United States Vaccine Research: A Delicate Fabric of Public and Private Collaboration

National Vaccine Advisory Committee*

ABSTRACT. In the last 20 years, two thirds of all new vaccines provided worldwide have been produced by a US network of independent industrial, governmental, and academic partners engaged in vaccine research and development. Vaccines are complex products and the science of vaccinology is difficult. To achieve the full promise of modern science and technology to prevent and treat disease by immunization, the delicate fabric of America's cooperative and collaborative vaccine research relationships must be sustained and strengthened. The major partners are the federal government; four large companies--two US-headquartered (Wyeth-Lederle Biologics and Vaccines and Merck & Co), two foreign firms (SmithKline Beecham and Pasteur Mérieux Connaught); and academia. Of the $1.4 billion that fund US vaccine research and development annually, 46% comes from vaccine sales, 36% from taxpayers, and 18% from risk capital. Vaccine innovation could be strengthened by improved public and policy maker understanding of the vaccine development network; declarations of partnership; interactive dialog with federal advisory bodies; public forums for government and industry to listen to patients, providers, and researchers; sabbatical assignments between partners; mechanisms to share industries' market research with public immunization programs; continued active industry participation in the Advisory Committee on Immunization Practices and the National Vaccine Advisory Committee; increased collaboration be tween industry and the National Institutes of Health for clinical research; harmonization of the Advisory Committee on Immunization Practices vaccine recommendations and the Food and Drug Administration package inserts; and public policies to foster the partnership's collaboration and robustness. The optimal size and configuration of the US vaccine enterprise should be debated only in the context of a full understanding of how the current system works and its record of effectiveness. These National Vaccine Advisory Committee recommendations are directed at developing public policies to foster and sustain vaccine innovation and ensure the timely introduction and supply of new vaccines needed by this nation and the world. ***Pediatrics* 1997;100:1015-1020; *vaccine, vaccine research and development, immunization.***

ABBREVIATIONS. NIH, National Institutes of Health; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; DOD, Department of Defense; USAID, US Agency for International Development; ACIP, Advisory Committee on Immunization Practices; CRADA, Collaborative Research, and Development Agreements.

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Vaccines have achieved wonderful successes in preventing infectious diseases. Even more may be expected in the future, as the promises of modern molecular biology, immunology, and technology are fulfilled and interest in cost-effective prevention grows with the expansion of capitated managed care.

The United States has been extraordinarily successful in vaccine research and development, contributing more than two thirds of all new vaccines approved worldwide in the last 20 years.[1,2] This success is the product of a fragile network of interdependent industrial, governmental, and academic partners engaged in vaccine research and development in the United States. This highly effective, yet fragile, network was not designed, but evolved, in response to scientific, public health, and economic forces during the past 50 years.

EXPECTED BENEFITS FROM NEW VACCINES

A quarter of a century of remarkable biologic and immunologic discoveries has raised expectations for further advances in vaccine development. The smallpox vaccine was developed in 1796. It took almost a century before a second vaccine was developed, followed by only a few others in the early 20th century. As this century closes, however, one or two new vaccines will likely be licensed every year, with many more expected later--not only for infectious diseases, including emerging infections and acquired immunodeficiency syndrome, but for fertility control, certain cancers, and autoimmune diseases as well. Among the infectious disease vaccines just over the horizon are pneumococcal conjugate vaccines for otitis media and invasive disease attributable to *Streptococcus pneumoniae*, including multiple resistant pneumococci; rotavirus vaccines; and a vaccine that prevents infection with human papillomavirus, which causes genital warts and also cervical cancer.

The very multiplicity of childhood vaccines presents challenges to immunization programs in America: a child now needs 15 to 16 injections or oral administrations of vaccines in the first 2 years of life. By engineering these vaccines into new pediatric combinations, we expect to reduce greatly the delivery problems inherent in the current pediatric immunization schedule.

Vaccines are complex products and the science of vaccinology is difficult. To achieve the full promise of modern science and technology to prevent and treat disease by immunization, America's cooperative and collaborative relationships in vaccine research and development are interwoven into a fabric of innovation. This must be maintained and strengthened. It is important to understand the nature of these relationships to prevent inadvertent damage to this delicate fabric.

VACCINE DEVELOPMENT: A COLLABORATIVE VENTURE

The US network of partnerships is woven by a number of partners (Table 1). In the federal government, the major player in speeding the identification and evolution of potential vaccines is the National Institutes of Health (NIH). The Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) play significant, but different, supportive roles, as does the Department of Defense (DOD) and, to a more limited, but important, extent the US Agency for International Development (USAID). Two state governments, Michigan and Massachusetts, have a limited capacity to develop vaccines.

Four large companies in the world sell products on the US market--two headquartered in the United States, one in Belgium, and one in France. The two US companies are Merck & Co, Inc and Wyeth-Lederle Biologics and Vaccines, a division of American Home Products; and the foreign firms are SmithKline Beecham and Pasteur Mérieux Connaught, a division of Rhône Poulenc. In addition, Chiron Vaccines is an intermediate-sized company headquartered in the United States. A number of smaller US and foreign companies are also involved, as are academic centers. For example, Japanese firms played a major role in the development of acellular pertussis and varicella vaccines, as did US universities in the development of recombinant hepatitis B vaccines.

Small companies are often referred to as biotechnology companies and large companies as manufacturers. Both terms are misnomers. Biotechnology refers to a type of science that many small companies do not pursue. Large companies conduct biotechnology research other types of research, clinical and process development, marketing, and distribution in addition to manufacturing. Thus,

Table 1. US National Vaccine Development Network

Federal government
NIH, CDC, FDA
DOD
USAID
State governments
Michigan
Massachusetts
Large companies
2 United States, 2 foreign
Small companies
Academia

Abbreviations: NIH, National Institutes of Health; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; DOD, Department of Defense; USAID, US Agency for International Development.

large and small are more useful designations. However, the most important distinction is not whether firms are biotechnology companies or manufacturing companies, but how they obtain money to support research.

VACCINE RESEARCH AND DEVELOPMENT FUNDING

Basic funding sources for vaccine research and development in the United States--and elsewhere--include: government (ie, taxes), profits from sales of products, and risk capital (Table 2). The NIH competes with other federal agencies and programs for taxpayer funding. Although the NIH conducts some intramural research, most resources are provided to academic centers and other health-related agencies as grants. DOD conducts much intramural research, but also funds academic research. USAID funds research through direct grants predominantly to institutions in less developed countries, to US universities, and to international organizations such as the World Health Organization. Nongovernmental organizations--such as the American Academy of Pediatrics, American College of Physicians, and the March of Dimes Birth Defects Foundation--also play an important supportive role. In 1995, total federal funding accounted for approximately $500 million for vaccine research and development (data from NIH Office of Legislative Policy and Analysis).

Vaccine companies, like larger pharmaceutical companies, seek a profit by selling products. On average, pharmaceutical companies reinvest approximately 18.8% of the profits from product sales into research and development (data from Pharmaceutical Research Manufacturers Association). Information available suggests that this portion is similar for vaccine companies. Estimates based on

Table 2. Vaccine Research and Development: Sources of Funding 1995

Source	Estimated Amount in Millions
Taxpayers	$500 (36%)
NIH	
Intramural	
Grants to academia	
Other	
Vaccine sales	$650 (46%)
Large companies (15 to 20% sales)	
Risk capital	$250 (18%)
Small companies	
Total	$1400 (100%)

company annual reports suggest that approximately $650 million was generated for vaccine research and development from such sources in 1995 (estimates from annual reports of companies and from H. Grabowski, 1996 personal communication). In contrast, risk capital from private investors is the primary source of funds for small companies. It is difficult to estimate the total amount generated for vaccine research and development through risk capital, but it was at least $250 million in 1995 (estimates from polling chief executive officers of small companies and from annual reports).

Although of great public health importance, vaccine research and development form a relatively small part of the pharmaceutical industry's research and development and are in general governed by its economics. Therefore, candidate vaccines are more likely to be aggressively developed and evaluated when there is a potential for providing a substantial economic return--vaccines for which there is a large potential market, particularly in the United States and other developed nations. The system works less well to develop potential vaccines needed for which the principal market is less developed nations; there is only a small, specialized market such as the DOD; or the disease is of low incidence, such as hantavirus pulmonary syndrome.

CONTRIBUTIONS OF THE PARTNERS

Table 3 displays, in a simplified manner, the relative contributions of the various partners to the vaccine research and development network. Several kinds of research are done. Basic research is pursued in fields that might eventually have something to do with vaccines, such as recombinant DNA technology and immunology, although such a connection may not be apparent at the time the research is being done. Targeted basic research is more specific to vaccine development and might include such projects as studying a microorganism--for example, tubercle bacillus--to characterize antigens that might be protective. Vaccine-related epidemiologic research is directed toward understanding the causes of disease, risk factors for disease, and the nature and magnitude of their public health impact.

Development includes both clinical and process components. The clinical component involves studies of the effects of vaccines on patients for safety and efficacy, and process development involves investigations of manufacturing techniques necessary to transfer laboratory procedures to mass production with consistency and safety. Because process development is a difficult job for biologic products, it is just as costly as clinical development. Postlicensure studies of the safety and efficacy of vaccines are essential and represent an additional large cost.

The NIH supports most of the basic research that eventually leads to vaccine development. Much of this is funneled into academic institutions but some is done by scientists at the NIH. Targeted

TABLE 3. US Network Partners' Relative Contributions to Vaccine Research and Development*

	RESEARCH		DEVELOPMENT			
	Basic/Related	Targeted	Process	Clinical	Manufacture	Postlicensure Studies
NIH	+++	+++		++		
CDC						++
FDA		+	+	+		+
DOD	+	+	+	+		+
USAID		+		+		
State			+	+		+
Large company	+	+++	+++	+++	+++	+++
Small company	+	+++	±	±	±	
Academia	+++	+++		+++		
NGOs		+		+		

Abbreviations: NIH, National Institutes of Health; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; DOD, Department of Defense; USAID, US Agency for International Development; NGO, nongovernmental organization.

*Relative contribution:+++, major; ++, intermediate; +, minor; ±, varies by company.

research is also done, in large part, by the NIH, but also significantly by large and small companies. Again, much of the work, from each of the sources, is funneled through academia.

Expertise in process development resides almost exclusively in the large companies; there is no other resource for such development. Clinical development is also done mostly by the large companies, but a portion is funneled through academia and internationally through the World Health Organization.

The DOD performs targeted basic research and vaccine development to prevent the infectious diseases most likely to be encountered by US military personnel. Emphasis is on the protection of young adults before their deployment outside the United States. Resulting vaccines benefit not only US military personnel, but also US travelers and residents of endemic areas. The DOD maintains research laboratories outside the United States for clinical testing of new products in settings where the diseases occur. The DOD has a limited capacity to produce pilot lots of investigational vaccines, which accelerates the process of bringing bench products to Phase I, but much of this work is done in cooperation with large and small companies.

The CDC is the lead agency for conducting epidemiologic studies and the surveillance needed to identify risk factors, define the magnitude of public health impact of diseases, and establish public health priorities for vaccine development. Because of its role in developing recommendations for vaccine use through the Advisory Committee on Immunization Practices (ACIP) and procurement of public sector vaccines, the CDC has a substantial impact on demand and potential profit associated with vaccines.

As the agency responsible for licensing new pharmaceutical products, the FDA establishes standards for the processes, facilities, and prelicensing and postlicensing clinical studies to ensure that vaccines used in the United States are safe and effective. These standards have a profound impact on the nature and direction of vaccine development and related costs.

The USAID supports targeted research and development related to those vaccines which potentially will have the greatest impact on children under the age of 5 years in developing countries. Resulting vaccines contribute to global disease control efforts, benefiting US citizens as well as the global community. Clinical development is undertaken in collaboration with vaccine manufacturers.

Professional organizations such as the American Academy of Pediatrics and the American College of Physicians make recommendations for vaccine usage as does the ACIP. Usage recommendations affect market size for any vaccine and therefore the resulting revenues to large and small companies.

THREATS TO THE DEVELOPMENT PROCESS

In the late 1970s, William Jordan and his colleagues at the NIAID made two important observations. First, modern molecular biology and genetic engineering in particular could revolutionize vaccine development. Second, in many cases, development was hindered by the lack of investment to obtain a missing piece of scientific knowledge or technology. Just as the new molecular biotechnology was becoming available, there was an awareness of a lack of coordinated planning and funding to assure that each step in vaccine development followed as rapidly as possible the preceding one. Although the United States can point to major triumphs in vaccine development in the past 20 years, these old problems have not been eliminated.

Many partners are involved in developing vaccines, All are needed to make the network robust and healthy, so that complete and rapid development of multiple new products that will aid human health can be accomplished. If any partner is weakened, the system may fail (Table 4).

This delicate fabric of partnerships is highly sensitive to environmental changes, including changes in policy and market opportunities. A squeeze on funding in one area will have an adverse impact on discovery and development across the board. For example, in the past few years federal agency budget cuts have put at risk funding for vaccine research and development. Such reductions in federal funding for vaccine research and development will have a secondary effect in academia and thereby on the United States capacity to engage in vaccine research.

If the regulatory climate becomes cumbersome, regulation itself can become a hurdle, making it more difficult for new companies to enter the vaccine research and development arena.

Table 4. Threats to Vaccine Innovation: If Any Partner Is Weakened, the System May Fail

Threats	Partners Affected
Federal budget cuts	National Institutes of Health, Department of Defense, US Agency for International Development, Centers for Disease Control and Prevention, Food and Drug Administration, academia
Regulatory climate	Large companies, small companies, academia
Price controls	Large companies, small companies, academia
Single-source purchaser	Large companies, small companies, academia

Price controls are a source of concern to both large and small companies and discourage potential venture capital investment in vaccines, because investors fear that potential profits will be compromised.

Single-source federal government purchase may pose a significant threat to both large and small companies. Increased purchase of vaccines by federal, state, and local government through federal contract, at discount prices, not only reduces companies' revenue by reducing the private market and increasing the public discounted market, but may create an unpredictable market subject to rapidly changing government policies (Mercer Management Consulting. *Report on the United States Vaccine Industry*. Unpublished consultation report commissioned by the US Department of Health and Human Services; June 14, 1995). Conversely, award of government contracts to two or more manufacturers for similar new vaccines may encourage vaccine development by assuring a substantial market once the approval process has been completed and the vaccine recommended by the ACIP.

RECOMMENDATIONS

To develop public policies that ensure the introduction and supply of new vaccines needed by this nation and the world, the National Vaccine Advisory Committee's recommendations include the following:

1. Improve public and policymakers' understanding of the nature of the vaccine development network, the uniqueness of each partner, and the interdependence of all partners. The US vaccine research and development network represents the future for improving the public health by immunization not only in this country but for the world. By determining federal agency budgets and priorities, by formulating rules for the government purchase of vaccines, by mandating health insurance benefits, by implementing public health recommendations, by regulating and licensing, by deciding the extent of the United States interest in global public health problems, US policymakers directly and indirectly impact vaccine research and development. To make wise policy and avoid unintended adverse consequences, policymakers need to understand the nature of the development process, the uniqueness, and interdependence of each partner.
2. Solicit and publish explicit declarations of partnership by the leaders of each sector. All partners should recognize publicly the role of others, and all partners should articulate to public policy decision-makers, to Congress, and to other state and federal officials the message that the vaccine development network may be endangered by a threat to any component of this delicate fabric.
3. Foster an interactive dialogue among vaccine companies, advisory groups, and federal agencies. Dialogue among the CDC, NIH, FDA, the advisory committees, and the vaccine companies should be more interactive, and should occur early in the vaccine development cycle. As was suggested in an excellent workshop on resolving conflicting guidelines for the use of vaccines, [3]by engaging in early and wide-ranging discussions with companies, the advisory committees and the CDC staff can review broad criteria concerning future needs for and address what-if scenarios regarding candidate vaccines--eg, if a respiratory syncytial virus vaccine had these characteristics,

would it be considered for use in high-risk infants only or all newborns? The companies can often review early directions in research and development with the advisory bodies, although confidentiality because of the competitive forces of the marketplace will sometimes limit such discussions.

4. Develop public forums for government and industry to listen together to mutual customers--patients, providers, and researchers. Joint public forums by the CDC, the advisory bodies, and mutual customers (for example, practicing family physicians and pediatricians, state and local public health workers, managed care administrators, consumer groups, and others) would help to assure that industry and government are responsive to the needs and concerns of vaccine users.
5. Offer cross-functional Intergovernmental Personnel Act and sabbatical assignments among industry, government, and academia. Such assignments would improve understanding within the public and private sectors.
6. Develop mechanisms to share industries' market research data with relevant public sector immunization programs. Industry has formidable expertise in marketing, research, and analysis, which would be relevant to improving the success of domestic and international public health immunization programs; for example, by increasing parents' awareness of the immunization schedule and parents' understanding of the appropriateness of administering vaccines during visits for minor acute illnesses.
7. Continue industry's active participation in the National Vaccine Advisory Committee and the ACIP. To serve the public interest, government advisory committees must be independent of industry, but such committees cannot be relevant and effective if isolated from the expertise and experience of the industry, which is the principal funder of vaccine research and development.
8. Increase collaboration between industry and the NIH for clinical research. Expansion of existing vaccine and treatment evaluation units or additional similar units are needed to speed trials needed to support licensing combination vaccines and assess the safety and efficacy of concomitant administration of multiple vaccines and other needs.
9. Review and address conflicts between the ACIP vaccine recommendations and the FDA package inserts. Harmonization of the ACIP vaccine recommendations and the package inserts is crucial to clarify vaccine precautions and contraindications. Joint funding of postlicensing clinical studies may be needed to modify labeling that makes implementation of the ACIP recommendations difficult. No matter the rationale, conflicts between two government vaccine documents, such as the ACIP vaccine recommendations and the FDA package inserts, create confusion that tends to undermine public confidence in the ability of the government to ensure the safety of vaccines, and thereby adversely impacts the entire immunization enterprise.
10. Promulgate public policies that foster the partnership's collaboration and robustness. The possibilities for developing desired vaccines, and the benefits that such vaccines will have for human health, are enormous. The scientific base exists. The network for development exists. To fulfill this promise, there is a need, however, to foster the existing collaboration among industry, academia, and federal agencies through wise public policy directed at improving the public health. One method to accomplish this is by use of Collaborative Research and Development Agreements (CRADA), which enable government agencies and industry to apply their specific expertise to accomplish important tasks like producing and exploring potential vaccine antigens for immunoprotection. A recent change in the NIH policy which removed pricing controls from CRADA now makes it possible for many companies to collaborate with the NIH, which they would not have done with the pricing controls in place. Pricing controls had not been a feature of CRADA with other government agencies. The DOD has had a successful track record with CRADA; the FDA approval of Japanese encephalitis vaccine in 1992 and hepatitis A vaccine in 1995 were direct results of industry-DOD partnerships through CRADA.

CONCLUSIONS

Throughout the last 50 years, vaccine research and development in the United States has yielded an array of wonderful vaccines that have had an enormous impact on the global public health. Based on its track record, the US development system is the best yet devised. Collaboration and cooperation of government agencies, such as NIH, CDC, FDA, USAID, DOD, large vaccine companies, small

research companies, and academia are essential to continue success and fulfill the promise of recent advances in science and technology.

Threats to any part of the delicate vaccine research and development network jeopardize the rapid development and supply of new life-saving and life-enhancing vaccines for the American people. What is the optimal size, scope, and configuration of the US vaccine enterprise? These questions should be debated only in the context of a full understanding of how the current system works and its record of effectiveness. These National Vaccine Advisory Committee recommendations will help to ensure that public policies take into consideration this research and development network and foster and sustain it to facilitate the timely introduction and supply of new vaccines.

APPENDIX

The National Vaccine Program was established in 1986 by the Public Health Service Act to achieve optimal prevention of adverse reactions to vaccines. The program is responsible for coordination and direction of government and nongovernment activities on research, licensing, production, distribution, and use of vaccines, The director is the Assistant Secretary for Health, with the National Vaccine Advisory Committee serving as advisor. The committee consists of 15 voting members appointed by the director, in consultation with the National Academy of Sciences, including individuals in vaccine research or manufacture, physicians, members of parent organizations, and representatives of health agencies and public health organizations. The committee also includes 5 nonvoting members: Regina Rabinovich, MD, from the National Institutes of Health; M. Carolyn Hardegree, MD, from the Food and Drug Administration; Walter A. Orenstein, MD, from the Centers for Disease Control and Prevention; Caryn Miller, PhD, from the US Agency for International Development; and William H. Bancroft, MD from the Department of Defense. (This committee report has been submitted to the Assistant Secretary of the US Department of Health and Human Services.)

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