, J.O. 1984. Testimony on H.R. 5810 before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, December 19, 1984, Washington, D.C.
19. Shaw, D. 1984. Testimony for Wyeth Laboratories on H.R. 5810 before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, December 19, 1984, Washington, D.C.
20. Johnson, R.B. 1984. Testimony for Lederle Laboratories on H.R. 5810 before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, December 19, 1984, Washington, D.C.
21. Sarett, L.H. 1982. Testimony for Merck & Company before the Subcommittee on Investigations and General Oversight, Committee on Labor and Human Resources, U.S. Senate, July 22, 1982.
22. American Medical Association. 1983. Physicians' Professional Liability Experience, Socioeconomic Monitoring Systems Detailed Tabulations. Chicago, Ill.: American Medical Association.
23. Beale, A.J. 1985. Modern approaches to the development of vaccines: perspective of a traditional manufacturer. Pp. 377-381 in Vaccines 85. Molecular and Chemical Basis of Resistance to Parasitic, Bacterial, and Viral Diseases, R.A. Lerner, R.M. Chanock, and F. Brown, eds. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory.
24. Medicine in the Public Interest. 1984. Impediments to Vaccine Research. Boston, Mass.: Medicine in the Public Interest, Inc.

7

An Approach to the Problems of Communication, Coordination, and Collaboration in Vaccine Policy

Vaccine development and immunization efforts are dependent on an intricate public-private partnership in which many different "players" have traditional roles and responsibilities (Chapter 2). These players include government funding agencies and researchers, university personnel, pharmaceutical firms, health professionals, and the public. Each responds to a wide variety of factors affecting the nature and extent of its involvement, and decisions are made on many different levels.

The system is highly interactive, but it lacks any formal means to coordinate the establishment and attainment of public health goals. Few parts of the system communicate regularly and discussions involving a majority of the participants are very rare. Because no structure exists to promote such collaboration, participants may have an incomplete understanding of how their actions fit into the overall effort. The committee identified numerous problems that result from this situation and believes there is an urgent need for an organization to develop and promote an effective and socially responsible national vaccine policy.

HISTORICAL BACKGROUND

The history of previous ad hoc groups convened to address problems related to vaccine availability and use has been discouraging and emphasizes the need for a continuing national body to monitor developments in these areas.

In November 1976, the Office of the Assistant Secretary for Health convened a National Immunization Conference, which was followed by workshops on specific policy issues. It was expected that the output of the conference and the work groups' recommendations would be used by the Office of the Assistant Secretary to develop an integrated national immunization policy for "departmental guidance and transmittal to Congress."[1] The principal recommendation arising from the endeavor was to establish a National Immunization Commission, but the report also contained comprehensive analyses of and recommendations on virtually all areas of vaccine development and use. The recommendations from this exercise were not implemented, probably because of

personnel changes in key positions within the then Department of Health, Education and Welfare.

Three years later, the congressional Office of Technology Assessment (OTA) produced a study of federal vaccine and immunization policies relating to (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. Policy options were identified in each of these areas.[2] For the major issues discussed in the current report—ensuring sufficient levels of vaccine research, development, and production—the options were:

1. Establish a permanent interagency body within the Department of Health, Education and Welfare 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.
2. Establish either a small-or a large-scale federal vaccine production program.
3. Subsidize vaccine production by private industry.

In regard to the first option, the OTA report noted:

> 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.[2]

No action was taken on the second or third options, but an Interagency Group to Monitor Vaccine Development, Production, and Usage was formed in 1980 within the Public Health Service.[3] The organization, composition, and purview of this body, are considerably more restricted than those outlined in the OTA study. All of the interagency group recommendations must be reviewed and approved by the Assistant Secretary of Health and/or the Secretary of the Department of Health and Human Services. Because participation is limited to the executive agencies of the federal government (and does not include industry, private health practitioners, or the public), the interagency group may not have the scope necessary to deal with some of the major issues affecting vaccine supply and use (e.g., liability).

Two other actions resulted from the OTA study. First, reimbursement for pneumococcal vaccine was authorized under Medicare.[4] (This remains the only preventive vaccine for general use that is reimbursed by federal medical systems [tetanus toxoid is reimbursed for use in wound management] .) Second, early in 1980, the Interstate and Foreign Commerce Committee of the House of Representatives asked OTA to delineate the specific elements and principles necessary for inclusion in a legislative proposal to implement a compensation system for vaccine-related injury. The OTA technical memorandum Compensation for Vaccine-Related Injuries was completed in November 1980.[5] To date, no action has been taken to resolve problems in this area.

In general, the specific actions envisaged by previous ad hoc groups have not been implemented, for reasons unrelated to their potential utility. When these groups dissolved, attention focused on their activities waned. Unfortunately, the problems with which they dealt remained and, in some areas, worsened.

THE EXISTING STRUCTURE

The effort to make vaccine innovation activities more responsive to public health needs depends on an understanding of problems inherent in the existing structure.

Federal Agency Interactions

The traditional roles and responsibilities of the National Institute of Allergy and Infectious Diseases (NIAID), the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), and the Department of the Army are described in Chapter 2. Despite the existence of the Interagency Group to Monitor Vaccine Development, Production, and Usage, these agencies still act largely independently, without the benefit of an overall policy framework or set of objectives.

One consequence of this lack of coordination is that infectious disease problems are often approached in a compartmentalized or sequential fashion. For example, problems with potential under-utilization of a vaccine (arising from public or provider misperceptions) often are ignored until laboratory studies have been completed. Addressing these problems earlier could save valuable time and improve the public health returns on vaccine investments.

Lack of an overall immunization and vaccine development policy does not appear to have greatly affected vaccine regulation. Concern has been expressed, however, that no specific mechanism or forum exists for the systematic review or revision of FDA regulations on vaccines.[6]

Molecular biology and immunology offer many powerful new research tools and production techniques for biologics. The committee found that no mechanisms exist for the systematic dissemination of knowledge about these advances and their applicability to vaccine development.

Also, no procedures are available to encourage their use in cases in which commercial incentives might be inadequate, e.g., for vaccines of interest to developing countries.

Public-Private Sector Interactions

In the background papers prepared for this committee, and at the conference sponsored by the committee in November 1983, a variety of concerns were raised about interactions between federal agencies and the vaccine industry. Some of these concerns related to reluctance on the part of industry scientists to discuss current activities, Presumably for fear of losing a commercial competitive advantage.[7] This fear may be grounded partly on a belief that it is difficult for the federal government to ensure confidentiality in its dealings with industry. Industry also may refrain from interactions with federal agencies in the research and development phases because of the complexity of federal contracting and reporting procedures. These factors may have played a role in the lack of a commercial response to a NIAID request for proposals to develop an improved pertussis vaccine.[7]

Concerns about the effectiveness of public-private sector communications also were raised during recent congressional hearings on the events preceding and following recommendations made by the Interagency Group to Monitor Vaccine Development, Supply, and Usage in response to the anticipated DTP vaccine shortage.[8,9]

Provider and Recipient Perceptions

Chapter 3 describes the tendency in the current health care system to emphasize the use of diagnostic and therapeutic technologies rather than preventive technologies, even when the latter have been documented to be highly beneficial and cost effective. This tendency serves as a commercial disincentive for vaccine innovation and production, and also deprives the public of appropriate health protection measures. Health care providers, with the exception of pediatricians, often are not adequately informed about the benefits of prevention generally, and of immunizations in particular. Also, their perceptions of the risks of certain diseases and of the relative risks and benefits of vaccines may be inaccurate. These problems have been recognized by various groups concerned with the public's health. Numerous efforts have been made to promote increased awareness, including the development of guidelines on adult immunization by the American College of Physicians.[10]

These efforts also could lead to more accurate perceptions among the general public of the benefits and risks of immunizations. The committee believes that all potential vaccine recipients (or their parents) should receive (from a health care provider or another appropriate source) accurate information about the risks of vaccine preventable diseases and the benefits and risks of specific

immunizations, including contraindications to vaccination. Accomplishing this task will require concerted and coordinated efforts by public health agencies and those individuals and organizations involved in the dissemination of information to health professionals and the public.

The role of responsible and well-informed media coverage should not be overlooked. In the past, news reports concerning vaccines have focused extensively on risks, perhaps leading to confusion about relative risks and benefits.[11] The media should be encouraged to provide complete, accurate information about all aspects of vaccine development, production, and use in this country.

PROBLEMS WITH THE PRESENT SITUATION

The problems that arise from the absence of a body to coordinate the attainment of public health goals through vaccine development and use generally are those of omission rather than commission. They include delay or inefficiency in achieving a socially beneficial outcome, and failure to identify or tackle problems in a timely fashion for which no existing group has direct responsibility. The government invests heavily in R&D associated with vaccines and in the promotion of their use; a body charged with general oversight of these processes would help ensure that taxpayers' funds are used in the most effective way possible.

Over the past two decades, several situations have arisen that demonstrate the need for such a coordinating body. In all cases, existing agencies or organizations have performed adequately, but the overall results have been less than satisfactory.

The first involves the response to public concern over pertussis vaccine. In the mid-1970s, injuries related to the administration of DTP vaccine became a major public health issue in Japan, Sweden, and the United Kingdom. Vaccination policies or acceptance changed in these countries, resulting in resurgence of pertussis. Concern also emerged in the United States; by the end of the decade, the potential importance of an improved pertussis vaccine was clear.

Such a vaccine has not been developed, however, in part because no existing organization has the responsibility or the power to set priorities for vaccine improvement. One consequence of this arrangement is that the resources necessary to obtain new knowledge for vaccine improvement are often diverted to tackle other problems (e.g., the control of diseases for which no vaccines exist). Commercial efforts to develop an improved pertussis vaccine have been impeded largely by lack of understanding of the organism and the pathogenesis of the disease. A recent study by another Institute of Medicine group—the Committee on Issues and Priorities for New Vaccine Development—concluded that while the health benefits of an improved pertussis vaccine would be small compared with those of new vaccines for certain other diseases, a pertussis improvement project deserves immediate attention for humanitarian and public policy reasons.[12]

The second situation pertains to the coordinated development of

vaccines and immunization policies specifically to protect adults from infectious diseases. Although some medical specialty organizations have taken the lead in establishing immunization recommendations for adults, the development of new vaccines for older individuals still may be impeded by the perception that the utilization of such vaccines would be low.

The history of the pneumococcal vaccine illustrates one aspect of this problem. The development of a vaccine against this common cause of lobar pneumonia was undertaken during the 1970s as a priority of the NIAID. The anticipated principal target population consisted of high-risk adults, particularly the elderly.[13]

At that time, substantial evidence (including reports on the use of influenza vaccines) indicated that adults and the physicians serving them were not attuned to the risk of pneumococcal disease (Chapter 3). Early, coordinated efforts to correct public and physician misperceptions of this matter could have resulted in utilization rates considerably higher than the estimated 10 to 25 percent achieved in the target population once the vaccine's efficacy had been scientifically verified.[12,14] (The committee recognizes that, initially, low utilization of the pneumococcal vaccine also may have been due to the scientific controversy surrounding its efficacy.)

Concerted immunization and/or vaccine development efforts for adolescents and young adults who may have missed school immunization programs and for health care providers have not yet been undertaken but are highly desirable.

The third situation in which the existence of a coordinating body might have allowed more efficient resolution of a serious problem was the development of an improved rabies vaccine to replace one with unacceptably high levels of adverse reactions. Although a vaccine was produced eventually, it appears that inconsistency in support for the project lengthened the development time.[15]

Finally, the lack of informed public debate on the relative risks and benefits of U.S. vaccine development and immunization policies suggests the need for a national forum. Public concerns have a legitimate role to play in policy decisions about the relative risks and benefits of vaccines and immunization strategies. Also, the scientists who make decisions in highly technical areas should have access to information about the goals and concerns of those who support and will eventually benefit from their work. The ongoing debate on the optimal vaccination strategy for combating poliomyelitis (while minimizing risks)[16] is an example of an area in which a mechanism for broad policy comment could be useful.

RECOMMENDATION FOR A VACCINE COMMISSION

At the Institute of Medicine Conference on Barriers to Vaccine Innovation in November 1983, several of the working groups recommended that the committee consider a national advisory body. The committee accepted this recommendation for reasons outlined in the foregoing

sections. Its proposal resembles that presented in the National Immunization Work Groups' report, but includes several new elements to reflect the committee's analysis of present needs.

Rationale for Establishment

A successful immunization program must be based on a consensus among research scientists, developers, producers, program administrators, and recipients that the program is needed, that benefits exceed the risks, and that it is practical and feasible. Currently, no formal mechanism exists to bring the interested parties together or to provide a forum for debate.

Mechanisms for gaining public and professional acceptance of immunization recommendations, especially for adults, also need improvement. One way to accomplish this would be to provide more opportunities for those who administer and receive vaccines to participate in the decision-making process. The commission, as envisioned by the committee, would provide these opportunities.

The Secretary of the Department of Health and Human Services, as the individual responsible for policy and legislative initiatives in the health field, also would benefit from such a commission. No existing advisory body has a membership that allows it to present the viewpoints of all participants in the vaccine enterprise.

The commission would work to conserve the effective components of the present system; thus, society would continue to benefit from the expertise concentrated in the relevant government agencies, the pharmaceutical industry, and the advisory bodies described in Chapter 2. These groups would be encouraged to assist in the development of new approaches to sustaining and stimulating commercial interest in production and innovation, ensuring improvement of vaccines, designing clinical and epidemiological research, restructuring liability and compensation, and increasing public and professional awareness. A commission or similar body also would provide an appropriate forum in which to explore applications of new scientific technologies to vaccine development.

Purpose and Functions

The objectives of the proposed commission would be (1) to advance the control of infectious diseases by promoting the continued innovation, production, and use of vaccines and (2) to ensure that this goal is achieved in a socially responsible and just manner.

The commission would monitor all aspects of immunization efforts in the United States, acting in a consultative and advisory capacity; one of its primary responsibilities would be early identification of problems. It also would help to educate and inform the public, physicians, and government decision makers about appropriate immunization actions and policies. As necessary, the commission would

become an impartial broker to promote production and supply of needed vaccines and to coordinate collaborative activities.

Reporting

The commission would report at least annually to the Congress and the President, and on other occasions if immediate action is required to avert threats to the public health.

Location, Establishment, Membership

The base from which the commission operates could have a significant effect on its ability to fulfill its purpose, which is to identify national needs for vaccine development, production, and utilization and to promote programs to meet the needs. Furthermore, optimal functioning of the commission will require certain attributes that would be achieved more readily under some auspices than others. These attributes include:

- Stature and credibility sufficient to command acceptance of commission recommendations. Important factors in this will include:

  —participation of all relevant parties—government, industry, health professionals, and the public;
  —the capacity to pursue public health goals in a responsible and just manner, independent of political considerations and commercial interests;
  —members with outstanding knowledge and experience, appointed without regard to political views;
  —the capacity to identify solutions to immunization problems independent of the activities and responsibilities of a parent organization.

- The capacity to ensure that necessary programs are instituted. This will probably require:

  —the ability to sustain commission efforts irrespective of fluctuations in the level of political interest in its mission;
  —the ability to make direct representation to the federal legislature on budgetary matters related to its mission;
  —the ability to call upon existing federal agencies in the collaborative pursuit of objectives;
  —the ability to elicit greater industry interest in collaborative efforts than is presently forthcoming, possibly through the use of direct contracts;
  —the ability to receive funds from any source (e.g., private foundations, industry) and direct them to achieving the commission's objectives.

A variety of possible modes of operation for the commission were

identified, some of which have been the subject of previous proposals. It could be established within either the executive or legislative branches, be affiliated with an independent entity such as the National Academy of Sciences, or be created as a federally chartered, nonprofit corporation.

Options identified by the committee, and their advantages and disadvantages are listed below:

- Creation as a presidential commission.
- Although such a location would confer high visibility on the enterprise, presidential commissions are often short-lived and can become overly influenced by partisan concerns. This option therefore fails to confer many of the attributes described above.
- Establishment within the Department of Health and Human Services (DHHS).

  This location would give the commission the most immediate influence on existing agencies in the implementation of its recommendations. However, interactions between federal agencies and the private sector generally have not exhibited the level of coordination and collaboration that would be required for successful operation of the commission, perhaps because of the complexity of federal administrative rules. Additionally, location within DHHS might result in pressure on the commission to modify evolving recommendations in light of other departmental priorities (see the discussion in Chapter 3 of funding requests for a vaccine stockpile).

  The analysis conducted by the National Immunization Work Groups for the Assistant Secretary of the then Department of Health, Education, and Welfare (DHEW) led to the suggestion that a vaccine commission be appointed by the Secretary (National Immunization Work Groups, 1977). To date, however, the executive branch has not acted to establish such a commission. Nor has action been taken to create within DHEW/DHHS the broad-based interagency body envisaged by the Office of Technology Assessment (Office of Technology Assessment, 1979).

  If a broad-based body were established within DHSS with the appropriate safeguards for its independence and with mechanisms to facilitate interaction with the private sector, it could perform many of the functions the committee envisages for the commission. Its independence from political influence might be still subject to question or misperception because of its location within the executive branch.
- Affiliation with the Congressional Office of Technology Assessment (OTA).

  Such a location would confer the benefits of close association with national policy makers. However, the policy recommending and operational activities of the commission would depart significantly from OTA's traditional role, namely, the identification of policy options.

- Affiliation with the National Academy of Sciences, e.g., association with the Institute of Medicine.
  Such a location or association would confer the advantages of good access to expertise in pertinent scientific and health related areas, established structure and procedures resulting in recognized independence of judgment, and an existing federal advisory responsibility/ role on matters of science and health. However, the envisaged policy formulation and promotion, and possible operational activities of the commission are not roles taken up by an advisory organization such as the National Academy of Sciences or the Institute of Medicine.
- Establishment as a congressionally chartered, nonprofit corporation.
  This option would enable the commission to establish an intermediary role between federal agencies, industry, and health professionals without the perception of control by any of these groups. The commission would be in a position to accept funds from federal and other sources and disperse them in an efficient manner. It could maintain an impartial, independent focus on vaccine development and immunization problems and, through reports submitted directly to Congress and the President, draw their attention to issues of concern. It is recognized, however, that some existing quasi-independent corporations serving general public needs have not operated in financially successful fashion due to difficulty in raising funds from private sector sources or revenues. Funding of the commission is discussed further below; but these types of problem, if encountered, could result in overreliance on public appropriations.

If created as a nonprofit corporation, the commission's influence on the activities of existing federal agencies and others would derive solely from the persuasiveness of the arguments behind its recommendations. Such a situation could be helpful in ensuring broad and thorough discussion of the issues that the commission identified as needing attention.

Public accountability of such a body would be ensured by its creation under congressional charter and the manner of appointment of its members.

Based on its analysis of the potential options and its knowledge of the fate of previous recommendations, the committee favors establishment of the commission as a congressionally chartered, nonprofit corporation. However, certain other loci for its operations are not altogether incompatible with the purposes of the commission. (It is understood that public and elected officials must consider recommendations in light of the pros and cons of the alternatives as seen from the perspectives derived from their responsibilities.)

As envisioned by the committee, the commission would have a relatively small board of directors with members drawn from the fields of biotechnology, immunology, infectious diseases, public health, public representation, health care policy, health care economics, health care delivery, bioethics, behavioral science, law, or medicine.

The manner of appointment should be designed to ensure that the commission attains the attributes of authority and credibility discussed above. In developing a slate of candidates for possible membership on the commission's board of directors, recommendations should be sought from all relevant groups (see Appendix J).

Representatives of the National Institute of Allergy and Infectious Diseases, the Centers for Disease Control, the Office of Biologics of the Food and Drug Administration, the Department of Defense, the Health Care Financing Administration, the Veterans Administration, and the Agency for International Development should be appointed as liaison members.

Funding

Preliminary projections indicate that a budget of about $1 million per year would be required for a minimum level of effective activity by the commission. A federal appropriation would be the simplest mechanism for ensuring rapid establishment of the commission. In the long term, it would be desirable for funding to be obtained from a variety of public and private sources to ensure the body's independence and credibility.

Possible Areas of Activity

The mode of operation of the commission and its initial activities should be determined by the commission itself. Efforts that might be initiated include (not in order of priority):

- monitoring the availability of existing vaccines to anticipate problems resulting from production difficulties or commercial decisions affecting supply
- monitoring the need for improvement of existing vaccines and setting priorities in this area
- monitoring vaccine innovation activities in the public and private sectors to determine whether they accurately reflect U.S. public health needs and the special needs of the military
- monitoring the vaccine needs of developing countries and promoting efforts to meet those needs
- evaluating the potential applications of advances in basic biotechnology to vaccine development
- evaluating the application of knowledge from the behavioral sciences in the design of campaigns to promote vaccines
- reviewing the effectiveness of promotional campaigns
- monitoring and evaluating patterns of infectious disease as an aid to determining priorities
- monitoring the training of personnel needed to ensure continued vaccine innovation
- monitoring and evaluating legal issues related to vaccine development and use

CONCLUSIONS

The lack of a formal mechanism to promote cooperation in the innovation, production, and use of vaccines limits the benefits obtainable from existing immunization programs and hampers the development of new programs. The problems associated with the absence of such a mechanism are primarily those of omission rather than commission: They include delay or inefficiency in achieving desired outcomes and failure to tackle problems for which no existing group has direct responsibility.

The history of earlier ad hoc groups convened to address problems related to vaccine availability and use has been discouraging. Specific actions envisaged by such groups have not been implemented for reasons unrelated to their potential utility. When these groups disbanded, attention focused on their activities waned.

To overcome these difficulties, the committee recommends the establishment of a national vaccine commission. This commission would monitor all aspects of immunization efforts in the United States. One of its primary responsibilities would be early identification of potential problems affecting vaccine supply. It also would help to educate and inform the public, physicians, and government decision makers about the effects of various immunization actions and policies. When necessary, the commission would become an impartial broker to promote the availability of needed vaccines and to coordinate collaborative activities for which no suitable mechanism exists.

Based on its analysis of the options and its knowledge of the fate of previous recommendations, the committee favors establishment of the commission as a congressionally chartered, nonprofit corporation. However, certain other loci for its operations are not altogether incompatible with the purpose of the commission. It should report at least annually to the Congress and the President, and on other occasions if immediate action is required to avert threats to the public health.

The committee recognizes that the creation of a vaccine commission should not be undertaken without due consideration; however, it stresses the need for rapid action. Failure to act on earlier proposals has contributed to the growing severity of problems of vaccine supply and innovation.

REFERENCES AND NOTES

1. National Immunization Work Groups. 1977. Reports and Recommendations of the National Immunization Work Groups. McLean, Va.: JRB Associates.
2. U.S. Congress, Office of Technology Assessment. 1979. A Review of Selected Federal Vaccine and Immunization Policies. Washington, D.C.: U.S. Government Printing Office.

3. Mason, J. 1984. Testimony on H.R. 5810 before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, December 19, 1984, Washington, D.C.
4. The Social Security Act Amendment of 1980, P.L. 96-611, December 28, 1980.
5. U.S. Congress, Office of Technology Assessment. 1980. Compensation for Vaccine-Related Injuries: A Technical Memorandum. Washington, D.C.: U.S. Government Printing Office.
6. Cohen, P. 1983. An Overview of the Factors Which May Impede Public-Private Sector Relationships Affecting Vaccine Development and Use. Paper prepared for the Institute of Medicine Conference on Barriers to Vaccine Innovation, November 28-29, 1983, Washington, D.C.
7. Jordan, W.S., and Galasso, G.J. 1983. The Interaction of Federal Agencies and Pharmaceutical Companies in Vaccine Development. Paper prepared for the Institute of Medicine Conference on Barriers to Vaccine Innovation, November 28-29, 1983, Washington, D.C.
8. U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Health and the Environment. Hearings held December 19, 1984 on H.R. 5810, Washington, D.C.
9. Centers for Disease Control. 1984. Diphtheria-tetanus-pertussis vaccine shortage—United States. Morbid. Mortal. Weekly Rept. 33:695-696.
10. American College of Physicians, Committee on Health and Public Policy. 1985. Guide for Adult Immunization, 1st ed. Philadelphia: American College of Physicians.
11. Collins, C., and Hanchette, J. December 1984. The Vaccine Machine, A Special Report. Washington, D.C.: Gannett News Service.
12. Institute of Medicine. 1985. New Vaccine Development: Establishing Priorities, Volume 1. Diseases of Importance in the United States. Washington, D.C.: National Academy Press.
13. Austrian, R. 1983. The Development of Pneumococcal Vaccine. Paper prepared for the Institute of Medicine Conference on Barriers to Vaccine Innovation, November 28-29, 1983, Washington, D.C.
14. U.S. Congress, Office of Technology Assessment. 1984. update of Federal Activities Regarding the Use of Pneumococcal Vaccine. Washington, D.C.: U.S. Government Printing Office.
15. Mitchell, J.R. 1983. Vaccine Development Incentives and Disincentives. Paper prepared for the Institute of Medicine Conference on Barriers to Vaccine Innovation, November 28-29, 1983, Washington, D.C.
16. Institute of Medicine. 1977. Evaluation of Poliomyelitis Vaccines. Washington, D.C.: National Academy Press.

8

Vaccine Injury Compensation and Liability Remedies

The committee believes that the goal of advancing the control of infectious diseases with vaccines should be pursued in a socially responsible and just manner. Its review of available scientific information led to the conclusion that a small number of severe adverse reactions are inevitable with existing vaccines, even when they are manufactured according to licensed procedures and administered in accordance with recommended medical practice. Most vaccines are promoted (or required) by the government for the public good; therefore, the committee believes that society has a responsibility to develop some means of compensating those with vaccine-related injuries.

At present, injured individuals or their families can seek compensation through the tort system, but the results are not certain and the process is protracted (Chapter 6). In addition, the courts' unpredictable handling of liability for vaccine-related injuries has created apprehension among manufacturers that ultimately could threaten the vaccine supply in the United States.

The committee recognizes that solutions to the problems of providing just compensation for vaccine-related injuries and maintaining vaccine supply and innovation must be forged in a political setting. It concluded, therefore, that its most useful contribution would be to identify and evaluate a series of options available to those seeking alternatives to the current situation.

Following a description of these options, the committee examines the rationale for compensating those with vaccine-related injuries and the major features desirable in a potential compensation system.

COMPENSATION AND LIABILITY OPTIONS

The need to compensate injured individuals and the need to reduce deterrents to vaccine manufacturing are two separate but closely related problems. Some of the possible solutions to the compensation problem would markedly increase the predictability of the liability situation; others would not. In contrast, certain actions that would provide greater predictability for manufacturers on the potential

magnitude of costs resulting from vaccine-related injury would not necessarily ensure compensation to injured individuals. A range of possible options and combinations of options are:

1. A supplementary (non-exclusive) compensation system, established by federal legislation, would give claimants an alternative to pursuing a tort remedy.
2. A compensation system with restricted tort options, established by federal legislation, would provide a way for individuals to recover expenses resulting from vaccine-related injury. Under such a system, manufacturers (but not others) would be protected from tort actions brought directly by individuals; the administrators of the compensation system would be empowered to pursue action for reimbursement in cases of misconduct in manufacturing (or deviation from recommended medical practices).
3. Mandatory claim review by a compensation board with tort option , established by federal legislation, under which claims for alleged vaccine-related injury would be reviewed by a compensation board that would render opinions on (1) whether the injury is vaccine related and hence eligible for compensation and (2) whether there is evidence of misconduct in manufacturing or administration. Claimants would then be free to pursue tort action irrespective of the compensation system's decisions, but not if they accept compensation.
4. A vaccine supply public insurance program, created to protect manufacturers against excessive payments for defense and settlement of vaccine-related injury claims (see Appendix B), would operate in conjunction with the current tort system.
5. No-fault insurance for vaccine-related injury could be promoted by groups such as medical specialty organizations. Under this approach, an insurance contract would be established whereby health care providers (through insurers) would, before a vaccine is administered, guarantee to tender within a set period to a person seriously affected by a vaccine the claimant's net economic loss. The criteria of eligibility would be predetermined in the insurer's contract. The claimant would be given a set period to accept the tender or to choose to pursue the claim under tort law. upon acceptance of the tender, the claimant would be required to waive tort claims against the tendering party, and in some instances, against other parties as well (see Appendix C).
6. A supplementary compensation system and a vaccine supply public insurance program could operate as tandem mechanisms.
7. A vaccine supply public insurance program and promotion of no-fault insurance for vaccine-related injury also could be linked.
8. Change the tort law relating to liability for vaccine-related injury. Two examples are described in tables 8.8 A and B. Both could be used in conjunction with other schemes. Under example A, "failure to warn" would be eliminated as grounds for action against a manufacturer (but not others); liability would be limited to misconduct during manufacturing (e.g., deviation from approved procedures). Under example B, limits would be set on the types and amount of damages recoverable through vaccine-related injury claims.

9. Federal assumption of liability for all vaccine-related injury could create a system similar to that resulting from the swine flu statute.
10. Acceptance of vaccine price increases to cover liability costs would entail assuring manufacturers that federal purchasers would allow increases in the prices of vaccines sufficient to cover anticipated future liability losses—the current tort system would continue.

The first three options focus on different approaches to compensation. Possible alternatives in this area range from a purely supplementary compensation system to a totally exclusive system, precluding vaccine-related injury claims against manufacturers or physicians. Between these poles lie a host of options in which tort rights can be broadly or narrowly defined and the timing of the surrender of those rights can be varied. Resource constraints prevented the committee from undertaking a detailed legal, operational, and economic analysis of injury compensation systems in other fields (Appendix D); however, such an analysis might prove useful to those involved in the operational design of a vaccine-injury compensation system. Information on arrangements made in other countries for payments to vaccine-injured individuals are described in Appendix E.

The fourth and fifth options involve two types of insurance programs that could contribute to the resolution of current problems. The vaccine supply insurance program addresses the unpredictability of manufacturers' liability costs, but would not provide compensation. No-fault insurance would provide payments to those injured individuals covered by the insurance. The sixth option examines the effects of combining a vaccine supply public insurance program with a compensation system, and the seventh explores the impact of providing both forms of insurance.

Option eight presents two of many possible changes in the tort law relating to vaccine injury. Changes in tort law could be used to complement other approaches to these problems. Fuller assessments of these options appear in Tables 8.1 to 8.10. Their probable effects are compared in Table 8.11.

The public health consequences of failing to deal with the vaccine injury compensation and liability issues are difficult to predict. Manufacturers may raise vaccine prices substantially to protect themselves against the expected costs of settling future injury compensation claims; or manufacturers may be unwilling to operate in a market characterized by an unpredictable risk of potentially overwhelming financial loss. Large increases in price could have adverse consequences for the federal consolidated vaccine purchases by which states obtain their vaccine supplies for public programs.

If the remaining single-supplier companies were to withdraw from vaccine production, the committee believes that it is unlikely that other companies would enter the market. If replacements were found from domestic or foreign sources, new suppliers probably would be aware of the potential liability costs and set prices accordingly.

TABLE 8.1 A Supplementary (Nonexclusive) Compensation System

Intent

To provide (as an alternative to the tort system) compensation to individuals sustaining vaccine-related injury.

Precedent

Similar system proposed as part of S.2117 and H.5810, National Childhood Vaccine-Injury Compensation Act.

Requirements for Establishment

Federal legislation.

.Operational Features

Requires development of schedules of compensable events and payments. Early waiving of tort rights by claimants entering the system desirable to reduce administrative costs. Costs could be covered by surcharge on vaccine prices.

Suggested Benefits

Establishes a more certain means of providing payments to injured parties than the tort system. May reduce the number of tort claims. Creates a central location for collection of information on vaccine-related injury claims. Maintains liability incentives to promote safe performance.

Suggested Disadvantages

Would not relieve manufacturers' apprehensions over the unpredictability of claims and/or settlements for vaccine-related injury. Extent of recovery for some events would be limited.

Time to Effects

Time to establishment depends on enactment of federal legislation; some delay anticipated before effects (if any) are observed on manufacturers' apprehensions over liability.

Additional Comments

Probably no immediate effect on certainty of vaccine supply. Could be used in combination with other systems.

TABLE 8.2 A Compensation System with Restricted Tort Options

In tent

To provide a compensation system for individuals sustaining vaccine-related injury; to maintain incentives for safe performance.

Precedent

Legislation related to compensation for workplace injuries (Appendix D).

Requirements for Establishment

Federal legislation.

Operational Features

System would require development of a schedule of compensable events and payments. Claimants would waive tort rights (if any) as a condition of receiving payment from system. Manufacturers (but not others) protected from individual tort actions involving alleged vaccine-related injury. Administrators of the system required to review cases for misconduct in manufacturing (e.g., failure to follow approved procedures) or deviation from recommended medical practices, and empowered to take action in cases of probable misconduct. Vaccine price surcharge could cover costs.

Suggested Benefits

Establishes a more certain means of providing payments to injured parties than the tort system. Relieves manufacturers of apprehension over the unpredictability of claims and/or settlements relating to "unavoidable" vaccine injury. Maintains duty to warn and incentives for safe performance. Creates a central location for collection of information on vaccine-related injury claims.

Suggested Disadvantages

Loss of the individual's right to sue manufacturers for misconduct, which reduces the number of possible sources of tort action, perhaps dilutes the pressure for safe performance by manufacturers. System administrators may not pursue misconduct actions vigorously. Extent of recovery for some events would be limited. Removes whatever incentives present tort system has to improve vaccines.

Time to Effects

Time to establishment depends on enactment of federal legislation. Relief of manufacturers' apprehensions would be immediate.

Additional Comments

Probably would have immediate beneficial effect on certainty of vaccine supply.

TABLE 8.3 Mandatory Claim Review by a Compensation Board with Tort Option

Intent

To provide a compensation system for individuals sustaining vaccine-related injury; to maintain the option for tort action; to provide an impartial opinion on the possibility that injuries are vaccine-related and the question of misconduct.

Precedent

The mechanism for handling medical malpractice claims in New Mexico (Medical Malpractice Act, 41-5-1 to 41-5-28 NMSA 1978).

Requirements for Establishment

Federal legislation.

Operational Feature s

All claims relating to alleged vaccine-related injury would be filed initially with the administrators of a compensation system. Within a short predetermined period the administrators would render opinions on (1) whether the injury is vaccine related and hence eligible for compensation and (2) whether there is evidence of misconduct in manufacturing or administration. Claimants then would be free to pursue tort action irrespective of the system's decision, but not if they accept compensation.

Suggested Benefits

Establishes a more certain means of providing payments to injured parties. Maintains the right to tort action. In cases in which claimants are eligible for compensation, encourages rapid settlement rather than protracted, uncertain tort remedy. Hence, may reduce the number of tort claims. Creates a central location for collection of information on vaccine-related injury claims. Provides impartial information to the courts on the probable cause of the injury and the question of misconduct.

Suggested Disadvantages

May cause brief delay (while system administrators process cases) in the filing of tort claims. Does not preclude tort action. Hence, does not totally remove uncertainty for manufacturers.

Time to Effects

Time to establishment depends on enactment of federal legislation. Some delay anticipated before effects (if any) on manufacturers' apprehensions over liability.

Additional Comments

Could be used in combination with other systems, e.g., with a vaccine supply insurance program. Experience with malpractice prescreening panels in various jurisdictions suggests that the terms of reference need to be established carefully.

TABLE 8.4 Vaccine Supply Public Insurance Program

Intent

To protect manufacturers against excessive costs from vaccine-related injury claims.

Precedent

Federal Deposit Insurance Corporation; Federal Savings and Loan Insurance Corporation; Small Investor Protection Corporation for brokerage houses; Price-Anderson Act (protecting operators of nuclear reactors against excessive liabilities).

Requirements for Establishment

Federal legislation.

Operational Features

Manufacturers would be protected against vaccine-related injury claim losses above a predetermined amount. Requires specification of the limits of manufacturers' responsibilities (e.g., production by approved procedures and duty to warn). Costs of defense and settlements must be reviewed to determine eligibility for reimbursement. Manufacturers would remain responsible for organization of the defense of all claims, including "unavoidable" injuries, if no compensation scheme is created.

Suggested Benefits

Could provide relief of manufacturers' apprehensions over the unpredictability of vaccine injury claims and/or settlements.

Suggested Disadvantages

Establishment of such a system alone would not provide a more certain or equitable system of dealing with vaccine injury, because of continued reliance on the tort system to provide compensation.

Time to Effects

Time to establishment depends on enactment of federal legislation.

Additional Comments

Could be used in combination with other systems.

NOTE: See Appendix B for detailed explanation.

TABLE 8.5 Promotion of No-Fault Insurance for Vaccine-Related Injury

Intent

To establish an insurance option that requires the liability carrier (on behalf of the health-care provider) to make an offer to the injured party to reimburse economic losses in exchange for a release of tort rights, if any.

Precedent

Similar no-fault insurance schemes have been adopted for serious high school athletic injuries under the auspices of the National Federation of High School Athletic Associations.

Requirements for Establishment

No legislative involvement.

Operational Features

Criteria for eligibility (and possibly payments) would be specified in the insurance contract.

Suggested Benefits

If widely adopted, would offer a more certain means of providing payments to injured parties than the tort system. May reduce the number of tort claims. Could be adopted immediately.

Suggested Disadvantages

Availability of compensation provided by such insurance would depend on its adoption by providers, i.e., universal availability of compensation would not be guaranteed. Does not preclude tort claims—manufacturers still at risk from tort claims for unavoidable injuries.

Time to Effects

Dependent on rate of widespread adoption of such insurance. Ultimate effects on the predictability of vaccine injury tort claims and the certainty of vaccine supply not clear without operational experience.

Additional Comments

Differences between insurance contract tenders and post-injury, out-of-court settlement offers are discussed in Appendix C. Medical specialty organizations could have a role in promoting the availability and adoption of such an option.

NOTE: See Appendix C for detailed explanation.

TABLE 8.6 Supplementary Compensation System and a Vaccine Supply Public Insurance Program

Intent

To provide compensation for individuals injured by vaccines (as an alternative to the tort system); to protect manufacturers against excessive costs from vaccine injury claims.

Precedent

See separate comments for each option. Similar scheme proposed in National Childhood Vaccine Injury Compensation Act of 1985, S. 827.

Requirements for Establishment

Federal legislation for both components of scheme.

Operational Features

See comments for each option.

Suggested Benefits

Establishes an option of more certain payment than the tort system and could provide relief of manufacturers' apprehensions over unpredictability of vaccine injury claims and/or settlements. Number of tort claims may be reduced.

Suggested Disadvantages

Manufacturers and vaccine providers still at some risk from tort claims for injuries that are unavoidable and still responsible for organization of defense of tort claims.

Time to Effects

See comments for each option.

Additional Comments

Administration may be complex.

TABLE 8.7 Vaccine Supply Public Insurance Program and Promotion of No-Fault Insurance for Vaccine-Related Injury

Intent

To protect manufacturers against excessive losses from vaccine injury claims; to establish an insurance option under which injured parties would receive an offer of rapid settlement of economic losses in exchange for a waiver of tort rights.

Precedent

See comments for each option, no precedent for such a joint venture.

Requirements for Establishment

Federal legislation required for one component of scheme.

Operational Features

See comments for each option.

Suggested Benefits

Could provide compensation and some relief of manufacturers' apprehensions over unpredictability of vaccine injury claims and/or settlements.

Suggested Disadvantages

Uniform availability of compensation for injuries is dependent on widespread adoption of the no-fault insurance aspect of the joint scheme. Manufacturers still at some risk from tort claims for unavoidable injuries.

Time to Effects

See comments for each option.

TABLE 8.8A Change in Tort Law (Example A)

Intent

To eliminate "failure to warn" as grounds for action against a manufacturer, but not others; manufacturers' liability would be limited to misconduct in manufacturing, e.g., deviation from approved procedures.

Precedent

None.

Requirements for Establishment

Action at the federal level or by all state legislatures.

Operational Features

Would operate through tort system.

Suggested Benefits

Manufacturers, in theory, would not be liable for unavoidable injury.

Suggested Disadvantages

Manufacturers still would be required to defend all claims. If action were at the state level, differences among states might make the situation unclear. Theoretically, unavoidable injuries would not be compensated.

Time to Effects

Legislation likely to be delayed by need to establish that vaccine-related injury liability deserves unique treatment. Operational experience needed to gauge effects.

Additional Comments

This is one of many possible changes in the tort law pertaining to vaccine-related injury liability; chosen for illustrative purposes only. Alone, it does not address the fundamental need for rapid and equitable compensation. Could be used in combination with other approaches.

TABLE 8.8B Change in Tort Law (Example B)

Intent

To limit the damages recoverable from manufacturers for vaccine-related injury and therefore provide them a greater degree of predictability.

Precedent

None.

Requirements for Establishment

Action at the federal level or by all state legislatures.

Operational Features

Would operate through the tort system. A limit could be placed on some types of recovery (e.g., for pain and suffering); other types (e.g., punitive damages) could be eliminated.

Suggested Benefits

Manufacturers would be better able to predict the extent of their potential liability for vaccine-related injury.

Suggested Disadvantages

Manufacturers still would be required to defend all claims. If action were at the state level, differences among states might make the situation unclear. Theoretically, unavoidable injuries would not be compensated. Could reduce incentives to safe performance.

Time to Effects

Legislation likely to be delayed by the need to establish that vaccine-related injury liability deserves unique treatment. Operational experience needed to gauge effects.

Additional Comments

This is one of many possible changes in the tort law pertaining to vaccine-related injury liability; chosen for illustrative purposes only. Alone, it does not address the fundamental need for rapid and equitable compensation. Could be used in combination with other approaches. Constitutionality issues regarding the removal of tort rights (without compensation) would need to be addressed before this approach could be implemented.

TABLE 8.9 Federal Assumption of Liability for all Vaccine-Related Injury

Intent

To have the federal government assume responsibility for all injuries occurring as a result of vaccine administration, providing compensation to those injured and protection of manufacturers from liability disincentives to production and innovation.

Precedent

Under the Swine Flu Act (P.L. 94-380) the government became the defendant in swine flu vaccine-injury tort claims, accepting liability for certain types of conditions, i.e., Guillain-Barré syndrome, occurring within 10 weeks of vaccination.

Requirements for Establishment

Federal legislation.

Operational Features

Basically operates through the tort system, but changes the defendant. Could operate in similar fashion to the swine flu compensation system, i.e., through Department of Justice. Government action for misconduct on the part of manufacturers or providers possible. Source of funds could be general revenues or a vaccine surcharge.

Suggested Benefits

Protects manufacturers from direct suits from claimants and limits manufacturers' liability.

Suggested Disadvantages

Costs would be met from general revenues unless provision were made for some other means of raising funds, hence, could mask true cost to society of vaccinations. The burden of handling claims would fall on the Department of Justice (or some other government legal office); resources devoted to the defense of claims against the government are often limited (see Chapter 6 for a discussion of the swine flu cases).

Time to Effects

Time to establishment depends on enactment of federal legislation. Time required to establish that vaccine injury deserves unique treatment. Once instituted, immediate relief of manufacturers' apprehensions.

TABLE 8.10 Acceptance of Vaccine Price Increases to Cover Liability Costs

Intent

To encourage manufacturers to continue vaccine production.

Precedent

Military procurement negotiations with sole suppliers.

Requirements for Establishment

Increased appropriations for federal purchases.

Operational Features

Manufacturers and providers would continue to defend injury claims under tort system. Price paid on federal purchases would be raised to cover tort losses; private sale prices also would be increased.

Suggested Benefits

May encourage manufacturers to continue production.

Suggested Disadvantages

Continued reliance on tort system, making doubtful the certainty and equity of access to compensation. Would not improve predictability of situation for manufacturers with regard to tort losses. Could encourage a cycle of price increases and increased tort awards. Increased appropriations required to maintain federally supported immunization programs.

Time to Effects

Could be instituted rapidly.

Also, it is unlikely that foreign vaccine manufacturers would enter the market. Few foreign firms now hold U.S. licenses; of those that do, few distribute products. Leaders in foreign manufacturing companies have indicated that liability is a major reason for not entering this market.[1,2] A failure of vaccine supply would lead to a drop in immunization levels and resurgence of some diseases.

Failure to resolve the problems of liability and compensation for unavoidable vaccine injury also may contribute to a failure to reap the public health benefits of recent advances in biotechnology. Public health needs will remain unmet if liability considerations deter commercial production of technically feasible vaccines.

The Rationale for Providing Compensation for Vaccine-Related Injury

Although in one sense the provision of appropriate compensation for vaccine-related injuries is part of the broader problem of providing compensation for all unintentional injuries, vaccine supply and administration are sufficiently different from other injury-causing behaviors to justify separate treatment. Vaccine-related injuries differ from most other injuries in several important respects. First,

TABLE 8.11 Probable Effects of Selected Options Addressing Problems Arising from Vaccine-Related Injury

Option	Provision of Compensation for Vaccine-Related Injury	Manufacturers' Apprehensions Over Unpredictability of Vaccine-Injury Claims/Settlements	Availability of Tort System to Injured Parties in Cases of Suspected Misconduct	Comments
A supplementary (non-exclusive) compensation system (Table 8.1)	Assured, rapid, equitable	Probably reduced to some degree	Unaffected	
A compensation system with restricted tort options (Table 8.2)	Assured, rapid, equitable	Reduced	Action against manufacturers precluded	Compensation system administrators could take action for suspected misconduct
Mandatory claim review by a compensation board with tort option (Table 8.3)	Assured, rapid, equitable	Probably reduced	Unaffected	Number of tort claims might be reduced
A vaccine supply public insurance program (Table 8.4)	Continues to be via tort system;[a] uncertain, slow	Removed	Unaffected	
No-fault insurance for vaccine-related injury (Table 8.5)	Remedy only for those who received vaccine from insured physician or other health care provider; rapid	Probably reduced	Unaffected	Full benefits depend on widespread adoption
A supplementary compensation system and a vaccine supply public insurance program (Table 8.6)	Assured, rapid, equitable	Removed	Unaffected	
A vaccine supply public insurance program and promotion of no-fault insurance for vaccine-related injury (Table 8.7)	Remedy only for those who received vaccine from insured physician or other health care provider; rapid	Removed	Unaffected	Full benefits dependent on widespread adoption of no-fault insurance

Option	Provision of Compensation for Vaccine-Related Injury	Manufacturers' Apprehensions Over Unpredictability of Vaccine-Injury Claims/Settlements	Availability of Tort System to Injured Parties in Cases of Suspected Misconduct	Comments
Change tort law relating to liability for vaccine-related injury				
A. Manufacturers (but not others) relieved of duty to warn (Table 8.8A)	Continues to be via tort system;[a] uncertain, slow	Probably reduced to some degree	Availability unaffected but causes of action limited	
B. Limitation on recovery of damages (Table 8.8B)	Continues to be via tort system;[a] uncertain, slow	Probably reduced to some degree	Availability unaffected but limits set on potential recovery	
Federal assumption of liability for all vaccine-related injury (Table 8.9)	Possibility of rapid compensation would depend on government settlement policy	Removed	Removed	Government could pursue action if misconduct were suspected
Acceptance of vaccine price increases to cover liability costs (Table 8.10)	Continues to be via tort system;[a] uncertain, slow	Possibly reduced but management still difficult (see comments)	Unaffected	Potential liability costs are unpredictable, hence, the required price increases are not calculable

NOTE: Other combinations of options would be possible.

[a] Under well-established legal principles, vaccine manufacturers and others are not liable for injuries caused by vaccines that are properly manufactured, labeled, and administered. Thus, compensation through the tort system is uncertain; each claim requires a complex adjudicative procedure to establish liability.

immunization programs often are mandatory; when not required, they are often encouraged by the government. Therefore, vaccine recipients and their families lack the free choice about participation and risk-taking that characterizes many medical situations.

In addition, vaccination programs are justified as being for the public good. In some cases, the principal reason to vaccinate a person is to protect others from a disease. Thus, the victim of an adverse reaction to a vaccine may be seen as a casualty of the public health, and therefore especially deserving of compensation. Moreover, assuring potential vaccine recipients, providers, and producers that compensation for untoward consequences is available would remove one potential disincentive to participation in vaccination programs.

Other publicly promoted or required activities also involve a combination of risk to the individual and benefit to society. Examples include military conscription, travel to and from school, and the use of food preservatives. Vaccine injury is unique, however, in that individuals are required to submit to an invasive medical procedure for their own and society's benefit. To suggest that the victims should bear their own losses (in cases in which there is no misconduct) because they could have avoided injury and the resulting medical and economic expenses simply by not obtaining a vaccination would be unreasonable. (The question of informed consent is discussed later in this chapter.)

The nature and current state of the vaccine industry suggest additional reasons for treating vaccines differently from other injury-causing products and activities. The vaccine industry is vitally important to public health, yet the number of vaccine manufacturers in the United States continues to decline. Two manufacturers of pertussis vaccine ceased distribution of their products during the tenure of this committee (Chapter 3).*

The liability situation is a major source of concern for the industry. A small number of large tort awards, coupled to a confused and unstable legal situation (especially with regard to "unavoidable" injury), make liability difficult to predict and potentially destructive (Chapter 6). Therefore, the evaluation of options to provide compensation for vaccine-related injuries should include an assessment of their potential effects on the vaccine industry and, through vaccine supply, on public health.

Finally, the issue of compensation for vaccine-related injuries is especially unwieldy for the common law tort system. Like other medical and technical issues, putative vaccine injury poses very difficult problems of proof (Chapters 5 and 6). Judges and lay jurors, informed primarily by lawyers and hired experts (whose testimony has been structured by lawyers), are unable to determine with acceptable accuracy the likelihood of a causal relationship between a vaccine and an injury. The tort system is just beginning to consider ways to improve the use of scientific evidence[3,4] including the possibility

* Immediately prior to the printing of this report, Connaught Laboratories, Inc., resumed distribution of DTP vaccine.

of proportional damage awards in cases of statistically probable causal relationships that cannot be proved definitively.[5] Rather than allow potential injustice to injured claimants, continued apprehension and confusion on the part of manufacturers, and peril to the public health (from possible cessation of vaccine production), compensation for vaccine-related injuries should be restructured in a more fair, certain, and consistent manner.

Based on these considerations, the committee concluded that persons injured by vaccines should be compensated; that compensation should not imperil the vaccine industry, but should be seen as part of a general program to promote public health; and that any vaccine compensation mechanism must accommodate the fact that resolution of causation may not be possible in some cases.

The common law tort system is not able to provide predictable, rapid, and equitable compensation for vaccine-related injuries because each claim requires an extended, costly, and complex adjudicative procedure that results in unpredictable outcomes (Chapter 6).

THE COMPENSATION MECHANISM

The primary objective in designing a system to provide payments to individuals with vaccine-related injuries is to find an approach (or combination of actions) that (1) provides predictable, rapid, and equitable compensation for those injured; (2) ensures that no party is shielded from action for suspected misconduct; and (3) reduces or removes disincentives to vaccine manufacturing.

The compensation system envisioned by the committee would be created by federal legislation. It could be established within an existing government department or as a new entity. It would be empowered to raise and distribute funds to compensate persons with vaccine-related injuries. The compensation system administrators would be encouraged to obtain advice from the vaccine commission discussed elsewhere in this report, but the two bodies should be separate. Specific issues relating to the operation of the system are discussed below.

Provision of Payments

To achieve rapid payments, all claims made to the compensation system should be processed without regard to "fault," i.e., the possibility that misconduct may have occurred. A determination would be made with the assistance of a schedule of compensable events whether the alleged injury was vaccine related. Eligible parties would be compensated. A review of cases for misconduct would be required to determine if the system should recover payments from responsible parties. The conclusions of the system administrators about the relationship between vaccination and the alleged injury and about the possibility of misconduct would be made available to the courts (in addition to the scientific data and reasoning upon which they were based) to aid in any further evaluations.

The creation of a compensation system is not intended to provide protection for wrongdoers. Legal action should be possible if there is evidence of misconduct. The committee believes, however, that any injury resulting from a vaccine that has been correctly manufactured and administered in accordance with recommended medical practices should be treated essentially as a no-fault injury.[6] This position appears to be in accordance with the legal theory that some products are unavoidably unsafe (Chapter 6).

The committee was concerned that apprehensions over liability on the part of health care providers might become a disincentive to their participation in immunization programs. In its review of the state of the law, however, the committee found little evidence that liability had been imposed on health care providers except in situations involving failure to follow accepted medical procedures. The committee presently does not recommend any change in the rules applicable to health professionals because liability for improper administration is appropriate;* it recognizes, however, that if any proposal limiting recovery against manufacturers were adopted without provision for reasonable compensation, lawsuits might be redirected from the manufacturer to the administering professional. This could have deleterious effects on the willingness of health care providers to participate in immunization programs. Such a situation would require careful monitoring. Tracking shifts in litigation and recommending remedial action would be one of the functions of the proposed vaccine commission (Chapter 7).

The possible elimination of the individual's tort remedy against manufacturers (as envisaged in a compensation system with restricted tort options) would in no way affect other legal and administrative controls over vaccine manufacturers or providers, e.g., in cases of serious misconduct, such as the intentional falsification of data to obtain certification.

The Amount and Nature of Payments

The committee's conclusion that persons who suffer vaccine-related injuries should be compensated does not mean that they all should receive the same high compensation now awarded to some by the tort system. One distinguished critic of the tort system has referred to the current situation as a "lottery."[7] A plaintiff who enters the system has a large chance of winning nothing and a small chance of winning a great deal. Goals in vaccine injury compensation should be to remove chance from the system, to decide on an appropriate and fair level of compensation, and to ensure that all deserving claimants receive that amount.

An appropriate amount of compensation (1) removes financial

* The committee recognized that malpractice claims, in general, represent a major concern of the medical profession, but it did not feel that the malpractice issue was within the scope of its charge.

disincentives for participation in vaccination programs; (2) prevents financial devastation of victims and their families; (3) keeps vaccine costs low enough to permit universal use; (4) avoids disproportionate expenditures on an area of public health that, although important, is not the only legitimate claim on the nation's resources; and (5) avoids creating incentives to litigate.

These goals lead to several general suggestions. First, small injuries that do not pose a risk of significant financial loss should not be compensated. The compensation system should make no award to persons whose out-of-pocket losses are less than a specified minor amount, which should be reset periodically.

At the other end of the injury spectrum, limits should be placed on maximum recoveries. Predetermined dollar limits are undesirable, however, because they discriminate against those most severely injured. To ensure fair compensation and at the same time keep total costs reasonable, compensation for nonmonetary losses (e.g., pain and suffering, emotional distress, and loss of companionship) should be strictly defined and limited by the bodies establishing the schedules of compensable events and payments. Projections for the proposed National Childhood Vaccine Injury Compensation Act suggest that a large proportion of costs (90 percent) could arise from loss of future earnings.[8] Hence, any estimates of future earning potential should be made carefully. Because most injuries occur in young children, whose potentials are unknown, an award based on the "average" worker's earnings projected over the period of the claimant's working life expectancy appears reasonable. Finally, fees for the attorneys of claimants should be paid by the compensation system according to a fee schedule.

In sum, an injured person should be reimbursed for all present and future out-of-pocket losses for medical, hospital, nursing home, personal assistance, special training, special equipment, legal, and other expenditures plausibly caused by the vaccine injury, and receive a limited amount for lost earnings. Awards for future costs should be paid over time through a system of periodic payments so that the compensation fund is protected from depletion.

Defining Compensable Events

The scope of the schedule of compensable events and the manner in which it is established will affect operational costs of the system, the ease of administration, and the likelihood that it will be acceptable, or preferred over other remedies (if any are available).

Establishing a schedule of compensable events can begin with evaluation of pertinent scientific information, especially epidemiologic data, and proceed to the use of the resulting conclusions to formulate policy, i.e., the actual schedule. In the latter phase, the scientific evidence (and its limitations) must be balanced with other considerations, such as likely costs and ease of administration.

The section on untoward reactions to vaccines in Chapter 5 describes the problems of establishing association or causation in cases of possible vaccine injury. The difficulty of proving or disproving a causal relationship between a given vaccine and a particular injury suggests that if causation is required, for payment of compensation, outcomes will depend on who is required to carry the burden of proof. Moreover, these efforts to prove causation will be time-consuming, expensive, and probably inconclusive.

Given the current situation, little purpose will be served by efforts to determine causation on a case-by-case basis. The best way to control expenses for any payment system will be to establish a generally acceptable schedule of compensable events that can be administered without frequent specialist intervention or judgment. The schedule should reflect the best available scientific information and judgment on the existence (or absence) of associations between specific conditions and vaccine administration.

Only those conditions for which scientific evidence indicates a plausible association with vaccination should be included on the schedule of compensable events. To be eligible to receive payments, claimants also should meet at least two additional criteria—onset of the condition should be within some specified time after vaccine administration and there should be no evidence that establishes a different cause.

It was not within the committee's purview or resources to undertake elaboration of a detailed schedule of compensable events, although its review of untoward reactions to vaccines (Chapter 5) could serve as a starting point for such an effort. The committee recommends that if the decision is made to establish a compensation system, a group of experts in the necessary disciplines should be convened by an independent body or organization to develop it. In addition, it would be preferable to establish the schedule by administrative rule, rather than legislation, to allow updating. However, an interim schedule may be developed to allow rapid implementation of the compensation system.

Establishing a workable schedule would entail recognition of the fact that some individuals whose injuries were not actually caused by vaccination would receive compensation (i.e., those "background rate" cases of conditions listed on the schedule of compensable events but, in fact, related only temporally to the vaccination). Such "mistakes" are extremely difficult to avoid. They would be on the side of compensation and, if few in number, would be tolerable. The schedule of compensable events must be drawn carefully to ensure that such mistakes are few, that nuisance or fraudulent suits are discouraged, and that the social policy of promoting vaccine use while compensating its victims is not perverted by extraneous payments or administrative costs.

To minimize administrative costs, review and appeal mechanisms should be strictly limited. Judicial review should be limited to abuse of discretion. A board of scientific advisors could be convened to assist the system's administrators with cases in which interpretation or application of the schedule is unclear.

Establishing an Schedule of Payments

Final determination of medical and other costs (e.g., special education and rehabilitation) that should be covered for each condition and the size of different types of payments should be made by an independent group of experts in the economic analysis of medical costs. As with the schedule of compensable events, the payment schedule should be formulated administratively rather than legislatively to allow updating. Periodic (structured) payments rather than lump sums should be favored. Again, an interim schedule may be used initially.

Source of Funding

Because vaccine programs are for the public good and are frequently endorsed or mandated by government, public funds may appear to be an attractive source of compensation for those with vaccine injuries. However, promotion of a compensation system funded from general tax revenues would encounter several obstacles.

Such a system may be unattractive to many legislators because it could be characterized as a "give-away" program, an unjustified tax increase, or an undeserved windfall to one industry. These charges are difficult to refute, especially during a period of increasing concern about the federal deficit. Moreover, insistence on a federally financed compensation system would place an undue burden on the argument that the vaccine injury compensation problem is unique. Jeopardizing the proposal to establish a compensation system by exposing it to such political risks should not be necessary. Certain nonpolitical arguments provide support for an alternative approach to raising funds.

A well-designed vaccine price surcharge plan could assign injury costs in an economical, predictable, and therefore manageable way. Moreover, by revealing the true costs of vaccines (the cost of compensating injuries, as well as the costs of production, marketing, etc.), it would offer society an opportunity for rational decision making. For example, if it were learned that a vaccine caused $1 million worth of injuries per year and prevented $1 billion worth of injuries from the target disease, decisions about use of the vaccine would be very different from those made if the figures were reversed. In either event, there would be a basis for rational, rather than intuitive, decision making.

The surcharge ultimately would be paid by recipients of vaccines or others who purchase them. As a practical matter, it should be noted that because a large proportion of vaccines are purchased with federal funds for public programs, society at large would contribute to the compensation fund generated by the surcharge.

The surcharge should be based on the best available actuarial judgments about vaccine risks, and should be reset at least annually to reflect previous over-or underestimates of needs. The money obtained from the surcharge should be the primary source of

compensation for vaccine-related injuries. If the surcharge fund becomes exhausted at any time, the federal government should be obligated to lend the compensation system enough money to pay claims, and the system obligated to make sufficient adjustments in its future surcharges to repay the loan.

An early problem in establishing the compensation mechanism will be whether to establish one surcharge fund to pay all vaccine injuries or to have different funds for different vaccines. Each vaccine should have its own fund if the major goal is to reveal the true costs of these vaccines. However, that approach sacrifices the benefits of aggregation of resources and adds an element of luck to the fund's management. For example, if in any given year the pertussis fund were low and the measles fund were high, and the compensation system were faced with several pertussis and no measles claims, it would have to borrow to pay pertussis claims while hoarding measles money, or start borrowing from itself. In addition, the complexity of multiple funds would increase management and administrative costs, which should be kept low. Finally, a vaccine-by-vaccine approach would result in the creation of "orphan" injuries, for which no adequate compensation would be available and for which borrowing would not be feasible. For all these reasons, the committee favors creation of only one vaccine injury fund, although the amount of the surcharge may vary from vaccine to vaccine.

Informed Consent

Every effort should be made to promote the availability to potential vaccine recipients (or their parents) of information on the risks and benefits of vaccination. However, the overall goal of providing appropriate compensation expeditiously will be ill-served if the administrators must attempt to base eligibility for compensation on the difficult question of whether the vaccine recipient gave "informed consent." Indeed, informed consent may be a meaningless concept in the context of a public health program with legal requirements for vaccination. Attempting such a determination would slow dispute resolution and increase administrative costs. Thus, the giving of informed consent should not preclude eligibility for compensation.

Administrative Location

To be accepted as an alternative to the tort system, any new mechanism for achieving compensation for vaccine injury must be regarded as providing fair and adequate payments. It is essential, therefore, that the mechanism not be located in or associated with a body whose existing functions might be perceived as conflicting with the provision of equitable compensation. The administration of a vaccine-injury compensation scheme by the Public Health Service, whose responsibilities include the promotion of vaccine use, might be

regarded as a potential conflict of interest and therefore is not desirable.

A variety of alternative administrative locations are possible, including the Department of Justice, the Social Security Administration, the Health Care Financing Administration, and a nonprofit compensation corporation.

Additional Issues

A number of other issues should be resolved prior to the final design and implementation of a vaccine-related injury compensation system.

The purpose of establishing such a compensation scheme would be to provide a more rapid, equitable mechanism for payment to injured parties, not to increase the amount received by some individuals. Hence, the committee believes that payments from only one source should be possible. A claimant/plaintiff should be required to choose between the compensation system and tort remedy, or to waive tort rights a a condition of receiving payment.

Additional questions that must be answered include:

- Which vaccines should be covered? It seems logical to be comprehensive because the arguments for a compensation scheme do not hinge solely on the fact that some vaccines are mandatory. Vaccinations given to adults, like pediatric vaccinations, are desirable on the basis of overall benefits to public health, e.g., they reduce disease transmission. The injured parties are equally deserving of compensation.
- How are initial compensation funds to be raised? A number of options are available. A price surcharge could be applied for a number of years before the system goes into operation. Alternatively, a one-time government appropriation could be made or a loan negotiated.
- Will the system be retroactive? If so, to what extent, and how will tort claims in process be handled? Because immunization, especially of children, has been widely promoted for many decades, there is a potential backlog of claims for vaccine injury. A number of options are available on these questions. Resolution of questions over retroactivity is important because payments for previous injuries could, in the early years of operation, far outweigh the routine annual incidence of claims.[8] The question of whether these initial costs would be paid from general revenues or the surcharge set to recoup them also needs to be addressed.
- A number of questions involving the relative commercial competitiveness of present manufacturers and possible new entries into the vaccine market could arise depending on how retroactivity, claims in process, and the levying of the surcharge are handled. These must be resolved in an equitable fashion.
- Should new mechanisms be instituted at the state or federal level? Notwithstanding the fact that liability is currently governed by state law, a number of factors strongly support the proposition

that a federal solution is needed. A multiplicity of approaches probably would arise at the state level to what is essentially a uniform problem for the entire country. Undesirable differences would develop in access to and magnitude of compensation. Also, vaccine manufacturers operate on a national scale and it would be best to avoid a situation in which they are discouraged from supplying products to some areas where they remain subject to unpredictable litigation.

The committee did not attempt to prescribe detailed approaches to each of these sets of problems, but identifies them because the manner of their resolution could significantly affect the costs and operation of the compensation system.

SUMMARY AND CONCLUSIONS

A variety of methods exist for dealing with the problems arising from vaccine-related injury, the most serious of which are the need to compensate injured individuals and the need to reduce deterrents to vaccine manufacturing. The committee evaluated eight individual options and two combined approaches from the range of possible actions—some address only one facet of this complex situation and others address a broader range of issues. The 10 alternatives are:

- a supplementary (non-exclusive) compensation system
- a compensation system with restricted tort options
- mandatory claim review by a compensation board with tort option
- a vaccine supply public insurance program
- promotion of no-fault insurance for vaccine-related injury
- a supplementary compensation system and a vaccine supply public insurance program
- a vaccine supply public insurance program and promotion of no-fault insurance for vaccine-related injury
- changes in the tort law relating to liability for vaccine-related injury
- federal assumption of liability for all vaccine-related injury
- acceptance of vaccine price increases to cover liability costs

The committee believes that the goal of advancing the control of infectious diseases with vaccines should be pursued in as just and fair a manner as possible. Those who respond to the government's promotion of or legal requirement for vaccination convey benefits to other members of society because they reduce the risk of disease in the community. If vaccination results in an injury, the injured individual should be certain of receiving rapid and adequate compensation. The common law tort system can not be relied on to provide such compensation because each claim requires an extended, costly, and complex adjudicative procedure to establish liability. The results of these procedures are erratic and unpredictable, and therefore inequitable.

The committee urges political decision makers to develop a compensation system for vaccine-related injury with the features outlined in this report. It also recommends that action be taken to reduce the serious deterrents to vaccine manufacturing and innovation that arise from the unpredictable nature of the current liability situation (such action should not be designed to shield those suspected of possible misconduct). The information and analysis presented in this report should help guide policymakers in the choice of appropriate solutions.

REFERENCES AND NOTES

1. Beale, A.J. 1985. Modern approaches to the development of vaccines: perspective of a traditional manufacturer. pp. 377-381 in Vaccines 85. Molecular and Chemical Basis of Resistance to Parasitic, Bacterial, and Viral Diseases, R.A. Lerner, R.M. Chanock, and F. Brown, eds. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory.
2. Coe, F.A., Jr. 1983. A vaccine manufacturer's view of the vaccine market. Prepared for the Institute of Medicine Conference on Barriers to Vaccine Innovation, November 28-29, 1984, Washington, D.C.
3. Pharmaceutical Manufacturers Association. 1985. Jury rules that bendectin did not cause birth defects. PMA Newsletter 27:1.
4. Curran, W.J. 1983. The acceptance of scientific evidence in the courts. N. Engl. J. Med. 309:713-714.
5. See, e.g., Sindell v. Abbott Laboratories, 26 Cal. 3d 588, 607 P.2d 924, 163 Cal. Rptr. 132 (1980), Rosenberg, The Causal Connection in Mass Exposure Cases: A "Public Law" vision of the Tort System, 97 Harv. L. Rev. 849 (1984); Comment, DES and a Proposed Theory of Enterprise Liability, 46 Fordham L. Rev. 963 (1978).
6. In this regard the licensing approvals and Good Manufacturing Practices of the Food and Drug Administration and the recommendations of the Centers for Disease Control Advisory Committee on Immunization Practices should serve as guidelines.
7. Franklin, Replacing the Negligence Lottery: Compensation and Selective Reimbursement, 53 Va. L. Rev. 774 (1967).
8. Penner, R.G. 1984. Letter to Sen. Orrin Hatch, February 7, 1984, on preliminary Congressional Budget Office cost estimates of S. 2117, the National Childhood Vaccine Injury Compensation Act.

Appendix A

Product License Holders

Adenovirus Vaccine, Live, Oral, Type 4
Wyeth Laboratories, Inc.
Adenovirus Vaccine, Live, Oral, Type 7
Wyeth Laboratories, Inc.
Anthrax Vaccine Adsorbed
Michigan Department of Public Health
BCG Vaccine
Connaught Laboratories Ltd.
Glaxo Operations U.K. Ltd.
University of Illinois
Cholera Vaccine
Istituto Sieroterapico Vaccinogeno Toscano Sclavo
Lederle Laboratories
Merck Sharp & Dohme
Wyeth Laboratories, Inc.
Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed
Connaught Laboratories, Inc.
Eli Lilly and Company
Istituto Sieroterapico Vaccinogeno Toscano Sclavo
Lederle Laboratories
Massachusetts Public Health Biologic Laboratories
Merck Sharp & Dohme
Michigan Department of Public Health
Wyeth Laboratories, Inc.
Diphtheria and Tetanus Toxoids Adsorbed
Istituto Sieroterapico Vaccinogeno Toscano Sclavo
Lederle Laboratories
Massachusetts Public Health Biologic Laboratories
Michigan Department of Public Health
Wyeth Laboratories, Inc.
Diphtheria Toxoid
Connaught Laboratories, Inc.
Istituto Sieroterapico Vaccinogeno Toscano Sclavo
Wyeth Laboratories, Inc.

Prepared by A. Demers, Division of Product Certification, Food and Drug Administration.

Diphtheria Toxoid Adsorbed
Istituto Sieroterapico Vaccinogeno Toscano Sclavo
Michigan Department of Public Health
Wyeth Laboratories, Inc.
Hepatitis B Vaccine
Merck Sharp & Dohme
Influenza Virus Vaccine
Connaught Laboratories, Inc.
Lederle Laboratories
Merck Sharp & Dohme
Parke-Davis
Wyeth Laboratories, Inc.
Measles Virus Vaccine, Live, Attenuated
Merck Sharp & Dohme
Measles and Mumps Virus Vaccine, Live
Merck Sharp & Dohme
Measles and Rubella Virus Vaccine, Live
Merck Sharp & Dohme
Measles-Smallpox Vaccine, Live
Merck Sharp & Dohme
Measles, Mumps, and Rubella Virus Vaccine, Live
Merck Sharp & Dohme
Meningococcal Polysaccharide Vaccine
Connaught Laboratories, Inc.
Merck Sharp & Dohme
Mumps Virus Vaccine, Live
Merck Sharp & Dohme
Pertussis Vaccine
Connaught Laboratories, Inc.
Wyeth Laboratories, Inc.
Pertussis Vaccine Adsorbed
Michigan Department of Public Health
Plague Vaccine
Miles Laboratories, Inc.
Pneumococcal Vaccine, Polyvalent
Lederle Laboratories
Merck Sharp & Dohme
Poliomyelitis Vaccine
Connaught Laboratories Ltd.
Poliovirus Vaccine, Live, Oral, Trivalent
Lederle Laboratories
Poliovirus Vaccine, Live, Oral, Type 1
Lederle Laboratories
Poliovirus Vaccine, Live, Oral, Type 2
Lederle Laboratories
Poliovirus Vaccine, Live, Oral, Type 3
Lederle Laboratories
Rabies Vaccine (Human Diploid Cell)
Institut Merieux
Wyeth Laboratories, Inc.

Rubella and Mumps Virus Vaccine, Live
Merck Sharp & Dohme
Rubella Virus Vaccine, Live
Merck Sharp & Dohme
Wellcome Foundation Ltd.
Smallpox Vaccine
Connaught Laboratories, Inc.
Michigan Department of Public Health
Wyeth Laboratories, Inc.
Tetanus and Diphtheria Toxoids Adsorbed (for adult use
Connaught Laboratories, Inc.
Istituto Sieroterapico Vaccinogeno Toscano Sclavo
Lederle Laboratories
Massachusetts Public Health Biologic Laboratories
Merck Sharp & Dohme
Wyeth Laboratories, Inc.
Tetanus Toxoid
Connaught Laboratories, Inc.
Connaught Laboratories Ltd.
Istituto Sieroterapico Vaccinogeno Toscano Sclavo
Lederle Laboratories
Massachusetts Public Health Biologic Laboratories
Merck Sharp & Dohme
Wyeth Laboratories, Inc.
Tetanus Toxoid Adsorbed
Connaught Laboratories, Inc.
Istituto Sieroterapico Vaccinogeno Toscano Sclavo
Lederle Laboratories
Massachusetts Public Health Biologic Laboratories
Merck Sharp & Dohme
Michigan Department of Public Health
Swiss Serum and Vaccine Institute Berne
Wyeth Laboratories, Inc.
Typhoid Vaccine
Massachusetts Public Health Biologic Laboratories
Merck Sharp & Dohme
Michigan Department of Public Health
Wyeth Laboratories, Inc.
Yellow Fever Vaccine
Connaught Laboratories, Inc.

Appendix B

A Vaccine Supply Public Insurance Option

A vaccine supply public insurance program would provide one solution to the vaccine supply problem caused by manufacturers' concerns over unknown but potentially large liabilities.* This option would not require controversial tort law reform. It would involve creation by Congress of a statutory mechanism to provide the manufacturers with insurance coverage against total costs (beyond a specified, manageable amount), including legal expenses and amounts paid after settlements and judgments, resulting from the manufacture and sale of vaccines in accordance with regulatory standards.

It appears that such insurance is difficult to obtain at premiums considered by manufacturers to be reasonable.[1] The federal government could provide such coverage to the manufacturers in two ways. The government could simply obtain bids for such insurance on the commercial market and then pay whatever premiums are required. Alternatively, it could create a specialized insurance corporation to provide the insurance.

There are no precise institutional analogies. The swine flu statute, although not specifically providing insurance, effectively performed the same function because the federal government assumed all primary liability.

A close analogy is the Price-Anderson Act, designed to encourage the construction of nuclear reactors. It requires owners of nuclear reactors to carry the maximum amount of private liability insurance available (determined to be at least $60 million per nuclear occurrence), provides for indemnification by the federal government in the amount of $500 million per occurrence, and limits total liability per occurrence to $560 million.[2] In administering the program, the Nuclear Regulatory Commission is instructed to make use of the

* Manufacturers in certain industries have formed captive insurance corporations to provide their liability coverage (e.g., the ladder manufacturers formed Safe Step Insurance Corporation of Bermuda). A similar arrangement by vaccine manufacturers could provide access to insurance; however, it would not provide long-term security of vaccine supply because overwhelming financial losses could bankrupt the insurance corporation, removing the coverage it had offered.

facilities of private insurance organizations to "the maximum extent practicable."[3] Fees are charged to owners of nuclear power plants under this program.[4] This statute was held constitutional in Duke Power Co. v. Carolina Environmental Study Group, Inc.[5]

The specialized government corporations that have been created to provide depositors with insurance against the risk of failure of financial institutions also could be used as models. The Federal Deposit Insurance Corporation for banks, the Federal Savings and Loan Insurance Corporation for savings and loan institutions, and the Small Investor Protection Corporation for brokerage houses are government corporations with independent boards of directors, funded by fees assessed on the covered institutions, and backed by lines of credit from the federal government. Although the insurance they provide is not liability insurance, their organizational forms could be adapted to provide coverage for vaccine manufacturers.

The implementation of such a program would require a large number of technical decisions that Congress could delegate either to an administrative official or to a specialized corporation, with such guidance as Congress chose to provide. For example, to minimize the cost and administrative changes required to implement such a program, it probably would be desirable to leave the manufacturers with a basic level of liability up to amounts that do not create unmanageable risk. The firms could then continue to handle claims within these limits. The amount of such a "deductible" should be varied according to formulas that reflect the level of the manufacturer's business in the vaccine market.

Other decisions would involve the allocation of responsibility for and control of the defense of claims, the provision of information by the manufacturers to the insurance carrier or government corporation, the powers of the carrier or corporation to inspect or control the operations of the manufacturers to minimize risk, the terms and conditions under which new manufacturers would become eligible for coverage under the program, the level of fees or premiums charged to the manufacturers, the amount necessary for a reserve fund, and the extent and form of the manufacturers' continuing liability for negligence in the production process.

This option would enable Congress to protect vaccine manufacturers who have acted in accordance with regulatory standards from the risk of large losses, thereby ensuring continuation of the vaccine supply from private manufacturers. It would not require that Congress first resolve issues of tort law reform.

REFERENCES

1. U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Health and the Environment. Hearings held December 19, 1984 on H.R. 5810, Washington, D.C.
2. 42 U.S.C. sec. 2210.
3. 42 U.S.C. sec. 2210(g).
4. 42 U.S.C. sec. 2210(f).
5. 438 U.S. 59 (1978).

Appendix C

No-Fault Vaccine Injury Insurance

As discussed in Chapter 8, no-fault insurance coverage could be used to provide payment for vaccine-related injuries. The operation of such a system is described in the article that follows.

A system of no-fault insurance for sports injuries was in effect in more than 40 states for the academic year 1983-1984, under the auspices of the National Federation of High School Athletic Associations. Six eligible claims were filed and all opted to accept the insurance offer rather than pursue a torts claim.*

* O'Connell, J. 1984. Personal communication, University of Virginia Law School, Charlottesville, Va.

Views

No-fault insurance for vaccine related injuries

Jeffrey O'Connell proposes an alternative insurance scheme for vaccine-injury victims

Under tort law in effect throughout most of the western world, a party injured by adverse effects from a vaccine can be paid under a legal claim only by proving the manufacturer or its product faulty. If successful, the claimant would be paid not only for his medical expense and wage loss but for his pain and suffering. But proving (a) the defendant's conduct or product faulty and (b) the monetary value of nonmonetary loss (pain and suffering) is usually so complex that many injury victims are paid (1) not at all, or (2) only a fraction of their losses in settlement, (3) only after long delay, and (4) only after lawyers on both sides are paid large amounts of insurance dollars in litigation costs.

As at least a partial solution to the problems of tort liability for personal injury, including those arising from the production and use of vaccines (especially innovative vaccines), I suggested recently[1] the following: a statute under which a defendant against any claim for personal injury—including a producer or supplier of vaccines—would be given the option of foreclosing any such claim by offering within 180 days of the claim to pay claimant's net economic loss, consisting in most cases of medical expenses and wage loss above any of the claimant's own insurance already payable to him. Payment would also include reimbursement of claimant's reasonable legal fees, if any, in addition to claimant's actual losses. Claimants would be obligated to accept such payment of their net economic loss in total satisfaction of personal injury claims except when payment for such limited amounts would be deemed by a court unconscionable. Generally speaking, then, except when a claimant's psychic losses are totally disproportionate to his dollar losses, or when defendant has acted intentionally, no further litigation would be allowed.

Note that under this proposal, no vaccine producer or supplier is required to settle a case it would not settle today. This would be a safeguard against both spurious claims and astronomical new costs.

Jeffrey O'Connell is John Allan Love Professor of Law at the University of Virginia Law School, Charlottesville, Virginia 22901, USA

A bill entailing similar features applicable to medical malpractice claims was introduced in the US Congress by Representatives Henson Moore and Richard Gephardt in the spring of 1984[2].

Problems in law

The basic problem with my proposed statute is just that—it entails passing a statute. There are three main difficulties with trying to effect reform through legislation. First, trying to get today's legislatures' attention about any issue is difficult. Secondly, to get a legislature to pass controversial legislation is all the more difficult. Especially is this so in the face of very effective lobbying opposition—which is particularly true in the USA through opposition to tort reform by powerful trial lawyer lobbies, often independently abetted by some insurers hostile or indifferent to sweeping change. Thirdly, any legislation that does emerge may well be so watered down or distorted as to ill serve the objectives originally sought. Note, for example, the experience under inadequate no-fault auto insurance laws in the USA under which large no-fault benefits are provided, but too many tort claims are also preserved, thus making for expensive and arguably even unworkable reform.

In the past, in order to avoid the pitfalls of legislation, I have proposed elective no-fault insurance whereby, before time of sale of a product or service, a seller could, at its option, commit itself to pay no-fault benefits for economic (but not non-economic) loss in the event of a resulting personal injury, with the injury victim at the same time of sale binding himself/herself to accept no-fault benefits in lieu of a tort claim. Although I have argued that such a contract, entailing a valuable *quid pro quo* for surrender of tort rights, would be upheld by the courts, others, especially practicing lawyers advising businesses and health care providers, have questioned that a potential accident victim can validly waive his or her tort claim prior to injury, even in return for a guarantee of no-fault benefits. In order to avoid such difficulties, I hereby make the following proposal:

No-fault policy

I propose an insurance policy or product warranty whereby a vaccine producer or supplier (including a health care provider) can at its option, before a vaccine is sold, bind itself to tender within 90 days of any resulting serious injury a victim's net economic loss regardless of the existence of tort liability in any particular case; in other words, regardless of whether the defendant's conduct or product was faulty. Net economic loss will include any resulting medical expenses, including rehabilitation, and wage loss beyond the victim's own collateral sources such as accident and health insurance, sick leave, etc. Benefits will be payable month by month as loss accrues. The victim and anyone with a claim based on the victim's injury, such as members of his family, will then be given an additional 90 days to accept such tender *or* to claim in tort. In other words, upon acceptance of the no-fault tender of net economic loss, the victim will be required to waive this tort claim against the tendering party. In still other words, the plan allows a potential tort defendant to make a pre-accident commitment to make a no-fault post-accident offer of a potential accident victim's net

0264-410X/84/030173-04 $03.00

economic loss conditioned upon a postaccidenet abandonment of normal tort claims.

True, by giving the victim a post-accident option of accepting or rejecting payment of net economic loss, the possibility of adverse selection arises, i.e., those with valid tort claims could choose to sue in tort and those without them to accept the tender. But those who have suffered serious injury would seem especially likely to become risk adverse in choice between certain, if limited, benefits, as opposed to the gamble of a lawsuit.

Risks to insurer

Granted, however, that because of adverse selection, such an insurance programme may entail unusual risks of unpredictable costs for an insurer. One way to soften those risks would be for the tendering party, if it chose to do so, to require the victim to waive tort claims not only against the tendering party but against third parties as well. Thus a producer of an innovative vaccine tendering benefits would gain leverage to bargain with any third party also arguably contributing to the adverse reaction (such as a supplier of material or a health care provider) for a contribution to the pool of insurance funds required to pay net economic losses. Such a contribution could be exacted at the start of the policy period with any such third party becoming an additional insured under the policy in return for an annual contribution to the policy's premiums. Or the insurance contract might call for the right of the tendering party to designate any third party at the time benefits are tendered as also benefiting from the waiver of tort claims in return for a contribution to the pool required to pay a given victim. Nor would there be a need for the tendering and third party to agree immediately on the amount of the third party's contribution under either a pre-accident or postaccident sharing agreement; rather the parties might agree to arbitrate at their convenience their respective shares of the no-fault damages or pool. The point is, however, that by such devices a vaccine producer or supplier could gain help in funding its tender from others involved in the chain of delivery.

As to non-serious injuries, such victims of vaccines are today less likely than, say, victims of slips and falls or auto accidents to pursue tort claims. Thus, from the viewpoint of a vaccine producer or supplier, it would ordinarily make less sense to have a no-fault compensation system covering small injuries since they result less often in payment from the current system. Today, even when there is relatively clear liability, if the victim's loss is only a few thousand dollars and there is no residual disability, it is often not profitable for a competent plaintiff's attorney to pursue the case. But even assuming all that to be true, here lies the virtue of the flexibility of the contract approach outlined above: the contract calling for the tender of net economic loss can be structured, at the option of the vaccine producer or supplier, to exclude smaller cases. The contract could include a dollar deductible of, say, $10 000 or even higher, such that the tender need not be made in cases of lesser amount. In addition, further restrictions in the definition of the insured event calling for a tender of net economic loss could be devised, limiting tender to, say, certain types of adverse results occurring within a given time frame. Also the obligation to tender could be to a pilot programme covering a limited period or place after which the results of the programme could be assessed.

It might be asked how a pre-accident committment to make a post-accident tender of net economic loss differs from an identical post accident offer of settlement under present law?

In effect the tender scheme herein proposed entails a sale to a potential accident victim of the insurer's capacity at common law to resist making a prompt offer to settle the claim for the victim's real losses. And the price for that surrender of defendants' right to be intransigent is to surrender the victim's of common law tort rights, perhaps coupled with a higher price for the product or service in question. If enough accident victims with serious tort claims are sufficiently risk averse to accept the tender of net economic loss, it may well be that such tender for all accident victims can be completely financed out of the surrender of tort claims, with no need for additional funds to pay for the redemption of the tenders. If not, some additional cost may be necessary, but genuine value would seem to be transmitted for any additional costs. Early 20th century employers who backed workers' compensation in return for surrender of tort rights were not at all sure what the new no-fault benefits would cost compared to tort liability, but they were willing to take the gamble that either it would cost no more or that any additional cost would be worth a far saner insurance system. At least some of their grandchildren will probably be willing to make the same bet today. Indeed, that is the case with schools covering athletic injuries under a programme such as that outlined above and described in more detail below.

If at least some defendants will be willing to sell their right to take advantage of injury victims' tort plight, what of victims' lawyers? Note the new dilemma of such lawyers. A tender made pursuant to a pre-accident commitment—before the precise causation or circumstances of any injury can be known—is not an admission of any kind. Threats to take such an offer off the table after 90 days are much more credible than with a postaccident offer not made pursuant to a pre-accident commitment.

Legal advice

Thus, plaintiffs lawyers who advise seriously injured clients to reject such a prompt but transient offer covering such essential losses could well face malpractice actions themselves if the gamble of tort litigation fails. Indeed, a virtue of marketing the insurance plan to vaccine producers and suppliers is its appeal of allowing them to strike back effectively at the legal profession's perceived harassment of health care providers and businesses through personal injury claims. Under this plan plaintiffs' lawyers will be under similar pressure they now impose on vaccine producers and health care providers: (1) to get informed consent from, or to warn, clients as to the risks of rejection of the tender, and (2) to face litigation if services lead to a bad result. Such pressures on plaintiffs' lawyers, will likely lead to acceptance of the tender of net economic loss and thus to a lessening of the strains and difficulties on vaccine producers and health care providers now resulting from legal claims by injured users of vaccines.

Note that the insurance contract should probably call for payment of claimant's counsel fees for advice with respect to the receipt of benefits for net economic loss, in addition to the claimant's losses themselves. Such a fee, not entailing all the preparation of litigating a tort action, could be based on a scale tied to the present value of the projected benefits or just to reasonable counsel fees in the knowledge that they will be much

less than those accompanying tort litigation.

Economic considerations

In essence the tender scheme assures victims of adverse vaccine reactions an option of prompt payment of their real losses. Such a programme is unlikely to result in overall burdens greater than those imposed by tort liability. This stems from the huge savings in defence costs and in eliminating payment for pain and suffering by a tender of net economic loss. In other words, if claim frequency will increase under the tender plan, average claim cost will be drastically reduced. To give some idea of such savings consider the situation in the USA in Michigan under no-fault auto insurance. Prior to no-fault there, every motorist was required to carry $20 000 of tort liability insurance. Compulsory coverage under Michigan's no-fault law pays unlimited medical expenses, plus about $72 000 in wage loss, in addition to coverage of $20 000 for those tort claims preserved under the no-fault law. All this latter insurance is provided at a cost no greater, and apparently a little less, than the cost of only $20 000 of traditional tort liability. And if a motorist is willing to accept no-fault payment only to the extent collateral sources are not paid, one can further cut the no-fault premiums approximately in half.

Scheme for sports injuries

An insurance contract based on such a pre-accident commitment to make a postaccident tender of net economic loss is in effect in 47 states for serious high school athletic injuries (those entailing medical expenses over $10 000) starting in the academic year 1983–84, under the auspices of the National Federation of High School Athletic Associations. A similar programme for college athletic injuries will likely be in effect by the academic year 1985–86. The genesis and operation of a pilot programme for high school injuries in effect in the State of Washington for the academic year 1982–83 was discussed in the Seattle Times as follows:

> A thread of irony, spun by catastrophic injuries more than seven years apart, binds Chris Thompson of Seattle and Marty Wittman of Tacoma.
>
> Thompson was left paralyzed by a football injury suffered in 1975, when he was a 15-year-old sophomore at West Seattle High School. Wittman suffered a similar fate last December (1982) when, as a 16-year-old sophomore at Curtis High in Tacoma, he was injured while competing in a prep wrestling match.
>
> Because of those injuries, their lifestyles—and their families' lifestyles—were altered drastically.
>
> But while Thompson waits and wonders about whether he ever will receive any money from a $6.5 million jury award made 17 months ago, Wittman and his family are benefiting financially from an insurance policy created because of the lawsuit Thompson filed—and won.
>
> The policy. . . was endorsed on a pilot basis for the 1982–83 school year by the Washington Interscholastic Activities Association, which was desperate to provide liability coverage for its member schools in the wake of the Thompson verdict. It was designed, said Doug Ruedlinger, the plan's . . sales agent, because "we didn't want the high-school athletic associations being litigated out of existence." Now, he said, 47 state associations have endorsed the plan for the 1983–84 school year.
>
> The plan is basically a $10 000 deductable [sic], no-fault, liability insurance policy co-authored by Jeffrey O'Connell, a University of Virginia law professor... The premium is $1 a year for each athlete covered [payable by the school].
>
> "When an injury occurs and the claim exceeds $10 000, our policy is effected," said Ruedlinger, who heads the Doug Ruedlinger [Insurance brokerage] Co. of Topeka, Kansas.
>
> Above $10,000, the plan, according to Ruedlinger, provides for such things as medical and rehabilitation expenses, transportation costs, costs of remodeling the family home to accommodate a wheelchair plus wages lost by parents who have to take time off work to help administer care to the injured athlete. Also, the policy specifies it will provide up to $300 of income a week for life, if the beneficiary has less than $300 of income from other sources. [But nothing is paid for pain and suffering]
>
> There is a catch, or what Ruedlinger called an 'if.'
>
> The coverage will go into effect only if the beneficiary. . . [and his] family agree not to file suit against the school, school district or state [athletic] association.
>
> "They don't have to sign their right to sue away," Ruedlinger said. . . "But what this plan says is that so long as you don't sue, you're covered."
>
> Wittman, hospitalized for six months following the injury and now subject to rehabilitation two days a week on an out-patient basis, was the first beneficiary of the plan. Symbolically, Ruedlinger presented the keys to a new van to Wittman last month. The van has been modified to include hand controls and a wheelchair lift.
>
> Plans for remodeling the Wittman home have been completed and submitted for approval, said Randy's mother, Mrs Fred Wittman. Until the remodeling is completed, the family is living in an apartment.
>
> Mrs Wittman and Marty, following a period of negotiation, feel the Ruedlinger Plan is acceptable.
>
> . . .
>
> Nearly eight years after [Thompson, 22, now a student at the University of Washington] was rendered a quadriplegic by the football injury and 17 months after a jury ruled the Seattle School District liable for the injury, Thompson has received no compensation. The $6.4 million verdict in King County Superior Court has been appealed to the State Supreme Court.
>
> "I'm not only bitter, I'm kind of worn out about the whole thing," Thompson said. "And there's no real end in sight."
>
> After being told of the Ruedlinger Plan, Thompson said: "I think it's excellent. It seems to address the problems."
>
> There was, of course, no Ruedlinger Plan when Thompson was injured. "He had to go to court because he had no other recourse," said Ruedlinger. And [going to] court offers no guarantees.
>
> "I can show you half a dozen articles pointing out where the parents (of catastrophically injured athletes) have gotten [nothing]" Ruedlinger said.
>
> Doug McBroom, Thompson's attorney, agrees, saying that, after efforts to settle Thompson's suit out of court failed, "We rolled the dice in the courtroom."
>
> . . .
>
> Meanwhile, Thompson waits and wonders about the direction of his future, which changed so dramatically in the fall of 1975 when his spinal cord was injured during a game against Lindbergh High in Renton. Thompson contended in his suit that the school district was liable for damages because it failed to warn players not to lower their heads when blocking and tackling.
>
> Wittman, who was injured when he was slammed to the mat by an opponent from Clover Park High, said he is planning to return for his junior year at Curtis in September.

The nature of the prolonged, expensive, agonizing litigation arising out of high school athletic injuries, as well as other injuries, and the often irreconcilably conflicting testimony over elusive, and indeed often illusive facts, is revealed by a report of a recent District of Columbia case. Carl Greene, then a seventeen-year-old football player at Anacostia High School had his

Views

nerves severed in his left arm while making a tackle in a 1974 interscholastic game. According to the Washington Post:

> Greene . . . contended that his left arm was first injured during a practice and that [Anacostia] coach Wyman Colona negligently put him in the line-up two weeks later for Anacostia's homecoming game against Spingarn High School, in which Greene's arm was permanently paralyzed.
>
> Colona contended at the trial that Greene had never reported a serious injury prior to that game.
>
> . . .
>
> Greene testified that he told Colona of "burning and tingling" in his arm after the injury during a practice. Colona testified that Greene had reported only a bruise.
>
> According to Greene, the original injury occured during a practice a few days after Anacostia played its first 1974 regular conference game. Greene, who played as a linebacker, told the jury it was nearly dark when a offensive player broke through the line with the ball, and Greene tackled him.
>
> Colona testified that he did not hold practices in the dark and that practices during the regular season did not include tackling.
>
> According to Greene, Colona placed him in subsequent games after putting extra padding on the injured [left] shoulder. Colona said the padding had been placed on the right shoulder [not the left] to protect a bruise.
>
> Greene and former teammates, as well as the team's defensive coach at the time, testified that Colona discouraged reporting of injuries.
>
> Other former players and coaches who testified for the [defendant] City said Colona had the safety of his players uppermost in his mind and never would have put Greene in the line-up had he known he was seriously injured.
>
> A medical expert who testified on Greene's behalf said the nerves in the arm could not have been severed unless Greene had been injured previously.
>
> A medical expert for the City testified that there was no indication that Greene had suffered any earlier damage to the arm.
>
> City officials said at the trial that school medical records that might have documented an earlier injury could no longer be found.

The case finally came to trial in 1983—almost nine years after the injury—and resulted in a $1.5 million verdict for Greene. The City immediately indicated it would appeal. So the accident victim's uncertainty and delay is far from over[3].

Surely an alternative insurance device makes sense for injury victims, including those from vaccines. Not a device, it will be noted, that forecloses tort rights, if the victim wishes to pursue them. But a device that gives one a choice of prompt payment of one's actual losses as they accrue *versus* the delays and uncertainties of a tort claim.

Jeffrey O'Connell

1 O'Connell, in 'Offers That Can't Be Refused', 77 Northwestern University Law Review 589 (1982); Best's Review (Prop./Cas. ed.), December, 1982 p.12.
2 Moore and O'Connell, in 'Medical Malpractice Reform', forthcoming in Louisiana Law Review
3 *Washington Post*, April 23 1983 p. 1. cols 1–2

Prepared for the Conference on 'Barriers to Vaccine Innovation,' sponsored by the Institute of Medicine, at the National Academy of Sciences, Washington, D.C., November 28–29, 1983

Appendix D

Injury Compensation Systems in the United States

This appendix briefly describes existing injury compensation systems in the United States. Vaccine-related programs include the federal government's handling of the swine influenza situation and California's Department of Health Services Immunization Reaction Program. Workers' compensation, the Federal Black Lung Act, and social security disability compensation are examples of injury-compensation programs not related to vaccines.

VACCINE INJURY

Federal Legislation

P.L. 94-380, effective on August 11, 1976, provides for an exclusive remedy against the United States "for personal injury or death arising out of the administration of swine influenza vaccine under the swine influenza program and based upon the act or omission of a program participant."[1]

The statute, its operation, and statistics regarding claims and settlements are discussed in Chapter 6.

State Legislation

State of California, Department of Health Services Immunization Reaction Program The Immunization Reaction Program provides "for care, including medical, institutional, supportive, and rehabilitative care, necessitated because of severe adverse reactions to any immunization required by state law to be administered to children under 18 years of age."[2]

Compensation for injuries resulting from the administration of state-mandated vaccines (DTP, polio, measles, mumps, and rubella) is provided through the Immunization Adverse Reaction Fund, which lies within the state treasury and is administered by the state department of health.

Any severe adverse reaction recognized by a physician as being causally related to a vaccine and requiring hospitalization in an

acute care hospital for three or more consecutive days is covered. A severe adverse reaction is described as "one which manifests itself not more than 30 days after immunization and requires extensive medical care, as defined by regulation of the department."

Benefits are terminated when no further active, medical, institutional, or rehabilitative care is required, and compensation shall not exceed $25,000.

The state may claim reimbursement from third parties for an amount equal to that reimbursed by the state. The program is directly administered by the California Childrens Service.

Under the statute, no person involved in the production or administration of a vaccine to a minor may be held liable for injury, provided the vaccine is state mandated and no willful misconduct or gross negligence is involved.

COMPENSATION FOR OTHER INJURIES

Workers' Compensation

An analysis of workers' compensation laws in the 50 U.S. states (and in Canadian provinces) has been published by the U.S. Chamber of Commerce.3 Workers employed by the federal government, longshoremen and harbor workers, and those employed by the District of Columbia are covered by separate legislation. The aims of this body of legislation have been summarized by the Chamber of Commerce:

> In essence, workers' compensation laws hold that industrial employers should assume costs of occupational disabilities without regard to any fault involved. Resulting economic losses are considered costs of production—chargeable, to the extent possible, as a price factor. The laws serve to relieve employers of liability from common-law suits involving negligence.[3]

Six basic objectives underlie workers' compensation laws. They:

1. Provide sure, prompt, and reasonable income and medical benefits to work accident victims, or income benefits to their dependents, regardless of fault;
2. Provide a single remedy and reduce court delays, costs, and work loads arising out of personal injury litigation;
3. Relieve public and private charities of financial drains—incident to uncompensated industrial accidents;
4. Eliminate payment of fees to lawyers and witnesses as well as time-consuming trials and appeals;
5. Encourage maximum employer interest in safety and rehabilitation through an appropriate experience-rating mechanism; and
6. Promote frank study of causes of accidents (rather than concealment of fault)—reducing preventable accidents and human suffering.[3]

Most jurisdictions require employers to obtain insurance or prove financial ability to self-insure, i.e., to carry their own financial risk. Operation of the workers' compensation system was evaluated in 1972 by the National Commission of State Workmens Compensation Laws and in 1976 by the Inter-Agency Workers Compensation Task Force. Both groups reaffirmed the fundamental objectives of the system but recommended various operational changes to ensure that the laws lived up to their potential. Both Commission and Task Force rejected replacement of state programs with one federal program. Legislation introduced into the U.S. Congress to achieve "minimum standards" has never received sufficient support to move beyond the committee level.

Extensive information on the coverage of the laws, benefits provided, administration of the laws, and setting of premium rates are presented in the Chamber of Commerce analysis and in a brief summary prepared by the American Federation of Labor and Congress of Industrial Organizations (AFL-CIO).[3,4]

The Department of Health and Human Services estimated that employers spent slightly more than $22.9 billion in 1981 to insure or self-insure their work-injury risks, or just under $2 per $100 of payroll.[3]

Questions have been raised regarding the appropriateness of existing legislation—predominantly designed to deal with traumatic injury—for dealing with disease, especially chronic or delayed disease.[5,6] In relation to the operation of the laws, a senior official in the AFL-CIO stated:

> The AFL-CIO has long supported the traditional workers' compensation concept of exclusivity vis-a-vis the workers' employer. The certainty of the compensation payment, weighed against the uncertainty of traditional common law actions and defenses, has been the cornerstone of workers' compensation systems for more than 70 years.
>
> There are good reasons for this approach. Experience has shown that where workers have to seek redress against their employers in the courts, the time consumed has been extensive, the outcome uncertain and the awards, when they come, often net the worker very little after lawyer fees and costs. The employer also benefits by knowing the extent of his or her liabilities through the no-fault system.
>
> The AFL-CIO would urge one exception to this approach. Companies should not have the shelter and protection of exclusive remedy when occupational illnesses related to toxic substances are the result of willful or intentional misconduct. An employer who knowingly and/or willfully exposes workers to dangerous substances or dangerous conditions should forfeit any entitlement to an exemption from common law tort suits. The severity of the occupational disease problem in the United States requires that every means of encouraging preventive action be employed—including the deterrent effect of possible legal action.[7]

This testimony also supported replacement of the state workers' compensation laws with federal legislation. The AFL-CIO official said that few workers severely disabled by occupational disease receive benefits from the state systems, and when they do, it is usually only by litigation.[7]

Black Lung Compensation

As described in the U.S. Chamber of Commerce document:[3]

The Federal Black Lung Act (Title IV of the federal Coal Mine Health and Safety Act of 1969, as amended in 1972, 1978, and 1981) provides benefits for total disability or death caused by respiratory illness attributable to coal mining (black lung disease). The Act is administered by the Division of Coal Mine Workers in the U.S. Department of Labor's Office of Workmen's Compensation Programs and by the Social Security Administration.

Effective January 1, 1984, monthly benefits range from $315.60 to $631.10, computed at 137-1/2 percent of the minimum monthly pay for federal employees, plus an allowance for dependents equal to 50 percent, 75 percent, or 100 percent of the basic benefit, for 1, 2, or 3 or more dependents, respectively. Beneficiaries also receive an annual cost-of-living increase.

A total of $10 billion in black lung payments have been made to 500,000 claimants from 1969 through 1980.

A Black Lung Disability Trust Fund, financed by an excise tax on coal production, was set up by the 1978 amendments to pay claims where the last employment was prior to 1970 or where no responsible coal mine operator has been identified. The fund was in deficit by $22.2 billion as of January 31, 1984, despite 1981 amendments that doubled the coal tax and revised eligibility criteria in an effort to make the fund solvent.

Social Security Disability Compensation

As described in the U.S. Chamber of Commerce document:[3]

The federal Social Security Disability program pays benefits on behalf of disabled workers under age 65 whose disability is expected to last 12 months or result in death. A worker becomes eligible after a minimum period of employment covered by Social Security, measured in calendar quarters. There is a 5-month waiting period.

Cash benefits are payable monthly based on wages in covered employment, plus allowances for spouse and children. Effective January 1, 1984, the maximum is $854 for an individual, family maximum $1,281. Cost-of-living increases are payable effective each June.

Benefits are paid out of the Disability Trust Fund, financed from the federal Social Security tax.

Combined Social Security Disability and workers' compensation benefits may not exceed 80 percent of "average current earnings" prior to disability. The Omnibus Budget Reconciliation Act of 1981 requires that Social Security disability benefits supplement workers' compensation unless state law provided for a reverse offset on or before February 18, 1981.

REFERENCES

1. United States Congress. 1976. P.L. 94-380, National Swine Flu Immunization Program of 1976. Effective August 12, 1976.
2. State of California. 1977. California: Health and Safety Code, Division 1, Part 1, Chapter 2, Article 14.5 (Health and Safety Code Section 429.35-429.36).
3. Chamber of Commerce of the United States. 1984. Analysis of Workers Compensation Laws: 1984. Washington, D.C.: Chamber of Commerce of the United States.
4. American Federation of Labor and Congress of Industrial Organizations. 1984. Workers Compensation and Unemployment Insurance Under State Laws, January 1, 1984. Washington, D.C.: AFL-CIO.
5. Samuel, H. 1984. Testimony before the Subcommittee on Labor, Committee on Labor and Human Resources, U.S. Senate, May 21, 1984, Washington, D.C..
6. Samuel, H. 1984. The Broken Promise—Certainty, Speed, and Adequacy. Presented at the International Conference on Disability Compensation and Occupational Disease, June 7, 1984, New York, New York.
7. Young, K. 1984. Testimony before the Subcommittee on Labor, Committee on Labor and Human Resources, U.S. Senate, May 21, 1984, Washington, D.C.

Appendix E

Vaccine-Injury Compensation in Other Countries

This appendix describes vaccine injury compensation programs in Denmark, the Federal Republic of Germany, France, Japan, Switzerland, and the United Kingdom. The information was obtained either from foreign government responses to a questionnaire designed by the committee, or from information presented in a working paper from a study titled "Comparison of Compensation Programs for Vaccine Injury," conducted by Wendy K. Mariner of the Harvard University School of Public Health. Professor Mariner's assistance is gratefully acknowledged by the committee.

DENMARK

Compensation for Individuals Injured by Vaccines Act; Lovtidende, March 8, 1978, No. 82, pp. 305-306

This act of 1978 provides "compensation to a person or dependents for damages which in a reasonable probability may be considered caused by a vaccination performed in Denmark against a disease included in the Free Vaccination Against Certain Diseases Act." Characteristics of the system include:

Vaccines covered: whooping cough, diphtheria, tetanus, polio, and tuberculosis.

Compensable injuries: injuries that result in deterioration or permanent loss of working ability, or death.

Eligibility requirements: not specified in statute.

Type of compensation: medical expenses for treatment, rehabilitation aids, etc.; compensation for loss of working ability and "lasting harm"; interim benefits for dependents; and compensation for loss of provider.

Amount of compensation: not specified in statute but may be either lump sum or periodic payments.

Exclusivity: nonexclusive; civil court remedy available independently.

State subrogation: not specified in statute.

Administrative entity: Danish Sikringsstrylrelse of the National Social Security Office.

Source of funds: general revenue.

Claims procedures: claims presented to Sikringsstrylrelse. All physicians required to report probable injuries. The decision of the Social Security Office may be brought to the Board of Social Appeal.

Proof of causation: probable consequence.

Between 1978 and 1983, 10 claims were made: 3 for smallpox, 1 for whooping cough, 1 for BCG, one for DTP, 1 for tetanus, and 1 for polio. Six were approved; those not approved included 1 for smallpox and the 3 for whooping cough.

FEDERAL REPUBLIC OF GERMANY

Law on the Prevention and Control of Communicable Diseases in Man Sections 51-62, December 18, 1979. Bundesgesetzblatt, Part I, No. 75, pp. 2262, December 22, 1979, Corrigendum; Bundesgesetzblatt, Part I, No. 6, p. 151, February 22, 1980

Legislation pertaining specifically to compensation for vaccine injury is included in a larger statute that involves the control of infectious disease (the Federal Communicable Diseases Act). Many of the provisions in the legislation regarding administrative procedures are dictated by another statute, the Federal Social Assistance Law. The compensation program is administered by authorities in each Land, the political subdivisions in the Federal Republic of Germany.* Characteristics of the system include:

Vaccines covered: mandatory and recommended vaccines.

Compensable injuries: adverse postvaccinal effect, defined as any impairment to health exceeding usual extent of a postvaccinal reaction and involving a live virus vaccine; impairment to health resulting from contact with another person vaccinated with a live virus vaccine; impairment to health resulting from accidents during traveling to or from treatment.

Eligibility requirements: compensation is provided for a compensable injury resulting from a vaccine that is required by law or recommended by competent authority; ordered pursuant to the Act; or required for reentry into country.

Type of compensation: social assistance for health and economic consequences of injury or death benefit to survivors of victim of vaccine injury.

Amount of compensation: pensions to be uniform with Federal Social Assistance Act.

* Mariner, W. 1985. Working Paper No. 1. "Preliminary Typology of Vaccine Compensation Legislation." From the study "Comparison of Compensation Programs for Vaccine Injury." Harvard School of Public Health, Boston, Mass.

Exclusivity: not indicated in the statute.

State subrogation: state subrogated to rights of victim against third parties for the amount of social assistance provided.

Administrative entity: Lands or administrators of the Federal Social Assistance Act.

Source of funds: pensions shall be paid by authorities responsible for implementing the Federal Pension Law. Local responsibility is determined by Land government authorities.

Claims procedures: according to Federal Social Assistance provisions, with some variations.

Proof of causation: probable cause.

FRANCE

Public Health Code; Article L.10-1, Law No. 64-643 of July 1, 1964, as amended by Law No. 75-401 of May 26, 1975, Journal Officiel de la Republique Francaise, July 2, 1964, pp. 5762-5763, May 27, 1975, p. 5267. The entire text of the law states:

> Without prejudice to actions that could be instituted in accordance with the common law, the compensation of all damage directly ascribable to a mandatory vaccination administered in accordance with the [public health] code is paid for by the State.
>
> Up to the amount of the indemnity it has paid, the State is, if applicable, subrogated to the rights and actions of the victim against those responsible for the damage.

Characteristics of the system include:

Vaccines covered: mandatory pediatric or adult vaccines administered in accordance with public health law ("accordance" elsewhere includes only immunizations given by a physician or, in some cases, a midwife).

Compensable injuries: all damage directly attributable to vaccination.

Eligibility requirements: as specified by type of vaccine (mandatory) and circumstances of immunization (in accordance with Public Health Code).

Type of compensation: not specified in statute.

Amount of compensation: not specified in statute.

Exclusivity: nonexclusive as expressly stated in statute.

State subrogation: France may succeed to the rights of the injured party against any third party liable for damages to the extent that it has paid compensation to the injured party.

Administrative entity: tribunals resolve disputes over claims.

Source of funds: not specified in statute.

Claims procedures: not specified in statute.

Proof of causation: not specified in statute, but probably according to civil law liability rules.

JAPAN

The Preventive Vaccination Law: the Vaccination Act of June 30, 1948, 68 Ministries of the Treasury and Welfare

The Preventive Vaccination Law was amended in 1976 to provide relief for injury in cases in which, "through no fault of doctors or other personnel, extremely rare cases of unavoidably [sic] abnormal side effects result from preventive vaccination." Characteristics of the system include:

Vaccines covered: all vaccines for diseases specified in Japan's Preventive Vaccination Act and TB Central Law: pertussis, diphtheria, poliomyelitis, measles, rubella, tuberculosis (BCG), influenza, Japanese B encephalitis, Weil's disease, cholera, and smallpox.

Compensable injuries: satisfaction of one of the following: an unusual reaction caused (or suspiciously caused) by vaccination; sequelae resulting from a reaction caused (or suspiciously caused) by vaccination; or death resulting from a reaction caused (or suspiciously caused) by vaccination.

Eligibility requirements: injury or death as a result of mandatory vaccination.

Type of compensation: compensation includes medical and/or funeral expenses, disability pension, annuity for person caring for disabled individual, and a death benefit.

Amount of compensation: no specified limitation.

Exclusivity: nonexclusive; tort law remedies available.

State subrogation: not indicated in statute.

Administrative entity: committee appointed by Minister of Health and Welfare. Local governments also may have judgment committees. This would enable an injured person to receive compensation from local and/or national government.

Source of funds: national treasury (50 percent), prefectures (25 percent), and municipalities (25 percent).

Procedure for filing claims: claims are adjudicated by a committee to determine whether a causal relationship exists between injuries and vaccinations. The committee consists of experts from the fields of pediatrics, psychopathology, neuropathology, and immunology.

Proof of causation: judgments are based on available clinical information, interval between vaccination and onset of illness, and report in literature of similar adverse reactions.

From 1977 to 1981 the following claims were made:

- diphtheria -1
- diphtheria, tetanus -13
- diphtheria, pertussis, tetanus -46
- polio-15
- measles -33
- rubella -1

- influenza -68
- Japanese encephalitis -32
- tuberculosis (BCG) -17

Of these 226 cases, 167 were approved, 45 denied, and 14 were pending as of 1983.

SWITZERLAND

Federal Law on the Control of Communicable Diseases in Man, December 18, 1970, 818.101

Swiss Federal Law provides for cantons (Swiss political subdivisions corresponding to states in United States) to establish compensation for injuries resulting from either required or officially recommended immunizations. Cantons establish their own procedures to carry out this federal mandate. Compensation may be denied if it is available from another source.* Characteristics of the system include:

Vaccines covered: mandatory or officially recommended (by cantons) vaccinations.

Compensable injuries: all lesions arising subsequent to vaccination (excluding self-inflicted injury).

Eligibility requirements: not specified other than by type of vaccine (mandatory or officially recommended).

Type of compensation: not specified in statute but does indicate that compensation may be denied if it is available from another source.

Amount of compensation: not specified in statute.

Exclusivity: not indicated in statute.

Administrative entity: cantons establish procedures to administer program.

Source of funds: funds are provided by cantons, which receive a federal subsidy of 20 to 25 percent of their expenses.

Claims procedures: not specified in statute.

Proof of causation: not specified in statute.

UNITED KINGDOM

Vaccine Damage Payments Act 1979; 1979 C. 17; Current Law Statutes Annotated, 1979, pp. 17-17/13

* Mariner, W. 1985. Working Paper No. 1. "Preliminary Typology of Vaccine Compensation Legislation." From the study "Comparison of Compensation Programs for Vaccine Injury." Harvard School of Public Health, Boston, Mass.

Characteristics of the system include:

Vaccines covered: vaccines for the following diseases: diphtheria, tetanus, whooping cough, poliomyelitis, measles, rubella, tuberculosis, smallpox (if received prior to its discontinuance on August 1, 1971), and any other disease specified by the Secretary of State.

Compensable injuries: injuries from vaccination resulting in severe disability (80 percent or more as described by established rules).

Eligibility requirements: persons who incur severe disability after vaccination against specified diseases; as the result of a vaccination given to his or her mother before his or her birth; or as the result of a disease contracted through contact with a vaccinated person if contact occurred after 4 days but before 60 days following vaccination and the disabled person was caring for or was being cared for by the vaccinee. The requirements also state that the person must have received the vaccination in the United Kingdom or the Isle of Man on or after July 5, 1948 (before August 1, 1971 for smallpox); was less than 18 years of age (except polio and rubella), or was vaccinated during an outbreak; or was more than 2 years of age on date claim was made, or died after May 7, 1978 and was more than 2 years of age when death occurred.

Type of compensation: flat-rate, lump sum; not considered compensation for damages incurred but rather a benefit.

Amount of compensation: £10,000.

Exclusivity: injured persons may pursue civil remedy. However, amount of any payment received by compensation scheme will be deducted from court award. No claim considered if payment was made prior to passing of statute. For claims denied by tribunals, an application for reconsideration may be made within 6 years of date of determination.

State subrogation: see above.

Administrative entity: Department of Health and Social Security (DHSS) under Secretary of State.

Source of funds: public funds.

Claims procedures: claims must be made within 6 years of the latter of these dates: the date on which the disabled person reached the age of 2, the vaccination date, or May 9, 1978. Claimant must provide information and evidence necessary to determine claim and must undergo a medical examination by a physician appointed by the Secretary of State or by a tribunal to determine relationship between disability and vaccine (claims are adjudicated by DHSS physicians). Claims denied at stage 1 are referred to a vaccine damage tribunal appointed by the Secretary of State that consists of a lawyer as chairperson and two medical practitioners. Determinations require a majority tribunal vote and hearings are public unless otherwise excepted. Tribunal decision sent in writing to claimant. Any person making a fraudulent claim is liable for £1,000 fine (£400 in Isle of Man).

Proof of causation: determined on "balance of probability."

As of early 1983, 2,868 claims had been received. Most of these were related to vaccinations containing a pertussis element, usually in combination with one or more other vaccines. Of these claims, 370 awards were granted at stage 1 for the following: 165 against DTP, 64 against DTP and polio given concurrently, 63 against smallpox, 23 against measles, and 55 against other vaccines or combinations of vaccines.

Appendix F

Proposed Vaccine-Injury Compensation Systems

This appendix summarizes a range of proposed vaccine injury compensation schemes, including the revised National Childhood Vaccine-Injury Compensation Act (1985) introduced by Sen. Paula Hawkins (S. 827, 99th Congress);[1] the National Childhood Vaccine-Injury Compensation Act (1985) introduced by Rep. Edward R. Madigan (H.R. 1780, 99th Congress);[2] the American Medical Association's (AMA) proposal for a National Pediatric Vaccine-Injury Compensation Act, 1984;[3] a 1983 proposal by the American Academy of Pediatrics;[4] the proposed Vaccine-Injury Compensation Act of 1983, introduced in the Senate by Lloyd Bentsen;[5] model state legislation proposed by the AMA in 1980;[6] and a plan to create a Federal Immunization Insurance Corporation.[7]

Because the first two proposals were made public just prior to the printing of this report, time was not available for comprehensive analysis. The summaries below were derived from materials prepared by the offices of Sen. Hawkins and Rep. Madigan, respectively.

S. 827—NATIONAL CHILDHOOD VACCINE-INJURY COMPENSATION ACT

This bill is a revised version of the National Childhood Vaccine-Injury Compensation Act of 1983 (S. 2117, H.R. 5810, 98th Congress) which was introduced by Sen. Hawkins and Rep. Henry Waxman but was not enacted.[8] It would establish a no-fault, national program to compensate individuals who suffer permanent adverse reaction to any of the seven mandated childhood vaccines. This program would be an alternative to compensation through litigation.

The bill would establish a nine-member advisory commission on childhood vaccines to be comprised of three members who are health professionals, including two pediatricians; three members who are from the general public, including two who represent parents of children injured by vaccines; and three members of the field of law. The advisory commission would advise the Secretary of Health and Human Services (HHS) on the implementation of the program; recommend changes in the Vaccine Injury Table; recommend ways to improve the safety, efficacy, and supply of vaccines; and recommend changes in surcharge and research priorities.

The bill would require each health care provider administering vaccines to record and make available to patients information about the date of vaccination, the vaccine manufacturer, the lot number, and serious events occurring within 30 days after vaccination. It also would require each health care provider who administers a vaccine and becomes aware of a listed reaction occurring within a designated period after vaccination to enter all relevant information on the patient's permanent medical record and report it to the Centers for Disease Control.

Under this bill, the Secretary of HHS (after conducting broad-based studies) would be required to issue regulations regarding circumstances in which a vaccine should not be administered or should be delayed beyond its normal time of administration; and the groups, categories, or characteristics of potential recipients who may be at significantly higher risk of adverse reactions. This information would be disseminated to physicians, professional health associations, and state and local governments.

The bill also would require the Secretary to develop parent information materials containing information on the frequency, severity, and potential risks of both the vaccine and the disease to be prevented by the vaccine. The materials should include information regarding the symptoms and reactions to vaccines that should be reported to physicians, precautionary measures that should be taken to reduce the risk of adverse reactions, when and how and to whom parents can report any major adverse reactions; and a summary of relevant state and federal vaccination laws, including information about the availability of the National Vaccine-Injury Compensation Program.

Other Major Points

The proposed legislation contains several other major points:

1. Compensation would be limited to vaccine reactions resulting in complications or residual effects lasting at least 1 year, or in death.
2. The claimant would be required to make a binding election between the tort system and the compensation system at the time of filing of the lawsuit or compensation claim. In the case of a current lawsuit, parties would have 2 years after enactment to decide whether to drop their lawsuit in favor of the administrative remedy.
3. A manufacturer could not be held liable in a lawsuit solely because of failure to warn the parent directly. (This would not affect the manufacturer's duty to warn the health care provider or the health care provider's duty to warn the patient.)
4. HHS would be authorized, but not required, to provide reinsurance, pooling assistance, and even direct insurance to vaccine manufacturers. HHS could do this only if it found that adequate insurance was not available from the private sector and determined that the insurance arrangement would not undermine the incentives for development of safer products.
5. The administrative system would have a 270-day deadline to

reach a decision after the date of filing, and any appeals would be required to be briefed, argued, and decided on an expedited schedule.

6. The bill would establish a National Vaccine-Injury Compensation Trust Fund. The fund initially could borrow from general revenues, but within 18 months of enactment, the Secretary of HHS would be required to establish a uniform or variable annual surcharge on the manufacturer of each vaccine covered by the act. The Secretary could consider a variety of factors in determining the amount of each surcharge, including the amount of compensation paid resulting from injury or illness associated with each vaccine.

Revisions

Major differences between the new bill and S. 2117 include: the nature of the vaccine injury table; the timing of the election of remedies; the treatment of the statutory duty to warn; the institution of a reinsurance provision; the setting of a deadline for the compensation decision; the range of permissible items for compensation; the authority for citizen suits; the mandate for a review of manufacturers' warnings; the authority to fund facilities for the adult multiply handicapped; the procedures for reporting of adverse reactions; the provisions for recordkeeping and reporting of test results by manufacturers; and the authority of the Food and Drug Administration to recall vaccines and other biologics when warranted.

H.R. 1780—THE NATIONAL CHILDHOOD VACCINE-INJURY COMPENSATION ACT

Under the bill introduced by Rep. Madigan and Rep. James Broyhill, all claims for vaccine-related injuries would have to be filed with the Secretary of HHS, who would arrange for the convening of a hearing panel. Respondents, including both manufacturers and health care providers, would be asked to make an irrevocable election to participate in the hearing and be bound by any award. Private hearing panels, chosen by the parties from lists of experts compiled by the Secretary, would consider all claims. Hearing panels would determine whether the alleged injury was caused by a covered vaccine and would calculate the amount of damages. Respondents would pay all costs. The claimant must go to the panel first; if the respondent refuses to go, the claimant can sue in court and no ceilings would apply.

Compensation

Hearing panels would enter a binding award compensating claimants for:

- actual and projected out-of-pocket expenses, including costs of medical and custodial care and special education and therapy
- actual and projected losses of earnings

- pain and suffering
- reasonable attorneys' fees

Compensation would be capped at $1 million per claim, with $100,000 of this available for pain and suffering.

Claimants who accepted the hearing panel decision could receive immediate compensation from respondents (jointly and severally); disputes about their appropriate shares of the award would be handled in separate litigation for contribution or indemnity, without delaying payment to the claimant.

Claimants could reject hearing panel decisions for any reason or for no reason. Claimants who rejected hearing panel decisions could file civil actions for damages, but they would have to meet the standards of liability and proof set by otherwise applicable state or federal laws. The hearing panel's decision would be admissible in evidence. The statutory ceilings on awardable compensation would apply to any such actions, but they would not apply with respect to respondents who had declined to participate in the hearing panel proceedings.

AMA'S PROPOSED NATIONAL PEDIATRIC VACCINE-INJURY COMPENSATION ACT

The purposes of this proposal are:

1. To assure the continued development and availability of pediatric vaccines;
2. To assure the continued participation of physicians and other qualified persons in the administration of pediatric vaccines;
3. To encourage and assure appropriate immunization of all children;
4. To promote the identification and equitable compensation of persons severely injured by reactions to pediatric vaccines; and
5. To provide assurances to parents and their children and to producers and providers of vaccines, that the public at large, which benefits so greatly from the prevention of disease and disability, will accept responsibility for equitable payment of the cost of caring for those to whom government-mandated immunization results in severe disease or disability [Title XXI, Section 2101].

To meet these ends, the following would be established:

- National Vaccine-Injury Advisory Committee
- Office of Vaccine-Injury Compensation
- Vaccine-Injury Compensation Committee
- National Vaccine-Injury Compensation Trust Fund

National Vaccine-Injury Advisory Committee This committee, comprised of 15 members appointed by the Secretary of HHS from the fields of pediatrics, neurology, epidemiology, public health, and related disciplines, would prepare and revise as necessary a list of

severe adverse reactions (defined as "any injury from a vaccine which results in the long-term disability or death of the vaccine recipient"), and would designate clinical criteria for severe adverse reactions.

Office of Vaccine-Injury Compensation Directed by an appointee of the Secretary of HHS, this office would review claims for determination of a compensable injury. A compensable injury is one that results from a severe adverse reaction to a mandatory pediatric vaccine or that is contracted from a child who received live polio vaccine. The clinical criteria must be in accordance with those designated by the National Vaccine-Injury Advisory Committee. To be eligible for compensation, the claimant must satisfy the requirements above and file a claim within 2 years of the date of immunization.

Amount of compensation shall be provided for:

a. reasonable expenses incurred or likely to be incurred for medically necessary products, services, and accommodations reasonably needed for medical care, training, and other remedial treatment and care of an injured individual, including expenses for a procedure or treatment for rehabilitation and rehabilitative occupational training if the procedure, treatment, or training is reasonable and appropriate for the particular case, the expenses are reasonable in relation to the probable rehabilitative effects and the compensation benefits otherwise payable, and it is likely to contribute substantially to rehabilitation, even though it will not enhance the injured individual's earning capacity;
b. economic loss to persons eligible . . . from any work that the injured individual was unable to perform due to the individual's having been injured; and
c. noneconomic, general damages arising from pain, suffering, inconvenience, physical impairment, mental anguish, emotional pain and suffering, and all other noneconomic, general damages, except that no person shall receive such damages in an amount in excess of $100,000, and any such damages shall be payable only to the injured individual for his or her pain and suffering [Title XXI, Section 2105].

Vaccine-Injury compensation Committee This committee, comprised of 15 members appointed by the Secretary of HHS from the fields of actuarial science, economic analysis of financial loss from personal injury or death, and evaluation of medical impairment and disability, would prepare and revise as necessary a methodology for use by the Office of Vaccine-Injury Compensation to determine appropriate amounts of awards. The method would incorporate appropriate regional cost-differentials and differences in individual need.

National Vaccine-Injury Compensation Trust Fund This fund would be established within the Treasury of the United States, which would appropriate any necessary funds for the payment of awards.

This proposal represents an exclusive remedy—under no conditions would a person eligible for compensation be entitled to pursue civil

action against any party involved in the manufacture, distribution, or administration of the vaccine. The Secretary of HHS may bring such civil action against any of the above parties in cases of probable negligence. All damages may be recovered (whether or not previously paid to the claimant) including costs of litigation.

Claimants denied compensation may appeal to the U.S. Court of Appeals for District of Columbia Circuit. This appeal must be filed within 60 days of the Secretary's ruling and the Secretary must be notified of such action.

A PROPOSAL BY THE AMERICAN ACADEMY OF PEDIATRICS

Need for Legislation to Establish a Federal Compensation Program for Vaccine-Related Injuries in Childhood Immunization Programs

The proposed legislation, which was never enacted, suggested creation of a national program to compensate for injuries from vaccines used in state or federal childhood immunization programs. This would have included an incidence of contraction of polio by an adult due to contact with a child recently vaccinated against polio.

The system would have compensated for medical and rehabilitative costs, projected loss of income, and custodial and special education costs in cases of major adverse reactions manifested within a designated period of time and identified as vaccine related. No compensation would have been provided for pain and suffering, or for punitive damages.

The legislation would have specified which vaccines and adverse reactions would be compensable, but the Secretary of HHS would have been authorized to modify these lists when appropriate. Appropriate time limitations also would have been established.

The compensation system would have been optional, but the claimant would not have been allowed to seek award through both the compensation system and the existing judicial system.

This program would have considered only those cases not involving negligence. It would have considered as non-negligent inadequate warning of risks or lack of informed consent. The program would not have considered cases involving negligence in the manufacture or administration of vaccine. Such cases would have had to seek tort remedy.

Under the proposed legislation, the Secretary of HHS would have appointed a National Vaccine-Injury Compensation Commission or designated an existing body to adjudicate claims within 180 days of the date on which the claim was filed.

The procedure for making a claim would have involved documentation of the following: (1) that the claimant had received a vaccine covered under the compensation system; (2) the date of vaccine administration and date of manifestation of adverse reaction; and (3) that the claimant had suffered a major adverse reaction on the list (the claimant would have had to demonstrate a causal connection between vaccine and an adverse reaction not specified on the list).

The Secretary would have been responsible for final review of decisions by the commission, as well as prescribed rules and regulations concerning all aspects of its operation. Claimants who were denied compensation would have been able to appeal within 60 days of notification through the U.S. District Court. The appeal would have involved only the court's determination that the commission was acting lawfully.

Funds for operating the system would have been generated from a dosage surcharge on vaccines assessed against vaccine manufacturers. Surcharges would have been developed and implemented by the Secretary of HHS, who periodically would have reviewed and revised the amount of surcharge.

PROPOSED VACCINE-INJURY COMPENSATION ACT OF 1983

This proposed legislation, which was never enacted, would have required that the President of the United States design a government vaccine-injury program to compensate victims seriously injured by government-coordinated or government-sponsored vaccination programs. The program would have ensured that victims of episodic or mandated childhood vaccination programs would receive compensation.

It was proposed that prior to establishing a compensation program, the President would conduct an evaluation of the following issues: "(1) vaccines to be covered; (2) injuries to be covered; (3) type and size of compensation to be provided; (4) administrative structures; and (5) the relationship of this program with existing compensation options, such as lawsuits, private insurance, government medicare, medicaid, and social security programs, or state programs."

The resulting vaccine-injury compensation program would not have involved the creation of a new federal agency or required additional personnel. It would have ensured that victims of episodic vaccination programs were eligible for compensation and that participants in all childhood vaccination programs were eligible for compensation.

The proposed options would have included the imposition of a fee on vaccines to create a compensation trust fund. The program would have ensured that state governments participated in the administration of, and if appropriate, the expense of the compensation program.

AMA'S PROPOSED MODEL STATE LEGISLATION ON VACCINE COMPENSATION

This legislation, proposed in 1980, was intended to "provide some compensation for costs of care, including medical, institutional, supportive, and rehabilitative care, necessitated because of adverse reaction to any immunization mandated by state law where the person would be otherwise uncompensated for such vaccine-related injuries because of lack of liability of the manufacturer and person administering the vaccine." It was never enacted, primarily because the states showed little interest.

According to the proposal, a state's department of health would have compensated past, present, and future costs of a vaccine-related injury manifested within 90 days after vaccination, through an Immunization Adverse Reaction Fund established within the state's treasury. Reasonable legal expenses resulting from a successful administrative action pursuant to this act also would have been compensated.

A person filing a claim according to the established procedure would have received a hearing before the department of health, which would have determined eligibility based on whether the person would otherwise have been compensated. Any compensation received from the fund would have been offset by existing insurance entitlements.

This would not have been an exclusive remedy for persons sustaining vaccine-related injuries. Injured parties could have been compensated through tort awards as well. A determination by the department of health would not have been admissible in any court action. The state could have claimed reimbursements from third parties for the amount of compensation.

PROPOSED FEDERAL IMMUNIZATION INSURANCE CORPORATION

Prepared by Hans H. Neumann, M.D., and endorsed by the Connecticut Public Health Association in 1977, this proposal was intended to create a Federal Immunization Insurance Corporation that would have provided funds to compensate persons who suffered permanent injuries from mandatory or recommended immunizations. A summary of the suggested legislation, written by the bill's author, is presented.

> It is proposed to create a Federal Immunization Insurance Corporation [FIIC] whose purpose it shall be to insure the public against permanent adverse effects from immunizations and to provide specific benefits under this Act.
>
> The management of the fund shall be vested in a board of directors consisting of three members: one shall be a physician and a member of the Centers for Disease Control, one shall be an attorney, and one shall be appointed by the Secretary of HEW from a consumer group.
>
> Every vaccine manufacturer shall be entitled to apply to become a member of the FIIC and shall contribute a percentage of the listed price of each lot of vaccines released for distribution. Any manufacturer of vaccines may be approved or disapproved by the board for specific vaccines.
>
> All products approved for coverage should include a reference to membership in the FIIC on the label of each vial of vaccine.
>
> Through the regulations of the FIIC, the function of providing benefits for any permanent damage from approved vaccines covered under this act shall be assumed by the U.S. government and compensation shall be provided for such damages, under a predetermined schedule.

Notwithstanding the assumption of this function by the U.S. government, the government itself may have legal recourse to claim reimbursement from the manufacturer or providers of the vaccine in cases of negligence [7]

REFERENCES

1. U.S. Senate. 1985. S. 827. National Childhood Vaccine-Injury Compensation Act. Congressional Record, April 2, 1985, S3843-S3847.
2. House of Representatives. 1985. H.R. 1780. National Childhood Vaccine-Injury Compensation Act. Congressional Record, March 27, 1985, H1587-H1589.
3. American Medical Association. 1984. Draft Federal Legislation, Vaccine Injury Compensation. Chicago, Ill.
4. American Academy of Pediatrics. 1983. Need for Legislation to Establish a Federal Compensation Program for Vaccine-Related Injuries in Childhood Immunization Programs. Evanston, Ill.
5. U.S. Senate. 1983. S. 1987. Vaccine-Injury Compensation Act of 1983. Congressional Record, October 21, 1983, S14377-S14378.
6. American Medical Association. 1980. Model State Legislation on Vaccine Compensation. Chicago, Ill.
7. Neumann, H.H. 1984. Personal communication, Wilton, Conn.
8. U.S. Senate. 1983. S. 2117. National Childhood Vaccine-Injury Compensation Act. Congressional Record, Nov. 17, 1983, S16620-S16621. U.S. House of Representatives. 1983. H.R. 5810.

Appendix G

Mechanisms Used in Other Countries to Ensure Vaccine Supply

Country	Extent of Government Involvement
Belgium	The Office Vaccinogene within the Ministere de la Sante Publique et de la Famille is the only government-sponsored establishment producing vaccines. It produces only smallpox vaccine, which, at present, is used to maintain emergency stocks for Belgium. While the government has no financial holding in any vaccine manufacturer, it does maintain adequate supplies of the following vaccines by contracting with producers and importers: live polio (oral); tetanus adsorbed; diphtheria and tetanus adsorbed (DT); diphtheria, tetanus, and pertussis adsorbed (DTP); measles, mumps, and rubella (MMR), or combinations thereof; yellow fever vaccine (for international travel); and cholera and typhoid (for Army and international travel). The Ministry of Health also grants funds to the Institut Pasteur du Brabant for production of DTP, cholera, typhoid, and Bacillus Calmette-Guerin (BCG) vaccines.
Canada	The government has minority shareholding in Connaught Laboratories, Inc. through the Canadian Development Corporation. This shareholding will be returned to the private sector in the future. The government is not involved in company decision making.
Denmark	The National Serum Institute, which provides free vaccination against whooping cough, diphtheria, polio, tetanus, and tuberculosis, receives funds from the government treasury. The Institute produces most of the vaccines and imports a small amount. The Institute is currently the only vaccine manufacturer in Denmark.

Federal Republic of Germany	The government has no financial involvement in any vaccine production enterprise. In the past, Land Vaccination Agencies produced smallpox vaccine, but these were closed with the discontinuance of smallpox vaccination.
France	Rhone-Poulenc, a nationally-owned holding company, has a 51 percent interest in Institut Merieux. In Janury 1985, Institut Merieux acquired a 51 percent interest in the Institut Pasteur (production) and first rights to any vaccine research from the Pasteur Foundation.
Japan	Several independent manufacturers are subject to fairly tight government controls.
Nether lands	All vaccines included in the national immunization program (DTP-polio combination; DT-polio combination; rubella; measles; and BCG for high-risk groups) are produced at the National Institute for Public Health and Environmental Hygiene. In 1986, an MMR vaccine will be included in the national program.
Sweden	A state-owned institute manufactures or procures vaccines.
Switzerland	There is no government involvement in the Swiss Serum Institut.
United Kingdom	The Centre for Applied Microbiology and Research (of the Public Health Laboratory Service) is supported by government funds and currently produces anthrax vaccine and botulism toxoids for use in the United Kingdom. The government is not involved financially in any commercial production of vaccine. The Secretary of State for Social Services can apply for and hold product licenses for vaccines that manufacturers choose not to hold. The Secretary then arranges for production of such vaccines, and may underwrite costs. The government also purchases vaccine directly from manufacturers.

Appendix H

Background Papers

CASE HISTORIES

The Development of Pneumococcal Vaccine; Summary of Issues Affecting the Development and Utilization of Polyvalent Pneumococcal Vaccine by Robert Austrian, M.D.

A Case History: Rubella Vaccine by Louis Z. Cooper, M.D.

ISSUES

Issues in the Production and Supply of Vaccines from Domestic Manufacturers and Foreign Sources by Hope E. Hopps, M.S.

The Domestic Vaccine Industry: The Economic Framework by Lawrence M. DeBrock, Ph.D.

Legal Issues Affecting the Development and Distribution of Vaccines by Richard F. Kingham, J.D.

No-Fault Insurance for Vaccine Related Injuries by Jeffrey O'Connell, J.D.

Formulating Recommendations on Immunization in the United States by H. Bruce Dull, M.D.

PUBLIC SECTOR PERSPECTIVES

The Interaction of Federal Agencies and Pharmaceutical Companies in Vaccine Development (NIAID) by William S. Jordan, Jr., M.D., and George J. Galasso, Ph.D.

The Interaction of FDA and the Regulated Industry with Respect to Vaccine Development (FDA) by Paul D. Parkman, M.D., Hope E. Hopps, M.S., and Harry M. Meyer, Jr., M.D.

Vaccine Development and Use: A CDC Perspective (CDC) by Gary R. Noble, M.D. and Alan R. Hinman, M.D.

Impediments to the Development and Production of Immunogens of Interest to the Department of Defense (DOD) by David M. Robinson, D.V.M., Ph.D.

Role of the Massachusetts Public Health Biologic Laboratories (Massachusetts) by George F. Grady, M.D.

Vaccine Development Incentives and Disincentives (Michigan) by John R. Mitchell, D.V.M., Dr.P.H.

PRIVATE SECTOR PERSPECTIVES

A Manufacturer's View of the Vaccine Market (Burroughs Wellcome) by Fred A. Coe, Jr.

Issues in Vaccine Development from the Perspective of a "New Biotechnology Based Company" (Genentech) by David W. Martin, Jr., M.D.

An Overview of Factors Which May Impede Public-Private Sector Relationships Affecting Vaccine Development and Use (Merieux Institute) by Pinya Cohen, Ph.D.

Government Industry Interaction and its Effect on the Biological Business (Lederie) by Francis R. Cano, Ph.D.

Vaccine Innovation and the Private Sector (Eli Lilly) by Cornelius W. Pettinga, Ph.D.

Vaccine Development: An Industrial Point of View (Merck Sharp & Dohme) by Maurice R. Hilleman, Ph.D., D.Sc.

Appendix I

Biographical Notes on Committee Members and Consultants

JAY P. SANFORD is president of the Uniformed Services University of the Health Sciences (USUHS) and dean of the F. Edward Hebert School of Medicine, USUHS, Bethesda, Maryland. Prior to his arrival at USUHS in 1975, he was professor of internal medicine and chief of the Infectious Disease Service at the University of Texas Southwestern Medical School, Dallas. Dr. Sanford is a member of the Institute of Medicine and has served on numerous scientific advisory boards and on the editorial boards of more than 10 scientific journals; he is a former associate editor of the Journal of Clinical Investigation. He received his M.D. degree from the University of Michigan Medical School.

MARSHALL H. BECKER is professor and chairman in the Department of Health Behavior, School of Public Health, and professor in the Department of Pediatrics, School of Medicine, at the University of Michigan in Ann Arbor. From 1974 to 1977 he was associate professor in the departments of pediatrics, behavioral sciences, and social relations at Johns Hopkins University. He has published extensively on such topics as beliefs and attitudes as determinants of individuals' health-related behaviors, patient compliance with prescribed regimens, diffusion of innovations among health professionals, drug-prescribing patterns, and different approaches to organizing the delivery of medical care. He is a medical sociologist and holds M.P.H. and Ph.D. degrees from the University of Michigan.

LAWRENCE M. DeBROCK is assistant professor of economics at the University of Illinois in Urbana-Champaign. His research has focused on the effects of government policies on market outcomes, including such areas as invention and innovation, energy, and health care. He received his M.A. and Ph.D. degrees from Cornell University and his B.A. from Bradley University.

ROGER B. DWORKIN is professor of law and Harry T. Ice Faculty Fellow at the Indiana University School of Law, Bloomington, where he has been on the faculty since 1968. He also has served as professor of biomedical history at the University of Washington School of

Medicine. His primary research and public service activities involve the relationship between law and the biomedical sciences. He was educated at Princeton University and Stanford Law School.

BERNARD N. FIELDS is the Adele H. Lehman Professor and chairman of the Department of Microbiology and Molecular Genetics at Harvard Medical School, a position he has held since 1982. His research has focused on the molecular basis of viral pathogenesis. He has served on a number of scientific advisory boards, was chairman of the Experimental Virology Study Section of the National Institutes of Health, and is an editor of the Journal of Virology. He recently was elected to membership in the National Academy of Sciences. He received his M.D. degree from New York University Medical School and his B.A. from Brandeis University.

JERE E. GOYAN is professor of pharmacy and pharmaceutical chemistry and dean of the School of Pharmacy of the University of California, San Francisco. From 1979 to 1981, he was commissioner of the U.S. Food and Drug Administration. His research interests involve the physical chemistry of dosage form design. He is a member of the Institute of Medicine and has served on numerous scientific advisory boards and committees related to his research interests, pharmacy education, and drug regulation. He received his bachelor's degree in pharmacy from the University of California, San Francisco, and his Ph.D. degree in pharmaceutical chemistry from the University of California, Berkeley.

HENRY G. GRABOWSKI has been at Duke University since 1972 and is a professor of economics. He is also an adjunct scholar of the American Institute of Public Policy Regulation. Professor Grabowski has held visiting appointments at the Health Care Financing Administration and the International Institute of Management in Berlin, Germany. He has published numerous articles and books on the pharmaceutical industry, including studies of the research and development process, the international diffusion of new drugs, and the effects of various government policy actions. He also has authored cost-benefit studies of government regulatory actions in various other industrial sectors. He has served as an advisor and consultant to several organizations, including the National Academy of Engineering, the General Accounting Office, and the Office of Technology Assessment. Professor Grabowski received his undergraduate degree in engineering physics at Lehigh University in 1962 and his Ph.D. in economics from Princeton University in 1967.

SAMUEL L. KATZ is the Wilbur C. Davison Professor of Pediatrics and chairman of the Department of Pediatrics at Duke University, a position he has held since 1968. His research has focused on human virology, infectious diseases, and immunization. He is a member of the Institute of Medicine and has served on a variety of scientific advisory boards, committees and consultative groups, and editorial

boards relating to problems in infectious diseases and immunization. He received his M.D. degree from Harvard University and his B.A. degree from Dartmouth College.

EDMUND W. KITCH is professor of law and member of the Center for Advanced Studies, the University of Virginia. He is a member of the bars of the U.S. Supreme Court, numerous federal courts, and the states of Illinois and Kansas. He has written in the fields of antitrust, industrial torts and property, legal history, constitutional law, and law and economics. He received his B.A. degree from Yale University and his J.D. from the University of Chicago. From 1965 to 1982 he was a member of the faculty of the University of Chicago Law School. He has served the federal government as special assistant to the Solicitor General (1972-1973) and executive director of the Civil Aeronautics Board Committee on Procedural Reform (1974-1975).

LOUIS LASAGNA is academic dean of the medical school and dean of the Sackler School of Graduate Biomedical Sciences at Tufts University. Previously, he served as chairman of the Department of Pharmacology and Toxicology at the University of Rochester Medical School for 10 years. He is also director of the Center for the Study of Drug Development, which moved from Rochester to Boston in 1984, and has been chairman of the Advisory Board of the Center since its inauguration in 1976. He led the first unit of clinical pharmacology at Johns Hopkins University School of Medicine, where he held academic appointments for 16 years prior to his move to Rochester. He is a member of the Institute of Medicine. Dr. Lasagna received his B.S. degree from Rutgers University and his M.D. from Columbia University.

MARTHA L. LEPOW has been professor of pediatrics and program director of the Clinical Research Center at Albany Medical College since 1979. She is a specialist in infectious diseases; her principal research interest is in the development of vaccines against the meningococcus and Hemophilus influenzae type b, the commonest cause of meningitis in infants and young children. She has served on a number of scientific committees and consultative groups. Dr. Lepow received her B.A. degree from Oberlin College and her M.D. from Case Western Reserve University.

DAVID W. MARTIN, JR. is vice-president of Research and Development of Genentech, Inc. in South San Francisco, California. He is also adjunct professor of medicine and biochemistry at the University of California, San Francisco. He attended the Massachusetts Institute of Technology and Duke University, from which he received the M.D. degree in 1964. He is a member of the Recombinant DNA Advisory Committee of the National Institutes of Health, serves on several editorial boards of scientific journals, and is the major author and editor of Harper's Review of Biochemistry. His research involves inherited metabolic diseases, particularly disorders of purine metabolism and immunodeficiencies.

DONALD N. MEDEARIS, JR. is Charles Wilder Professor of Pediatrics, Harvard Medical School, and chief, Children's Services, Massachusetts General Hospital. He graduated from the University of Kansas in 1950 with an A.B. in chemistry and received his M.D. from Harvard in 1953. He interned in internal medicine at Barnes Hospital, St. Louis, and served a residency in pediatrics at Children's Hospital, Cincinnati. He has served on the faculties of Johns Hopkins, Pittsburgh, and Case Western Reserve, and on national advisory groups concerning general research support, clinical research, immunization, and graduate medical education. He is a member of the Institute of Medicine and was a member of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research from 1979 to 1982.

THOMAS C. MERIGAN is the first holder of the George E. and Lucy Becker Professorship in Medicine at Stanford University, and heads the Division of Infectious Diseases at Stanford. He is both an active clinician and an internationally known researcher in the field of infectious disease. He has served on the editorial boards of 13 journals, edited 6 books, and published more than 330 scientific papers. He has been a member of a number of national and international scientific advisory committees, including those of the National Institutes of Health, the Hartford and Lasker foundations, the American Cancer Society, and the World Health Organization. He is also a member of the Institute of Medicine. He received the Guggenheim Fellowship Award in 1972 and the Borden Award for Outstanding Research from the American Association of Medical Colleges in 1973. He received his undergraduate degree with honors in 1955 from the University of California, Berkeley, and his M.D. in 1958 from the University of California, San Francisco.

EDWARD A. MORTIMER, JR. has been Elisabeth Severance Prentiss Professor and chairman of the Department of Epidemiology and Community Health, and professor of pediatrics at the Case Western Reserve University School of Medicine since 1975. From 1966 to 1975 he chaired the Department of Pediatrics at the University of New Mexico. His interests have been primarily in epidemiology, especially of infectious diseases. He serves or has served on a number of advisory groups concerned with immunization and control of infection. He received his A.B. degree from Dartmouth College and his M.D. from Northwestern University.

JANE E. SISK is a project director in the Health Program of the congressional Office of Technology Assessment, a position she has held since 1981. She recently completed a project on the medical devices industry, and previously worked on studies of federal vaccine policies and on cost-effectiveness analyses of influenza and pneumococcal vaccines. From 1978 to 1981, she was a Veterans Administration scholar based at the National Center for Health Services Research, where she examined the use of medical technologies under different financing and organizational arrangements. She received a Ph.D. in

economics from McGill University and a B.A. in international relations from Brown University.

GENE STOLLERMAN is professor of medicine at Boston University School of Medicine and chief of the General Internal Medicine Section at University Hospital, Boston. From 1965 to 1981, he was professor and chairman of the Department of Medicine at the University of Tennessee College of Medicine, Memphis. He has served on many scientific advisory boards and is the editor of Advances in Internal Medicine and the "Capsule and Comments" section of Hospital Practice. He received his A.B. degree from Dartmouth College and his M.D. from the College of Physicians and Surgeons, Columbia University.

THOMAS H. WELLER is the Richard P. Strong Professor of Tropical Public Health at Harvard, a position he has held since 1954. In that year, he was awarded the Nobel Prize in Physiology and Medicine with his colleagues John Enders and Frederick Robbins for work that led to the polio vaccine. Trained as a pediatrician, his research has focused on viral diseases of children and on tropical diseases. He is a member of both the National Academy of Sciences and the Institute of Medicine. He has served as senior advisor for research programs of the World Health Organization, the U.S. Agency for International Development, the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, and the Centers for Disease Control. He received his A.B. and M.S. degrees from the University of Michigan, and his M.D. from Harvard Medical School.

Appendix J

Recommendations for the Proposed Vaccine Commission

In developing a slate of candidates for possible membership on the board of directors for the proposed vaccine commission (Chapter 7), recommendations should be sought from all relevant groups, including but not limited to:

- Presidents of the National Academy of Sciences and the Institute of Medicine
- American Academy of Pediatrics
- Federated Council on Internal Medicine
- American Medical Association
- Infectious Diseases Society of America
- National Medical Association
- American Nurses' Association
- American Public Health Association
- American Bar Association
- Pharmaceutical Manufacturers Association
- American Pharmaceutical Association
- national voluntary health associations
- public interest groups
- third-party payers of medical care
- international health organizations
- social science organizations involved in areas relevant to vaccine use.

Index

Index

N

O

P

W

Y