Federal Policies Affecting Vaccine Research and Production

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Summary. The federal government is the single most important determinant of the extent of vaccine research, development, and use in the United States. Federal actions having a positive effect include the financing of vaccine research and development and of major public immunization programs. Federal policies that may be contributing to a decline in the private sector's commitment to vaccine development include an unwillingness to resolve certain liability issues. The nation depends heavily on vaccines to prevent several childhood diseases. For that and other reasons, decisive government efforts are needed to help stimulate the creation of new vaccines and to ensure the continued supply and use of existing safe and efficacious vaccines.

The manufacture of vaccines in the United States has been declining since the 1940's, when because of the discovery and widespread acceptance of clinically effective antibacterial agents, such as sulfa drugs, the penicillins, and the tetracyclines (*1*), the emphasis in medicine began to shift from the prevention to the treatment and cure of disease. Antibiotics were often less expensive and less troublesome to administer than were vaccines; hence they became popular and profitable. During the 1950's American pharmaceutical companies expanded their research efforts to include several areas of therapeutics, and many companies curtailed their less profitable vaccine research and production. By 1968 only 36 licensed manufacturers produced vaccines for sale in this country, and that number has since declined to 18 (*1*). In the same period the number of licensed vaccine products has dropped from 385 to about 145 (Fig. 1).

Several factors may have contributed to this most recent decline. First, in 1972 the licensing branch of the Food and Drug Administration's (FDA) Bureau of Biologics (BOB) began a systematic effort to withdraw product licenses that were not being exercised. Second, some licensed establishments may have chosen to cease production of vaccines rather than comply with new standards for product safety and efficacy issued by FDA in 1972. Third, in recent years manufacturers have been faced with a static market and increasing production costs for vaccines. Finally, the manufacturers' increased liability for warning vaccinees about inherent risks in vaccination has become a formidable cost of remaining in the vaccine business (*1*).

Eight American pharmaceutical companies hold 70 percent of the licenses for vaccine products in this country; seven foreign-based establishments hold 17 percent; and two state governments and one American university hold the remaining 13 percent (Table 1). Altogether, these products are intended to provide immunity against about 23 different types of infections (Table 2). The full significance of the smallness of the number of vaccine manufacturers has not yet been determined. It is conceivable, however, that if technological or marketing problems were to cause a shutdown of production certain types of important vaccine products with only one manufacturer, for example, poliovirus, rubella, mumps, rabies, and measles vaccines, might become unavailable at least for a time.

Manufacturers' decisions to conduct vaccine research, development, and production are influenced by (i) the size of the potential market for a given vaccine product, (ii) the availability of the needed personnel and facilities, (iii) the cost and difficulty of complying with federal regulations concerning vaccine safety and efficacy, (iv) the ability to predict the potential costs of liability for harm produced through the use of a vaccine, (v) the availability of government financing for vaccine research, development, and possibly production, (vi) the prospect of establishing adequate selling prices for vaccine products, and (vii) the public need for a given vaccine and the extent to which the need is being met by other manufacturers.

The focus of this article is on the possible effect of federal government policies on some of these factors. The example of pneumococcal vaccine is used to illustrate how the federal government can finance vaccine research and development.

Federal Financing of Pneumococcal Vaccine

At the strong urging of Robert Austrian of the University of Pennsylvania, the National Institute of Allergy and Infectious Diseases (NIAID) in 1967 began financing research on and development of a pneumococcal polysaccharide vaccine. NIAID had been considering initiating a contract-supported program to develop bacterial vaccines, Austrian's research demonstrated a clinical need for a vaccine to help prevent pneumococcal pneumonia, and in 1967 no pharmaceutical manufacturer expressed interest in developing such a vaccine on its own (*2*).

Between 1968 and 1976 NIAID spent an estimated $6.5 million for that purpose (*3*), $2 million of it on basic research on the pneumococcus and epidemiologic research on pneumococcal diseases and $4.5 million on the development and testing of pneumococcal vaccines. The primary objectives of the research were to estimate the incidence of pneumococcal disease in the United States, to identify the types of pneumococci that caused it, to improve serological techniques for diagnosing pneumococcal infections, to evaluate the clinical safety and effectiveness of pneumococcal vaccines, and to stimulate licensure and commercial production (*3*).

NIAID contracted with Austrian and other researchers to conduct epidemiologic studies to determine the incidence of pneumococcal diseases, especially pneumonia, and it contracted with Austrian to develop serological methods of diagnosing pneumococcal disease and measuring antibody responses. NIAID awarded a contract to Eli Lilly & Company to develop experimental pneumococcal polysaccharide vaccines for use in clinical trials. In the early 1970's it al-

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so contracted with investigators to conduct clinical trials of pneumoccal vaccines (*1*, *4*).

Lilly eventually produced thousands of doses of monovalent and polyvalent vaccines of purified polysaccharide types 1 to 9, 12, 14, 18, 19, 23, and 25. In 1975, however, Lilly stopped producing experimental pneumococcal vaccines, and soon thereafter, in March 1976, also terminated most of its other vaccine research, development, and production programs, having found that its vaccine-related activities were not sufficiently profitable (*5*).

In 1970 Merck Sharp & Dohme intensified its own efforts to develop a pneumococcal vaccine. Working without direct federal funding, the company estimates that it spent $6 million between 1970 and 1978 to develop a marketable pneumococcal polysaccharide vaccine (*6*). In the early 1970's it conducted independent clinical trials among gold miners in South Africa (*7*). The safety and efficacy of Merck's vaccine in these trials were comparable to those found for Lilly's product, which was used by Austrian in clinical trials also conducted among gold miners in South Africa (*8*). On 21 November 1977 Merck was issued a product license to manufacture its polyvalent pneumococcal polysaccharide vaccine, and in February 1978 the company began marketing its 14-valent vaccine known as Pneumovax.

A third company, Lederle Laboratories, began developing a pneumococcal vaccine in 1970, and like Merck's, Lederle's work was done without direct NIAID funding. Lederle's application for a license, for a product identical to Merck's, was approved by FDA in August 1979. Lederle named its vaccine Pnu-Imune.

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

This history of pneumococcal vaccine illustrates the informal, often ad hoc process by which the public and the private sectors select diseases for intervention. NIAID's decision to fund pneumococcal vaccine research and development was not based on a comparative, quantitative assessment of the threat of pneumococcal diseases to the public's health. All efforts of both the private and the public sectors devoted to the development, evaluation, and marketing of pneumococcal vaccine were conducted in the absence of data about specific rates of incidence, prevalence, morbidity, mortality, and medical costs of pneumococcal diseases.

Two overriding factors led to the development and eventual marketing of pneumococcal vaccine. First, one man, Austrian, devoted his professional career to studying the mortality resulting from pneumococcal diseases and to developing a vaccine to prevent these diseases. Virtually singlehandedly, he persuaded NIAID and at least one pharmaceutical company to spend a total of $12 million to research, develop, and test the pneumococcal polysaccharide vaccine now on the U.S. market. Second, in 1967 NIAID believed that the development of pneumococcal polysaccharide vaccine to help prevent pneumococcal diseases was technologically feasible. NIAID's financial support greatly enhanced the coordination and visibility of the research and development efforts. That either Merck or Lederle would have pursued the independent development of a pneumococcal polysaccharide vaccine had NIAID not decided to become involved appears unlikely.

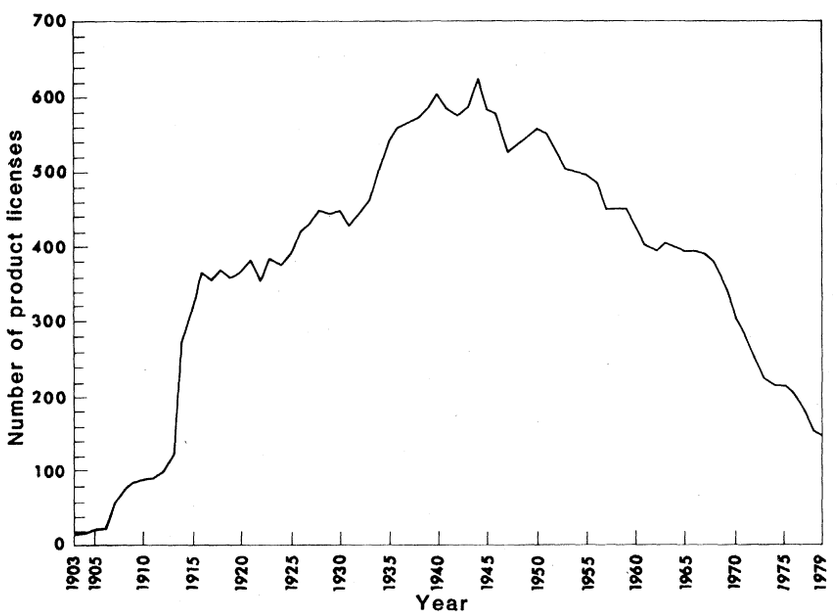

Fig. 1. Total number of vaccine products licensed in the United States, by year, 1903 to 1979 (the number for 1979 is estimated). [From (*1*)]

Safety and Efficacy Requirements

A company's ability and willingness to comply with government regulations concerning the safety and efficacy of a vaccine can influence its decision either to bring a new vaccine to the market or to continue producing a licensed product. BOB requires manufacturers' products to meet certain standards of purity, sterility, safety, and effectiveness (*1*). To assess the safety and efficacy of new vaccines, for example, BOB requires manufacturers to generate data from premarketing clinical trials. Once a product is marketed the manufacturer must test it and must submit samples to BOB for verification of the results.

The pharmaceutical industry often complains that the costs of complying with existing premarketing regulations have become so great, and the process so time-consuming, that the marginal value of developing or producing a new product is often too low to warrant the effort. Some researchers believe that federal regulations, promulgated by FDA for all prescription drug products, both increase the cost and delay the introduction of new products, and that these effects may be more detrimental to people's health than potential adverse reactions to less thoroughly tested drugs (*9*). FDA argues that current federal regulations have not kept any important new therapeutic or biological products off the U.S. market (*10*).

At present FDA does not have the authority or means to monitor the use of vaccines or to collect comprehensive data about adverse reactions to marketed products (*1*). It is attempting to obtain from Congress statutory authority to conduct postmarketing surveillance of selected prescription drugs.

Vaccine Purchasing Policies of the Federal Government

The federal government is the largest single purchaser of the vaccines produced in this country. Its purchasing policies therefore substantially affect pharmaceutical manufacturers' profits from vaccine sales. Some manufacturers cite inadequate profits from vaccine sales as a deterrent to research, development, and production; a few companies do earn profits on vaccines and reinvest these in vaccine research and development (*11*).

Government purchasing policies influence two factors that determine a manufacturer's profits from a particular vaccine product: the size of the market for the product, and the selling price. The federal government's purchasing of measles vaccines for its childhood immunization programs, for example, has been a major determinant of the size of the measles vaccine market. In 1965, by passing the Community Health Service Extension Act, Congress authorized provision of this vaccine through community immunization programs; as a result, in 1966 about 7.9 million doses of measles vaccine were distributed throughout the country (*12*). In 1969 and 1970 Congress authorized no funds for community immunization programs against measles, and in those years the total number of doses of measles vaccine distributed dropped to 4.9 million and 4.5 million respectively. When funding was resumed in 1971 about 8.1 million doses of measles vaccine were distributed.

In 1976 the federal government also dramatically altered the market for swine flu vaccine (*13*). In essence, by enacting the national influenza immunization program of 1976, under which almost the entire U.S. adult population was to be immunized, Congress created a huge temporary market for swine flu vaccine. Production of this vaccine totaled about 157 million doses; by the time the program was terminated about 45 million doses had been administered (*14*).

In addition to market size, government purchasing policies can affect the selling price of vaccines. To contain the cost of its immunization programs, the federal government purchases vaccines on a low-bid contractual basis (*15*). In theory, at least, government contracts are awarded to those manufacturers that are best able to cut costs and expand production. These policies may allow certain manufacturers to minimize their risks by obtaining secure shares of the vaccine market. Large-volume contracts also permit manufacturers to reduce their packaging costs and eliminate or reduce their advertising costs. Some vaccines purchased by the federal government are produced by only one manufacturer. Theoretically, a manufacturer who essentially has a monopoly on the market for a particular vaccine, such as poliovirus vaccine, is in a good position to negotiate with the federal government for a selling price that will yield the company a reasonable profit. In practice, however, profits from vaccine sales can be quite marginal (*15*).

Table 1. Vaccine manufacturing establishments licensed in the United States (1979) and number of product licenses they hold. [Data from (*1*)]

Name	Licenses
American pharmaceutical companies	
Connaught Laboratories, Inc.	15
Cutter Laboratories (includes Hollister-Stier)	3
Delmont Laboratories, Inc.	1
Eli Lilly & Co.	9
Lederle Laboratories	20
Merck Sharp & Dohme	12
Parke Davis & Co.	18
Wyeth Laboratories, Inc.	12
Foreign institutions	
Connaught Laboratories, Ltd.	5
Glaxo Laboratories, Ltd.	1
Instituto Sieroterapico Vaccinogeno Tuscano Sclavo	10
Pfizer, Ltd.	4
Recherche et Industrie Therapeutiques S.A.	1
Swiss Serum and Vaccine Institute Berne	2
Wellcome Foundation, Ltd., Wellcome Research Laboratories	1
Other	
Bureau of Laboratories, Michigan Department of Public Health	9
Massachusetts Public Health Biologic Laboratories	9
University of Illinois	1

The Liability Problem

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

Under the existing legal liability system, a person injured as a result of vaccination must take his or her case to court to seek compensation. The plaintiff generally sues one or more of the participants in the vaccination process, for example a party that manufactures, distributes, pays for, encourages the use of, or administers the vaccine.

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

In three major cases in the last 11 years vaccine manufacturers were held liable for injuries caused by nondefective and properly administered vaccines (*16–18*). One court argued that compensation for injury should be paid by the vaccine manufacturer as a cost of doing business, the cost being passed on to the general public in the form of price increases. In essence, this court ruled that, because no other mechanism to compensate injured vaccinees existed in society, the vaccine manufacturer should pay (*18*).

Current case law has placed ultimate liability for breach of the "duty to warn" vaccinees about the inherent risks of vaccines on vaccine manufacturers. At present the duty to warn is being contractually transferred by manufacturers to the Department of Health and Human Services (HHS, formerly the Department of Health, Education, and Welfare), which in turn is attempting to transfer this responsibility to state and local health agencies participating in public immunization programs. It remains unclear whether transfer of the duty to warn can be accomplished to the satisfaction of a court. There is no defi-

Table 2. Diseases against which there are licensed immunizing agents in the United States (1979). [Data from (*1*)]

General population	
Diphtheria	Mumps
Pertussis	Rubella
Poliomyelitis	Tetanus
Measles	
Special populations	
Adenoviral disease	Pneumococcal pneumonia
Anthrax	Rabies
Tuberculosis (BCG)	Rocky Mountain spotted fever
Cholera	Smallpox
Gas gangrene	Staphylococcal disease
Influenza	Typhoid
Meningococcal diseases	Typhus
Plague	Yellow fever

nite way to predict whether a court will find HHS's informed-consent statements and the way in which they are given to be adequate; nor is there any way to predict, in the event that a court finds the duty to warn has not been discharged, whom the court will hold liable (*19*).

If the federal government takes the position that responsibility for compensating injured vaccinees will be determined by the courts, then it will be doing its best to avoid compensating for injury. If HHS successfully defends its current position that underlying responsibility for the duty to warn still rests with the vaccine manufacturer, manufacturers' increased liability costs will be passed on to the federal government and other purchasers of vaccines in the form of higher prices. It is also conceivable that some manufacturers will stop participating in public immunization programs. Some, as one former major vaccine manufacturer did, might withdraw from vaccine production altogether (*20*).

Potential Options for Federal Action

If the federal government believes that the effect of its vaccine policies on the commitment of the pharmaceutical industry to develop and supply vaccines needs to be assessed, or if it believes that the recent decline in the number of vaccine manufacturers may portend a decline in the capacity of the pharmaceutical industry to develop and produce needed vaccines, then it might adopt one or more of the four options presented below.

1) HHS could establish an interagency body to review federal vaccine and immunization policies. Such a body could develop national priorities for vaccine-related research; monitor the U.S. pharmaceutical industry's commitment to vaccine research, development, and production; assess the federal government's capacity to produce vaccines; assess the effect of selected federal actions on manufacturers' vaccine-related activities; and report its findings to Congress periodically. Vaccine research communities in the pharmaceutical industry and academia, as well as consumers, could be represented.

2) The federal government could establish its own vaccine production program. A small-scale program could be designed to produce only products that are not commercially available, that is, "orphan" and experimental vaccines. A recent example of an orphan vaccine is Rocky Mountain spotted fever vaccine (*21*). Because a small program would likely leave intact industry's production of commonly used vaccines, it probably would not substantially affect industry profits from vaccine production.

Alternatively, a large-scale federal program could be implemented to manufacture all vaccines used in federally sponsored immunization programs. The federal government would then substantially control the availability of most vaccines in this country. A large government production program, however, would erode manufacturers' profits from vaccines. This erosion of profits could reduce even further the industry's diminishing commitment to vaccines, and might lead to a situation in which the federal government would be the sole producer of commonly used vaccines.

3) The federal government could subsidize manufacturers to produce selected vaccines. Payment could be provided either in the form of direct contracts for production or as a condition of purchase of vaccines by the federal government. To date, the federal government has not required any manufacturer to produce one vaccine as a condition of its purchase of another. Conceivably, however, it could make such a requirement.

4) The federal government could establish a procedure for directly compensating persons injured as a result of being vaccinated in public immunization programs. A frank compensation approach could range from modification of the current legal liability system, to integration into existing social insurance programs, to melding with approaches that have similar bases for compensation, such as that for compensating persons injured in medical experimentation.

To establish a federal compensation system, four principal issues would have to be addressed: (i) criteria for the selection of vaccinees eligible for federal compensation, (ii) the types and severity of injury for which compensation would be awarded, (iii) the limits to compensation, and (iv) financing mechanisms.

Conclusion

The limits to antibiotic treatment of infectious diseases are now well established. Pneumococcal infections, for example, have been treated with penicillin for about 30 years. In a study by Austrian, however, it was found that even with the best of antibiotic therapy 17 to 30 percent of high-risk patients with pneumococcal pneumonia accompanied by documented bacteremia died (*22*). Further, bacterial resistance to antibiotics is mounting (*23*).

Public policy-makers appear to be reevaluating the merits of disease prevention and health promotion, especially since the cost of disease treatment has escalated dramatically during the past decade.

The use of safe and efficacious vaccines have proved to be a cost-effective method of preventing certain childhood diseases in this country; polio is the most notable example. A strong commitment of the private sector to vaccine research, development, and production appears to be essential to the creation of new vaccines and to the continued supply of currently available vaccines. Because federal policies greatly affect that commitment, which now appears to be waning, a review of federal vaccine and immunization policies appears to be needed.

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