Fostering Partnerships for Vaccine Development: a Delicate Fabric

R. GORDON DOUGLAS, MD*

Vaccines have achieved wonderful successes in the fight against infectious diseases. They prevent disease, and with changing medical care systems and the advent of managed care, clinicians are interested in focusing even more on prevention than in the past.

The United States has been extraordinarily successful in vaccine research and development, contributing more than two-thirds of all new vaccines approved world-wide in the last 20 years.[1] This success reflects the cooperative and collaborative relationships that have existed among the key participants.

The future offers exciting new opportunities and challenges. Combinations of currently used pediatric vaccines will greatly simplify their administration and usage. New vaccines against important and widespread infections and, perhaps, certain cancers and autoimmune diseases, will improve health in the most cost-effective mode available.

To achieve these goals, the cooperative and collaborative relationships in vaccine research and development—a fabric of innovation—must be maintained and strengthened. In the recent past this network has been threatened. It is important to understand the nature of these relationships to prevent damage to this delicate fabric.

* R. Gordon Douglas is President, Merck Vaccines–Merck & Co., Inc., One Merck Drive, P.O. Box 100-WS3A-07, Whitehouse Station, NJ 08889-0100.

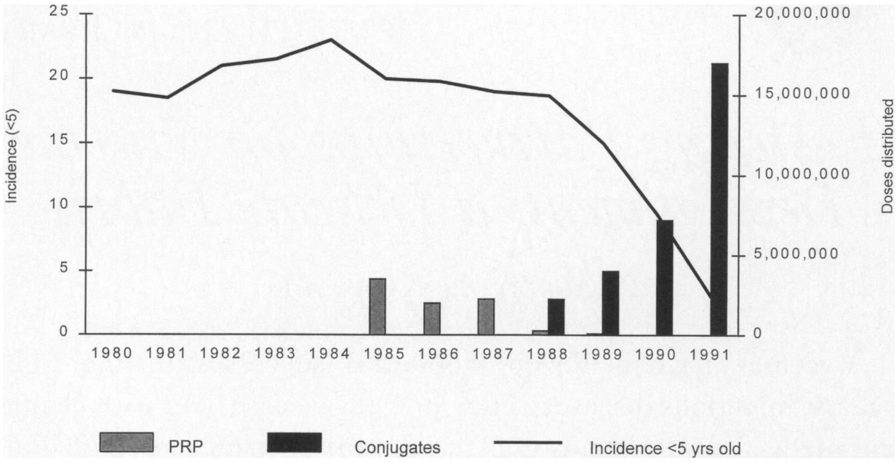

FIG. 1. *Haemophilus influenzae* vaccine doses sold or distributed and incidence of *H. influenzae* meningitis in children younger than 5 years old in the United States, 1980–1991. PRP, Polyribosylribitol phosphate vaccine. (Data from the National Bacterial Meningitis Reporting System [20 continuously reporting states], 1980–1991).

Benefits Obtained from the Use of Vaccines

A recent testimony to the benefit of vaccines is the near elimination of meningitis caused by *Hemophilus influenza* type B, or HIB, from this country (Fig. 1). By 1992, the incidence per 100,000 had fallen to almost zero with the advent of new pediatric conjugate vaccines that first became commercially available in 1988 and were universally recommended for infants in 1990. Some pediatricians in training report that they have not seen a case of meningitis, an almost unbelievable achievement because meningitis was one of the most important diseases that pediatricians had to deal with just a few years ago. One of the challenges to a pediatrician, when talking to a mother on the phone, has been to differentiate a serious illness such as meningitis from minor illness, such as some of those due to respiratory viruses.

Vaccines do not only prevent disease and death. Used properly, vaccines can eliminate disease. Smallpox—the scourge of centuries – has been eradicated from the globe, with stored stockpiles of viruses scheduled to be destroyed. A second disease, poliomyelitis (Fig. 2), has not been seen in the western hemisphere since 1992. A 13-year-old Peruvian named Juan was the last case in this

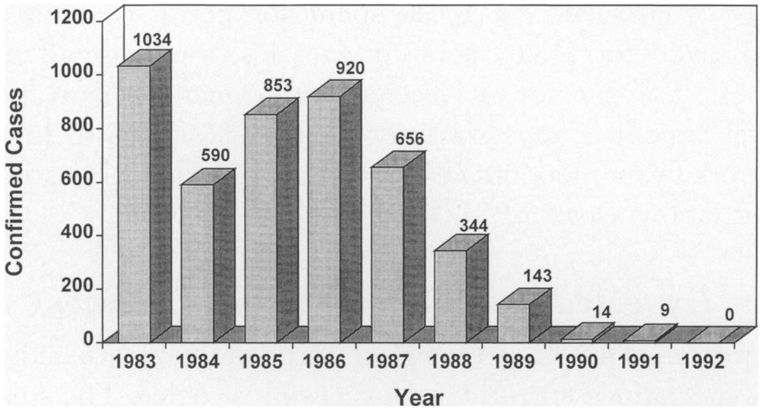

FIG. 2. Polio eradication effects in the Americas (Source: Pan American Health Organization).

hemisphere of a disease that I feared when I went to medical school, and that haunted physicians in training in the 1950s. The campaign against this crippling disease continues internationally. In 1995 alone, China was able to immunize 80 million children; there has not been a case of paralytic poliomyelitis since that campaign. The opportunity and the likelihood of eradicating poliomyelitis is imminent.

These are notable achievements. With the possible exception of safe water, no other intervention has eliminated disease with such power and such magnitude.[2]

Much popular talk today is about cost. Vaccines are, among all of the therapeutic and preventive modalities that we use today in medical care, the only ones that are actually cost effective (Table I). The cost-benefit ratio for selected vaccines varies from approx-

TABLE I
COST BENEFIT RATIOS FOR SELECTED VACCINES USED ROUTINELY IN THE UNITED STATES (HINMAN, 1988)

Vaccine	$ saved per $ spent
Measles	$11.90/$1.00
Mumps	$ 6.70/$1.00
Rubella	$ 7.70/$1.00
Combined M-M-R	$14.40/$1.00
Poliomyelitis	$10.30/$1.00
Pertussis	$ 2.60/$1.00

Savings in the United States from the use of M-M-R was about $1.3 billion per year by 1983.

imately $2.60 saved for $1.00 spent for pertussis vaccines, to $14.40 saved for $1.00 spent for measles, mumps, and rubella vaccines.[3] For the newest vaccine on the market, Varivax®, the medical benefit is approximately $1.00 to $1.00, but if time lost from work by mothers and fathers is factored into the equation, the benefit ratio is closer to $5.00 saved for $1.00 spent.[4]

Expected Benefits from New Vaccines

A quarter century of biological and immunological advances raise expectations for further advances in vaccines. The smallpox vaccine was developed in 1796. It took almost a century before a second vaccine was developed, followed by a few others in the early twentieth century. As this century closes, however, one or two vaccines appear every year, with many more expected in the near future, not only for infectious diseases, including emerging infections and acquired immunodeficiency syndrome (AIDS), but for cancer and other diseases as well. Vaccines are in development for fertility control. A pneumococcal conjugate vaccine for multiply resistant pneumococci will be available in the next few years. It works in the same way that the conjugated HIB vaccines work, by conjugating the polysaccharide to a protein carrier so that the immature immune systems in children less than 2 years of age will respond. Another vaccine that looks very promising now prevents human papilloma virus infection, which causes genital warts and also cervical cancer, in animals.

The very multiplicity of childhood vaccines is a source of difficulty in the United States: 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.

Vaccine Development: a Collaborative Venture

Vaccines are complex products and the science of vaccinology is difficult. Despite their complexity, the network that has evolved

TABLE II
US NATIONAL VACCINE DEVELOPMENT NETWORK

- Federal Government
  NIH, CDC, FDA
  DOD
  USAID
- State Government
  Michigan
  Massachusetts
- Large Companies - 4
  2 US, 2 Foreign
- Small Companies (Biotech)
- Academia

for vaccine development in the United States works. If nurtured, the system will continue to develop new vaccines. But the current political climate—focusing on cutting costs—puts this network at risk. The US network of partnerships is a delicate fabric woven by a number of players (Table II). In the federal government a major player is the National Institutes of Health (NIH), but the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) play significant roles, as does the Department of Defense (DOD) and to a more limited but important extent, the U.S. Agency for International Development (US-AID). Two state governments, Michigan and Massachusetts, still develop vaccines to a limited extent, albeit Michigan suspended production of DPT several months ago.

There are four large companies left in the world that deal with vaccines: two in the United States and two in foreign nations. The two US companies are Merck & Co., Inc. and Wyeth-Lederle Biologics and Vaccines, a division of American Home Products; the foreign firms are SmithKline Beecham and Pasteur Mérieux Connaught, a division of Rhône Poulenc. A number of small companies, often referred to as "biotechnology companies" are involved, as are academic centers.

"Biotechnology companies" is a misnomer for a number of reasons. First, large companies often conduct more biotechnology research than small companies. Large companies are commonly referred to as manufacturers, but that likewise is a misnomer

TABLE III
VACCINE R & D: SOURCES OF FUNDING

	$/Year*
1. Taxpayers	250M
NIH	
Intramural	
Grants to academia	
Other Agencies	
2. Vaccine Sales	450M
Large Companies (15 to 20% of sales is invested in R&D)	
3. Risk Capital	150M
Small Companies	

* Estimated 1992

because the large companies do research, development, marketing, distribution, and so on, in addition to manufacturing. "Biotechnology" also refers to a type of science that many small companies do not pursue, although they are referred to with that term. Thus, "large" and "small" are useful designations. In fact, the most important point of difference is not whether firms are biotechnology companies or manufacturing companies, but where they get their 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, profits from sales of products and risk capital (Table III). Taxpayers pay money to the government. The NIH competes with all other federal programs and agencies for some of that money. The NIH conducts intramural research and gives grants to academic centers and other health-related agencies. In 1992, NIH funding accounted for about $250 million for vaccine research and development.

Vaccine companies and larger pharmaceutical companies sell products. On average, these companies invest reinvest about 18.8 percent of the profits from these sales into research and development. Data suggest that this portion is similar for vaccine companies. Approximately $450 million was generated for research and development from such sources in 1992.

TABLE IV
RELATIVE CONTRIBUTIONS OF VACCINE PARTNERS

	Research		Development			
	Basic/Related	Targeted	Process	Clinical	Manufacture	Post-Marketing Studies
NIH	+++	+++		++		
CDC						++
FDA		+	+	+		+
DOD		+	+	+		+
USAID		+		+		
State (MI)			+	+		+
State (MA)			+	+		+
Large Co.	+	+++	+++	+++	+++	+++
Small Co.	+	+++	+	+	+	
Academia	+++	+++		+++		

Risk capital from private investors funds small companies. It is difficult to estimate the amount generated for vaccine research and development through risk capital, but it was at least $150 million in 1992.

Contributions of the Partners

Table IV displays, in a somewhat oversimplified manner, the relative contributions of these 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, such as the tubercle bacillus, to characterize antigens that might be protective.

Development includes both clinical development and process development. The former involves studies of the effects of vaccines on patients for safety and efficacy; process development involves investigations of manufacturing techniques necessary to transfer laboratory procedures to mass production with consistency and safety. Process development is a difficult job for biologic products or entities, and is just as costly as clinical development.

TABLE V
THREATS TO VACCINE INNOVATION*

Threats	Partners Affected
Federal budget cuts	NIH, other agencies, academia
Regulatory climate	Large companies, small companies, academia
Price controls	Large companies, small companies, academia
Single-source purchase	Large companies, small companies, academia

* If any partner is weakened, the system will fail.

Development also includes manufacturing itself and after-market studies of the performance of vaccines.

NIH supports most of the basic research that eventually is related to vaccine work. Much of this is funneled into academic institutions but some is done intramurally. Targeted 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.

Process development is almost exclusively the province of the large companies. All the expertise in the country resides there. There is no other resource to get such development done. Clinical development is done mostly by the large companies but also is funneled through academia.

Threats to the Development Process

Many players 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 will fail (Table V).

This fabric of partnerships is highly sensitive to environmental changes, including changes in policy and market opportunities. A squeeze on funding in one area will influence discovery and development across the line. For example, in the past few years, rumors and threats of federal budget cuts that would affect the NIH have put at risk money for vaccine research and development. Other agencies have faced funding cuts as well,

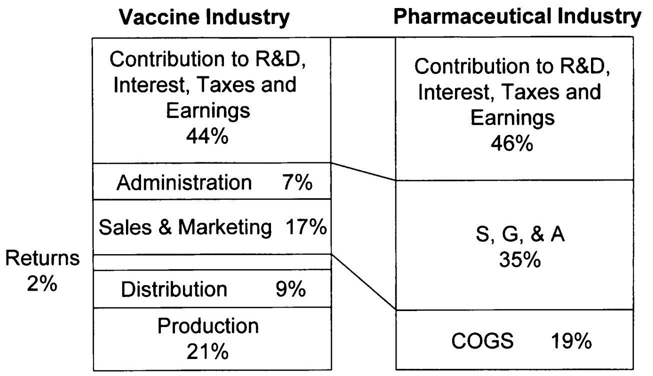

FIG. 3. Major US Vaccine Suppliers Value-Added Chain (*versus* Pharmaceutical Industry Averages), from Mercer Management Consulting. COGS: cost of goods sold. S, G, & A: sales, general and administrative costs.

and if realized, these cuts will have a secondary effect in academia.

As the regulatory climate becomes more difficult, regulation itself becomes a hurdle, making it more difficult for new companies to enter the vaccine research and development arena. This affects both large and small companies and, therefore, affects academia secondarily.

Price controls are greatly feared by industry and, thus, by both large and small companies. They are also threatening to investors, who fear that potential profits will be compromised.

The single-source purchase contained in the Vaccine for Children's (VFC) program was likewise a threat to both large and small companies because it reduced revenue to large companies by reducing the private market at the expense of the public and, therefore, discounted market. The Mercer Consulting Company did a study on the economics of the vaccine industry in Europe and, separately, a similar study in the United States (Fig. 3). The studies showed that the VFC program would reduce revenues by about $90 million to $120 million per year, approximately 40% of which would be available for vaccine research and development, because the last dollars in income go to support research and development disproportionately.[5] The study concluded that VFC would significantly diminish vaccine research and development in this country.

TABLE VI
HOW TO IMPROVE

- Explicit declarations of partnership by leaders of each sector
- Improve understanding of the nature of the network
  - Uniqueness of each partner
  - Interdependence of all partners
- Public policies to foster partnerships, collaboration, robustness inherent in multiple players
  - Recent CRADA change at NIH

Recommendations

It is important to understand that all players are needed for a healthy and robust system. In my opinion, explicit declarations of partnership by the leaders of each sector are required. 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 involved, the message that the entire vaccine-development network is endangered by a political climate that threatens any one component thereof. It is important to improve policy makers' understanding of the nature of vaccine development, the uniqueness of each partner, and the interdependence of all partners.

Instead of threats to the system, public policies that foster the partnership's collaboration and robustness are needed. An example of such a policy is the recent CRADA (collaborative research and development contracts between a government agency and private industry) change at the NIH, whereby the director, Dr. Harold Varmus, removed pricing controls from CRADAs. This will make it possible for many companies to collaborate with the NIH, which would not do so with the pricing controls in place. Pricing controls had not been a feature of CRADAs with other government agencies (Table VI).

The possibilities for developing vaccines that we want for the future, and the benefits that such vaccines will have for human health, are enormous. The scientific base exists. The network for development exists. There is a need, however, to protect industry, academia, and federal agencies, so that all can work together to develop these vaccines. With sound public policy, it can be done.

References

1. See Warren KS. New scientific opportunities and old obstacles in vaccine development. *Proc Nat Acad Sci USA*. 1986;83(24):9275–9277, and Halstead SB, Gellin BG. Immunizing children; can one shot do it all? *1994 Medical and Health Annual*, Encyclopedia Britannica Inc., 1993 for the "staircase" of vaccine development since 1976.
2. Plotkin SL, Plotkin SA. A short history of vaccination. In Plotkin SA, Mortimer EA Jr., eds. *Vaccines*. Philadelphia, PA: W.B. Saunders; 1988:1–7.
3. Hinman AR. Public health considerations. In Plotkin SA, Mortimer EA Jr., eds. *Vaccines*. Philadelphia, PA: W.B. Saunders; 1988:587–611.
4. Lieu TA, Cochi SL, Black SB, et al. Cost-effectiveness of a routine varicella vaccination program for U.S. children. *JAMA*. 1994;271:375–381.
5. Mercer Management Consulting. *Testimony on vaccine policy*, U. S. House of Representatives, Committee on Commerce, June 15, 1995.