Vaccine Research and Development: The Key Roles of the National Institutes of Health and Other United States Government Agencies

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Introduction

The impact and importance of vaccines cannot be overstated—they provide safe, cost effective and efficient means of preventing illness, disability and death from infectious diseases. Vaccines, along with the availability of improved medical care, living conditions, and sanitation, helped reduce mortality from infectious diseases in the Unites States more than 14-fold in the 20th century.

The United States government agencies charged with protecting and improving health traditionally have long made vaccine research and development a top priority. Together with partners in the public and private sectors, government-supported scientists have helped develop many of our most useful vaccines, including new or improved vaccines that protect against invasive *Haemophilus influenzae* type b (Hib) disease, pneumococcal pneumonia and meningitis, pertussis, influenza, measles, mumps, rubella, chickenpox, and hepatitis A and B. In addition to developing vaccines against classic infectious diseases, the National Institutes of Health (NIH) and other government agencies are working to develop new and improved vaccines against potential agents of bioterrorism, chronic diseases with infectious origins, as well as autoimmune diseases and other immune-mediated conditions. In this volume of *The Jordan Report*, several articles describe the many promising vaccine candidates currently being developed against a wide range of human diseases.

Progress and Challenges

Safe and effective vaccines, along with the operational expertise and political commitment to administer them, have led to some of the greatest triumphs in public health, including the eradication of naturally occurring smallpox and the near-eradication of poliomyelitis. Each year, immunization programs save 3 million lives worldwide, and more widespread administration of currently available vaccines could prevent at least another 3 million deaths every year.

A notable "success story" is the development and widespread use of polysaccharide-protein conjugate vaccines against Hib, developed by NIH and partners in the public and private sectors. Before these vaccines were licensed, approximately 20,000 cases of invasive Hib disease occurred among children each year, and Hib was the leading cause of childhood bacterial meningitis and postnatal mental retardation. The use of Hib conjugate vaccines has virtually eliminated invasive Hib diseases among children in the United States and other developed countries. Studies have confirmed the effectiveness of these vaccines in low-income countries, and widespread distribution of Hib vaccines could significantly reduce the global burden of this infection, which leads each year to 2-3 million cases of invasive diseases and at least 450,000 deaths worldwide. Ultimately, global vaccination programs could lead to the eradication of this terrible disease. Furthermore, the utilization of the polysaccharide-protein conjugate technology for improved pneumococcal vaccines has proven extremely promising.

Other examples of triumph in the field of vaccinology abound. For instance, vaccines that protect against Hepatitis B virus (HBV) have dramatically reduced the incidence of serious hepatic disease in countries where HBV vaccines are routinely used. As with conjugate Hib vaccines, NIH and multi-sector partners worked together to develop HBV vaccines. Efforts to increase global coverage with HBV vaccines hold great promise in significantly reducing the mortality associated with the virus, estimated to be about 900,000 deaths per year worldwide.

Despite significant progress in the development and distribution of vaccines, much remains to be accomplished. Infectious diseases remain the second leading cause of death and the leading cause of disability-adjusted life years worldwide (one disability-adjusted life year is one lost year of healthy life). Among children aged 0 to 4 years, infectious diseases cause approximately two thirds of all deaths worldwide. In 2001, approximately six million deaths were attributed to three diseases, for which no effective vaccines are available: AIDS, tuberculosis and malaria. Effective vaccines also are lacking for many other serious infectious diseases that exact an enormous toll worldwide, such as sexually transmitted diseases (other than hepatitis B), many parasitic diseases, respiratory pathogens such as respiratory syncytial virus, as well as a host of enteric diseases that contributed to more than two million diarrhea-related deaths in 2001.

In addition to endemic diseases, the world must cope with the ongoing threat of new and re-emerging diseases and the widespread development of antimicrobial resistance. More than 50 newly recognized infectious diseases and syndromes have been identified since 1980, including AIDS and its etiologic agent, the human immunodeficiency virus (HIV). HIV has now infected well over 60 million people worldwide, of whom more than a third of have died. Certain other emerging infections, such as Ebola virus and Nipah virus, are highly virulent but have so far involved relatively small numbers of people in

restricted geographic areas, and have yet to become global public health threats. Other re-emergent diseases, including vector-borne pathogens such as dengue virus and West Nile virus, continue to spread. The epidemic of West Nile Virus infections in the United States in 2002, which has markedly outstripped the initial encounter with this disease in 1999, is a stark reminder of the public health implications of re-emerging infections. In addition, the recent anthrax attacks in the United States underscore our vulnerability to infections that "emerge" because of an intentional human act.

Resistance to antimicrobial agents has been observed in virtually all classes of organisms, resulting in a diminished capacity to treat many serious infections. The world is faced with the continuing threat of antimicrobial resistance on a wider scale than ever before, with the emergence of resistant strains of a number of important microbes, including pneumococci, enterococci, staphylococci, as well as the malaria parasite *Plasmodium falciparum*, and the tuberculosis bacillus *Mycobacterium tuberculosis*. The development of viral resistance is also a major problem in the treatment of HIV-infected individuals, many of whom have been treated with all available class of antiretroviral drugs and harbor virus that that is multi-drug resistant.

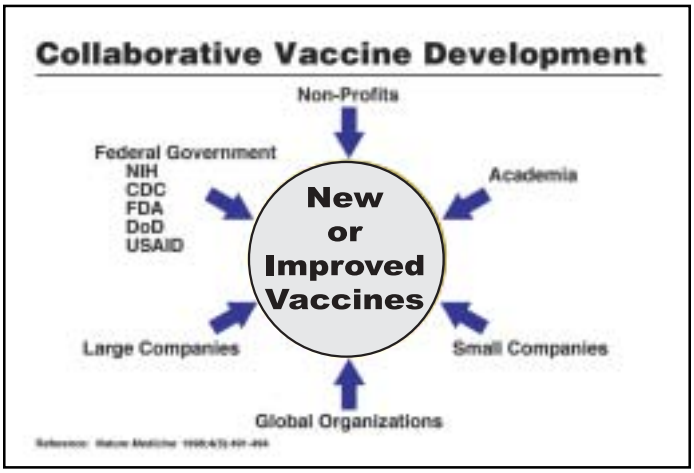
Unfortunately, safe and effective vaccines are lacking for most emerging and re-emerging diseases, as well as many endemic infections that are increasingly more difficult to treat because of antimicrobial resistance. The development of vaccines to prevent these conditions—with a particular focus on HIV/AIDS, tuberculosis, malaria, and potential agents of bioterrorism—is a critical priority of the NIH and other U.S. government agencies involved in biomedical research. Clearly, preventing an infection is preferable to attempting to treat it, especially in resource-poor settings where even rudimentary medical care is unavailable.

Collaborations and Commitment

The process whereby a vaccine is developed and tested is complex and requires many steps. The various partners in vaccine development bring perspectives, resources and skills that are sometimes unique, but more often productively overlapping and complementary. Industry provides expertise in product development and manufacturing, while many government efforts have traditionally focused on creating and expanding the scientific base in disciplines that underlie product development, a role sometimes described as "priming the pump."

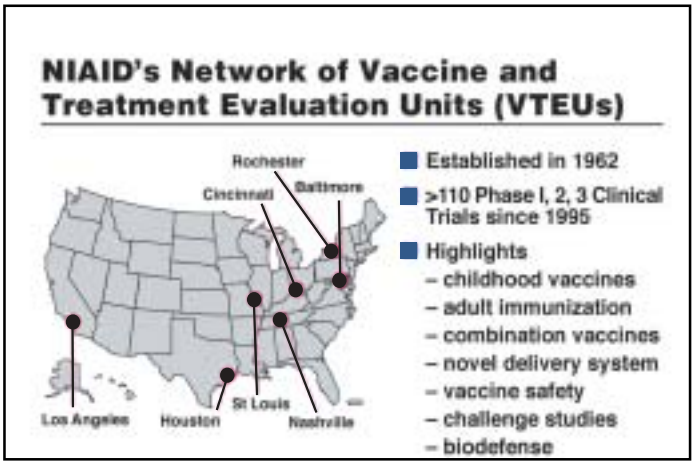
Most currently available vaccines, as well as those in the development "pipeline," have resulted from collaborations between partners in the public and private sector, including federal and state governments, global organizations, small and large companies, academic research institutions and non-governmental organizations (Figure 1).

Figure 1.



A prototypic example of successful partnerships across sectors is the development of "acellular" pertussis vaccines, based on individual components of *Bordetella pertussis*, rather than the whole bacterium. Basic research in government and university laboratories provided the insights that enabled industry to develop candidate acellular pertussis vaccines. Phase I and Phase II clinical trials of these products, supported by industry and government, were conducted at academic medical centers, notably within the National Institute of Allergy and Infectious Diseases' nationwide network of Vaccine and Treatment Evaluation Units (see Figure 2). International efficacy trials, funded and overseen by government and industry, and facilitated by public health officials through intergovernmental channels, helped provide the data that led to the licensure of acellular pertussis vaccines in the United States and abroad. These new vaccines are considerably less reactogenic than older whole-cell products and their availability has helped remove a major disincentive to vaccination against pertussis.

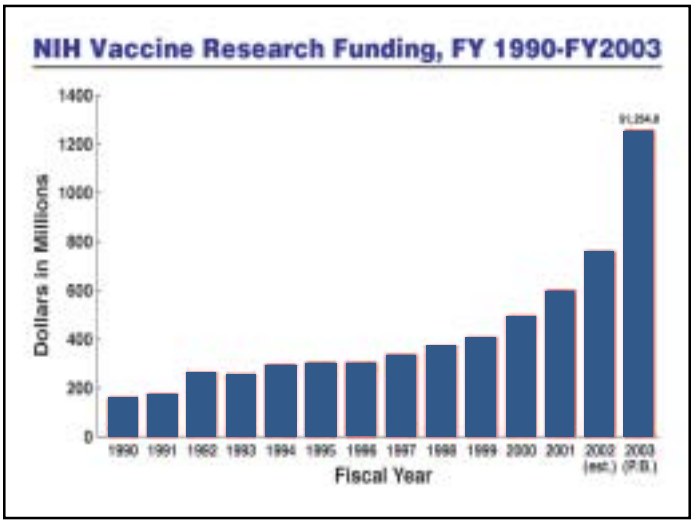
Figure 2.



The importance of vaccine development and the necessity for strong cross-sector partnerships have been recognized at the highest levels of government, both in the U.S. and internation-

ally. For example, in 2001 the United Nations General Assembly convened a special session on HIV/AIDS and adopted a resolution calling for increased investment to accelerate HIV/AIDS vaccine research. In the United States, both the executive and legislative branches have made immunization, including vaccine research and development, a top priority. In 2000, the Administration unveiled a Millennium Vaccine Initiative to promote delivery of existing vaccines in developing countries and accelerate development of new vaccines. The President's Fiscal Year 2003 Budget for vaccine research and development at the NIH calls for $1.3 billion, up more than x percent from 1990 (see Figure 3). In the US Congress, numerous legislative proposals are being pursued to support the discovery and to facilitate the delivery of vaccines (see http://thomas.loc.gov).

Figure 3.



In addition, the NIH, the Centers for Diseases Control and Prevention and other national research agencies participate in the development and/or support of public-private partnerships such as the Global Alliance for Vaccines and Immunization (GAVI), the International AIDS Vaccine Initiative, and the Malaria Vaccine Initiative, which combine the resources and skills of a wide range of collaborators. Such partnerships, which build on previous cross-sector collaborations for the donation and distribution of existing health-enhancing products, also play an important role in the research and development of new and improved vaccines. GAVI is a prototypic example; its partners include not only US government agencies, but also numerous other national governments in both rich and poor countries, pharmaceutical manufacturers, philanthropies and foundations such as the Bill and Melinda Gates Foundation, the World Health Organization, the United Nations Children's Fund (UNICEF), and non-governmental organizations.

The private sector also has demonstrated a renewed commitment to vaccine development. Recent advances in gene cloning and expression, peptide synthesis and other technologies have created new opportunities for developing patentable "bioengineered" vaccines with the potential for a substantial return on research and development cost. In addition, new initiatives such as the NIH Challenge Grant Program, which provides matching funds to companies who will commit their own dollars and resources toward developing new vaccines and other medical interventions, have helped engage the private sector and spur vaccine research and development. NIH Challenge Grants are milestone-driven awards, meaning that recipients must achieve predetermined product goals during the development process. Progress is assessed at each milestone, at which time decisions are made regarding continuing project funding.

The Government Players in Vaccine Research

Within the federal government, more than 20 different agencies have a role in vaccine research. Among these, NIH, CDC, the Department of Defense (DoD), the Food and Drug Administration (FDA), and the United States Agency for International Development (USAID) have the largest investment in vaccine development. The roles of these different agencies in vaccine development are related and complementary, and range from the support and conduct of basic research to licensure activities and program implementation. Table 1 lists examples of key roles for selected U.S agencies involved in vaccine research and development. In addition, the National Vaccine Program Office has important coordinating functions with regard to research, licensing, production, distribution and use of vaccines.

Table 1: Government Players in Vaccine Research

- **CDC** has a myriad of roles related to vaccines. Among them, the agency conducts the epidemiological studies and surveillance needed to define health priorities. In addition, CDC develops recommendations for vaccine use through the Advisory Committee for Immunization Practices (ACIP).
- **DoD** supports research into vaccines that likely will protect against pathogens that military personnel are likely to encounter.
- **USAID** supports research on vaccines of particular relevance to young children in developing countries.
- **FDA** establishes standards for the processes, facilities, and pre- and post-licensure activities needed to insure the safety and efficacy of vaccines.
- **NIH** supports, through its extramural and intramural programs, much of the basic research in microbiology and immunology that underpins vaccine development. NIH also provides research resources such as reagent repositories, genomic databases, and clinical trials support to identify vaccine targets and move candidates along the pathway to licensure.

Sources: Folkers/Fauci, 1998; National Vaccine Advisory Committee, 1997

The Key Role of Basic Research

Basic biomedical research funded by NIH and other agencies underpins vaccine development. Historically, scientific advances in microbiology and related disciplines have led to the development of new vaccines. For example, the identification of microbial toxins, as well as methods to inactivate them, allowed the development of some of our earliest vaccines, including those for diphtheria and tetanus. In the 1950s, new tissue culture techniques ushered in a new generation of vaccines, including those for polio, measles, mumps and rubella. In recent years we have seen rapid advances in our understanding of the immune system and the complex interactions between pathogens and the human host, as well as extraordinary technical advances such as recombinant DNA technology, gene sequencing and peptide synthesis. These developments have created opportunities for identifying new vaccine candidates to prevent diseases for which no vaccines currently exist; improving the safety and efficacy of existing vaccines; and designing novel vaccine approaches, such as new vectors and adjuvants.

NIH and other agencies actively pursue research portfolios that involve interaction with industry and academia and the transfer of technology to the private sector for commercialization. Historically, an important focus of these efforts has been to further explore concepts that may not be of immediate financial interest, including those for which the principal market might be less developed nations, but nonetheless are of great potential public health importance. The government also plays a critical role in vaccine development by providing scientists with reagents that might not otherwise be shared because of proprietary interests. Of growing importance are research resources such as reagent repositories, genomic databases, animal models, and clinical trials support, as well as milestone-driven partnerships and contracts. Increasingly, government agencies such as NIH have sought to overcome challenges to vaccine development by conducting translational research that takes basic research findings through the process of target identification, and preclinical and clinical development.

The use of the new technologies in the 21st century promises to provide a renaissance in the already vital field of vaccinology. In particular, the availability of the annotated sequences of the entire genomes of microbial pathogens will allow for the identification of a wide array of new antigens for vaccine targets. A number of government agencies, including NIH and DoD, support projects to sequence the genomes of medically important pathogens. Sequence information can be used in many ways, including identifying antigens to incorporate into vaccines. The success of the first microbe sequencing project—the delineation of the complete *Haemophilus influenzae* genome in 1995—encouraged the current government-sponsored efforts to sequence the full genomes of many other pathogens. NIH has made a significant investment in the growing field of microbial genomics, and has funded the genomic sequencing of more than 60 medically important microbes. Approximately 20 of these projects have been completed, including the sequencing of bacteria that cause tuberculosis, gonorrhea, chlamydia, cholera, the parasite that causes malaria, as well as the mosquito that transmits malaria. These sequencing efforts have been facilitated by technologies such as DNA chip technology and microarrays that enable the rapid, simultaneous analysis of tens of thousands of genes.

Addressing the Threat of Bioterrorism

The anthrax attacks of 2001in the eastern United States revealed significant gaps in our overall preparedness against bioterrorism, giving a new sense of urgency to biodefense efforts, especially with regard to vaccine development. NIH has significantly bolstered research efforts on vaccines against many of the pathogens considered to be bioterrorist threats, with an eye toward producing products that are safe and effective in civilian populations of varying ages and health status. Recently, a clinical trial conducted by several of NIAID's Vaccine and Treatment Evaluation Units demonstrated that existing stocks of the smallpox vaccine known as Dryvax could successfully be diluted at least five-fold and retain its potency, effectively expanding the number of individuals who could be immediately vaccinated against smallpox using existing stocks if a smallpox attack were to occur. In addition, a second-generation smallpox vaccine is now being produced in cell culture, and large supplies of this product are scheduled to be available by the end of 2002. This new product, as well as more than 75 million additional doses of smallpox vaccine that have been stored by a pharmaceutical company since 1972, will be tested for safety and immunogenicity by NIH-supported investigators. In the long-term, basic research promises to provide a third generation of smallpox vaccines that could be used in all segments of the population, including pregnant women and people with weakened immune systems. One such vaccine nearing phase I clinical trials is based on Modified vaccinia Ankara (MVA), which is related to the current smallpox vaccine strain, but may cause fewer adverse reactions. Additional bioterrorism vaccines also are in various stages of development. To name just two, a new anthrax vaccine, based on a bioengineered component of the anthrax bacterium called recombinant protective antigen (rPA), will soon enter human trials. On the NIH campus, researchers at the NIAID Dale and Betty Bumpers Vaccine Research Center have developed a DNA vaccine that protected monkeys from infection with Ebola virus, and that will undergo testing in human volunteers beginning in early 2003. In each of these endeavors, NIH is working closely with partners in the public and private sectors.

As we prepare for the public health challenges of endemic, emerging and re-emerging infectious diseases, it is imperative that a robust commitment to basic research and cross-sector

collaboration be maintained. Only with such collaborations can we successfully translate basic research findings and technological advances into improved health through immunization.

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Since 1984, Dr. Fauci has been Director of the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). He also is Chief of the Laboratory of Immunoregulation at NIAID.

Dr. Fauci has made many contributions to basic and clinical research on the pathogenesis and treatment of immune-mediated diseases. He has pioneered the field of human immunoregulation, making a number of scientific observations that serve as the basis for current understanding of the regulation of the human immune response. Dr. Fauci has made seminal contributions to the understanding of how the acquired immunodeficiency syndrome (AIDS) virus destroys the body's defenses.

At major medical centers throughout the country, Dr. Fauci has served as Visiting Professor. He has lectured throughout the world and is the recipient of numerous awards.

Dr. Fauci is a member of the National Academy of Sciences; Royal Danish Academy of Science and Letters; American College of Physicians; American Society for Clinical Investigation; Infectious Diseases Society of America; American Academy of Allergy, Asthma and Immunology; and other professional societies. He serves on many editorial boards and is author, coauthor, or editor of more than 1,000 scientific publications

Author's Biography

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Gregory K. Folkers is Special Assistant to the Director, NIAID. A 1981 graduate of Dartmouth College, Folkers holds an MPH from Johns Hopkins University and an MS in science journalism from Boston University. He has written extensively about HIV/AIDS and other global health issues.