Vaccines have led to some of the greatest public health achievements in history, including the worldwide eradication of naturally occurring smallpox and the near eradication of polio. In addition, vaccines have contributed to significant reduction in the disease burden imposed by measles, mumps, hepatitis, influenza, diphtheria, and many other infections. The science of vaccinology is dynamic; it unfolds as technology enables scientists to continue to create safer and more effective vaccines. Safety evaluation is integrated into every step of the vaccine research and development process.

The National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute at the National Institutes of Health (NIH) for research and development of vaccines against emerging and reemerging infectious diseases (Text Box 1). Together with partners throughout the federal government, in academia, and in the public and private sectors, NIAID-supported scientists have helped develop many important life-saving vaccines against diseases such as invasive Haemophilus influenzae type b (Hib), pneumococcal pneumonia, meningitis, pertussis, influenza, chickenpox, and hepatitis A and B. Use of these and other vaccines worldwide has made significant contributions to public health by reducing the morbidity and mortality associated with many dreaded infectious diseases (Text Box 2).

STAGES OF VACCINE DISCOVERY, DEVELOPMENT, AND EVALUATION

Discovery, development, and evaluation of vaccines are performed in multiple stages as promising ideas are developed into potential vaccine candidates. Developing a vaccine usually involves collaboration between federal agencies, academia, and industry. The NIAID’s role in vaccine development and testing extends from basic research through clinical evaluation (Fig 1).

Basic Research: Understanding Pathogenesis of the Microbe and the Host Response Is Instrumental in Creating Safe and Effective Vaccines

Basic research includes studies that characterize how microbes survive and multiply, elucidate complex host-microbe interactions, and increase understanding of how the host responds. Elucidating immunologic mechanisms and developing novel technologies applicable to vaccine design and development are important areas of basic research supported by the NIAID. Research on innate and adaptive immunity aims to increase our ability to manipulate immune responses through better understanding of the underlying molecular, cellular, and systemic aspects of natural host defenses and antigen-specific immunity.

Another important area of emphasis is research on activation of the innate immune system by vaccine adjuvants and establishment of long-
term protective antibody and T-cell memory responses. Basic research in these areas contributes to vaccine safety in 2 important ways. First, it provides the knowledge and analytical tools for understanding the immunologic basis of protective immune responses as well as a framework for approaching studies of adverse events. Second, basic studies of the immunology of pathogen-host interactions contribute to the overall goal of improved vaccine efficacy with fewer adverse effects. For example, identifying the pathogen-specific and non-specific components of immune responses of diverse subjects to different vaccine formulations has the potential to shed light on the genetics of vaccine responses and adverse effects. Such studies can also provide information on the immunologic basis of inflammation and on adjuvant activity. Knowledge gained can provide a basis for engineering simpler, better-defined immunogens and live attenuated viral vaccines. Research in animal models enables rapid discovery of immunologic mechanisms and detailed functional analyses. Ultimately, studies must transition to humans for development of new vaccines and adjuvants. The NIAID has been increasingly emphasizing human immunology research to address uniquely human immunologic mechanisms and the vast genetic diversity of human populations. Future studies are planned to define the capacity and quality of the immune response throughout infancy and childhood and to identify the molecular basis for different immune/physiologic responses to vaccination at different stages of life.

**Target Identification: In Vitro and In Vivo Assessments of Safety and Efficacy**

Basic research sets the stage for the target-identification phase in which researchers identify portions of the microbe that will stimulate a potentially protective host immune response. Preclinical development includes testing in vitro and in relevant animal models to evaluate safety, immune response, and efficacy before clinical research can begin. The NIAID provides extensive resources for researchers, including a diverse array of preclinical services (eg, access to in vitro and in vivo testing, animal models, samples and reagents, and special patient populations). (For more information on available research resources, visit www.niaid.nih.gov/LabsAndResources/resources.)

**Clinical Evaluation for Safety and Efficacy**

Once the preclinical data package has been approved by the US Food and Drug Administration, sequential phases of clinical evaluation, each of which includes careful and extensive monitoring for safety, can commence. Phase I, which involves a small number of participants (typically 20–80), is...
used to evaluate safety and determine the most appropriate dose and dosage. Phase II further evaluates safety and efficacy and continues to determine the appropriate vaccine dose in larger numbers of subjects (usually 100–300 participants). Phase III clinical evaluation, which involves larger numbers of subjects, is used to confirm efficacy, collect additional safety information, and, if applicable, compare with existing vaccines. Phase III studies typically involve 1000 to 3000 participants, although a recent NIAID phase III study of a vaccine against herpes simplex virus had a sample size of 7000. For the vast majority of vaccine candidates that reach phase III clinical trials, substantial safety information has already been obtained, because previous preclinical studies and clinical evaluation have typically eliminated those candidates for which acute safety concerns are immediately evident.

**UNDERSTANDING THE HOST IMMUNE RESPONSE**

A new dimension in vaccine-safety research is rapidly taking shape as a result of advances in the analysis of human immune responses. Advances include high-throughput gene-expression profiling, methods to study individual T and B cells that are antigen-specific, and integration of vast amounts of data by using bioinformatics and systems biology. For example, individual, antigen-specific human T cells can be isolated by using special reagents. These T cells can then be extensively phenotyped by using gene arrays and next-generation nucleic acid sequencing. Large-scale cloning of human antibodies from individual B cells is providing new understanding of their origin, specificity, and binding characteristics. Innate immune responses of human dendritic cells, macrophages, and other antigen-presenting cells are being phenotyped in detail.

These techniques enable the detailed phenotyping of human responses to various vaccines; the goal is to develop an “encyclopedia” of human immunity. By understanding the molecular and cellular pathways that lead to healthy, protective responses and how they may differ when responses are inadequate, short-lived, or deleterious, vaccine researchers will have the information and tools that enable the clinical testing of new vaccines and provide methods to analyze adverse events.

The NIAID supports several immunology networks that aim to better understand how the human immune system responds to infection and vaccination, as well as databases, reagent resources, and bioinformatics tools for immunologic research. (For more information on NIAID immunology programs, see www.niaid.nih.gov/about/organization/dait/programsNetworks.htm.)

**Immune Response to Microbes and Vaccines**

Genetic variations in humans may play a significant role in susceptibility to infection and quality of response to vaccinations. Several NIAID programs provide support to further the understanding of variability in human immune responses to infectious pathogens and vaccination. The NIAID supports a network of sites (Population Genetics Analysis Program: Immunity to Vaccines/Infections) that are studying these associations by analyzing protein-expression levels and protein function. For example, 1 site is examining the possible significance of genetic polymorphisms in immune response induced by vaccinia immunization.

The Atopic Dermatitis and Vaccinia Network supports research to reduce the incidence and severity of eczema vaccinatum, a disseminated viral infection that can occur in subjects with atopic dermatitis after smallpox immunization or inadvertent exposure to a vaccinated person. One of the findings from that program is that the cytokines in the skin of patients with...
atopic dermatitis contribute to a deficiency in antimicrobial peptides, one of the body’s innate immune defenses that is essential for protection of skin from infections.

The goal of the Cooperative Centers for Translational Research on Human Immunology and Biodefense is to further knowledge of human immune responses against infectious pathogens and to increase understanding of the molecular mechanisms responsible for both short-term immunity and long-term immune memory. For example, one center is examining smallpox immunization in people with cancer or eczema, and another is focused on research on vaccine-induced immunity in the young and aged.

Studies supported by the Immune Function in Children, Elderly, and Immunocompromised Populations program are focused on defining the molecular basis for differential immune capabilities in combating infection or responding to vaccination at different stages of life, or in people with different underlying health problems.

Human Immune Phenotyping and Vaccines

Vaccine-safety research requires the ability to understand factors that may contribute to variable immunization outcomes in recipients across genders, a wide range of ages, ethnic backgrounds, and immune competence. Currently, there is little information on what constitutes a “normal” human immune system, although that is beginning to change. The NIAID recently awarded grants for a new program designed to characterize diverse states of the human immune system (1) after infection, (2) before and after vaccination against an infectious disease, or (3) before and after treatment with an immune adjuvant that targets a known innate immune receptor(s). This program takes advantage of recent advances in systems biology, bioinformatics, and high-throughput multiplex assays that have resulted in the ability to more readily measure immune responses. (For more information, visit www.niaid.nih.gov/news/newsreleases/2010/Pages/HIPROCcenters.aspx.)

The potential benefit of human immune phenotyping for vaccine development was illustrated by a recent study in which responses to the yellow fever vaccine were analyzed. Using a systems biology approach to understand protection afforded by this well-established vaccine, NIAID-supported scientists identified gene-activity profiles that predicted immunity. Analysis of large data sets identified key genetic patterns; mathematical analysis enabled positive identification of 2 distinct sets of early immune genes that predicted the T-cell response with 90% accuracy and the B-cell response with 100% accuracy. Understanding the response of the human immune system to vaccination may facilitate design and development of better vaccines and identification of correlates of protection and help scientists identify novel approaches to protecting against diseases such as malaria and HIV for which no vaccines are currently available.

Predicting the immunogenicity of a new vaccine is only one of several benefits that may arise from the use of these new technologies. Recent advances in the field of vaccinology have revealed that vaccine responses are often far more robust than previously appreciated. The immunogenicity of a vaccine is not a complete predictor of its efficacy, and it is important to distinguish between response profiles that correlate with vaccine immunogenicity and protection from those that may signal an overly vigorous response. Thus, developing an understanding of human immune profiles that predict vaccine safety and effectiveness in different populations is a critical need.

Adjuvants and the Innate Immune System

The discovery and development of novel adjuvants, which include compounds that stimulate the innate immune system, are important components of the NIAID vaccine research and development program. Receptors of the innate immune system are “hard-wired” to detect elements unique to the microbe, such as components of the cell wall or forms of nucleic acid not found in vertebrates. By using high-throughput library screens to identify potential adjuvant candidates that stimulate an innate immune response, several lead candidates have been identified and subsequently optimized and evaluated in animal models in which they have proven efficacious. The best candidates are now being developed for phase I clinical trials. Knowledge gained from this research is likely to benefit future vaccine development and formulation.

Other NIAID-supported research is focused on increasing understanding of how adjuvants work. Recent research has revealed how the adjuvant alum interacts with, and stimulates, the immune system to help provide protection against infectious diseases. Alum seems to activate a cluster of proteins found in certain immune cells that regulate the release of substances that promote inflammation. This discovery, which identifies some of the cellular machinery that helps provoke an effective immune response, may help scientists develop safer and more effective vaccines against a wide variety of pathogens.

Clinical studies conducted by industry have analyzed the safety profile of adjuvants in people with chronic diseases, including those on immunosuppressive therapy. In these studies,
autoimmune symptoms did not seem to increase in people given adjuvants, which provides reassurance about their safety.

**SAFELY PERFORMING VACCINE-SAFETY RESEARCH**

At the NIH, vaccine safety is an integral part of every aspect of the development and evaluation of vaccines for specific diseases. Throughout the clinical research process, vaccine testing focuses on safety. When a study protocol is developed and before it is presented to the research community, safety concerns that would halt the study are clearly delineated. Likewise, measures to protect the safety of individual volunteers and reasons to discontinue a volunteer’s participation in the study because of safety concerns are also clearly delineated in the protocol. NIH vaccine research is performed with an investigational new drug application in place with the Food and Drug Administration (FDA). The FDA performs a review of the preclinical data, clinical data, and the protocol design for human volunteer concerns before a study can start.

Before a vaccine study starts, each NIH protocol is also reviewed and approved by an institutional review board. The institutional review board review and approval encompasses the ethics of performing a study and a determination of the balance between the risks and the benefits to each subject. During a vaccine study, each subject is actively questioned about both local and systemic reactions to vaccines. Information about reactions and adverse events is collected for at least 6 weeks and as long as 1 year after vaccination. The clinical investigator and the study staff are the first line of this data collection. Medical monitors, who are clinicians who work at the NIH, review safety data for each clinical study across all study sites. Also, safety-monitoring committees (SMCs) and data safety-monitoring boards (DSMBs) provide a second and independent review of the safety data. On the basis of the SMC or DSMB review of the safety data, the SMC or DSMB can recommend that clinical trials be stopped or modified or continue unchanged. Most NIAID vaccine studies are blinded and randomized, and many are placebo-controlled to maximize the chance of detecting a safety or toxicity signal. After completion of the study, the safety and efficacy data are reviewed to determine if further clinical trials with a vaccine candidate are necessary or warranted.

The NIAID has extensive internal resources to manage clinical trial execution. The focus is on human volunteer safety and the accuracy of the data collected. These resources help design and review the science, collect data, organize safety committees, and keep track of the progress of the studies. The NIAID participates in ongoing activities that include other organizations. Data from trials are submitted to the Vaccine Adverse Events Reporting System or to MedWatch as appropriate. During the recent H1N1 pandemic, the NIAID participated in a government-wide independent review of the safety of the H1N1 vaccine that was coordinated by the National Vaccine Program Office called the National Vaccine Advisory Committee working group: H1N1 Vaccine Safety and Risk Assessment Working Group. The safety data collected during the NIAID-sponsored clinical trials were presented to this group as part of the US government’s effort to make the safety profile of the H1N1 vaccine fully transparent.

In addition, the NIH supports research to address specific vaccine-safety research hypotheses. For example, when concerns about the effects of methyl mercury sparked questions about the safety of thimerosal, which contains a different mercury compound (ethyl mercury), the NIH supported studies to compare the 2 substances. Studies included comparison of ethyl and methyl mercury distribution in nonhuman primates and comparative pharmacokinetic and pharmacodynamic studies. Studies of how infants metabolized and excreted thimerosal after routine immunizations were also conducted. The results revealed important differences in the way that infants metabolized the 2 compounds. Ethyl mercury levels in blood and urine were uniformly low in all infants studied and, in many cases, too small to measure. There was no evidence of ethyl mercury accumulation in children between vaccinations. These results show that ethyl mercury is cleared from the body much more quickly than methyl mercury and confirm that methyl mercury is not an appropriate model for assessing risk from thimerosal.

Recently, several NIH institutes, including the NIAID, have collaborated on an ongoing initiative to encourage research to address important scientific questions and issues related to vaccine safety. It is hoped that this type of research will contribute to the overall understanding of issues surrounding vaccines and their safety. Examples of relevant research areas that are encouraged by this initiative include:

- detailed evaluation of various host immune/physiologic responses to currently licensed vaccine antigens and/or adjuvant combinations;
- evaluation of existing childhood immunization schedules to optimize safe and long-term protective immune memory;
- studies that define the capacity and quality of the immune response throughout infancy and childhood (can vaccines be further optimized...
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lovirus, or that might be deliberately re-

West Nile virus, rotavirus, and cytomega-

that either arise naturally, such as
cines against disease-causing agents
areas of focus include devising vac-
cines for those illnesses a focus of re-
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For this reason, the NIH continues to
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illness and death from the relatively
vaccine research, much remains to be
Despite the many accomplishments in

KEYS TO FUTURE SUCCESS

Despite the many accomplishments in vaccine research, much remains to be
done. Millions around the globe suffer
illness and death from the relatively
new disease HIV/AIDS and the ancient
 scourges of malaria and tuberculosis.
For this reason, the NIH continues to
make developing new or improved vac-
cines for those illnesses a focus of re-
search and development activity. Other
areas of focus include devising vac-
cines against disease-causing agents
that either arise naturally, such as
West Nile virus, rotavirus, and cytomega-
lovirus, or that might be deliberately re-
leased in an act of bioterrorism. Finding

ways to quickly, effectively, and safely
produce vaccines against strains of in-
fluenza that experts fear may spark a
pandemic is also an area of interest area
for the NIH.

Global demand for rapid development
of a vaccine against the 2009 H1N1 in-
fluenza pandemic highlighted the ur-
gey of developing new, faster, more
efficient methods of vaccine produc-
tion. Currently, influenza vaccines pro-
duced in the United States rely on
egg-based manufacturing methods. In-
fluenza vaccines have been prepared
in eggs for >50 years, but the process
is lengthy and requires hundreds of
millions of fertilized eggs. Cell culture-
based vaccines are currently licensed
only in Europe, and it may be some
time before vaccines produced by us-
ning cell cultures are licensed in the
United States. The NIH actively sup-
ports research to develop new and
improved vaccines and vaccine-
production technologies for influenza.
Innovative vaccine technologies being
developed by the NIH and its industry
partners include using recombinant
DNA to create subunit vaccines in
which various influenza virus proteins
are selectively produced in cultured
cells and are then purified and used in
a vaccine. This and other “next-
generation” vaccines will require re-
search effort and time to reach com-
mercial levels of manufacturing.

In addition to developing vaccines
against classic infectious diseases
and emerging microbes, the NIH is
working to develop new and im-
proved vaccines against chronic dis-
esases with infectious origins as well
as therapeutic vaccines against au-
toimmune diseases and other
immune-mediated conditions. Thera-
peutic vaccines that could be effec-
tive against cancer and other dis-
eases in which immune system
activation may be beneficial are also
being developed and tested.

Successful vaccine research and de-
velopment requires collaborative ef-
forts in which each partner plays a
unique role. For example, vaccines
against NIAID category A through C
priority pathogens (microbes and toxins
considered to be the most significant
threats to the nation’s well-being) are
of the highest public health priority.
However, the private sector has only
limited incentives to invest in develop-
ment of vaccines against these patho-
gens, given the absence of a substan-
tial commercial market, regulatory
hurdles, and extensive clinical trial re-
quirements. To remedy this situation,
the NIH offers services to facilitate the
movement of promising vaccine candi-
dates through the research and devel-
opment pathway. These services in-
clude preclinical planning, process
development and manufacturing,
formula and stability, assay develop-
mport, sample-testing, in vivo immuno-
genicity, and vaccine safety and
toxicity testing.

New understanding of human immune
responses to vaccination is poised to
emerge on the basis of better model-
ing of normal and adverse reactions,
novel technologies that can rapidly
and accurately determine immuno-
logic characteristics of clinical sam-

ultimately, the development of a vaccine
from idea through licensure cannot be
accomplished by 1 group or organiza-
tion. True partnerships between govern-
ment, academia, industry, foundations,
and other organizations hold the key to
creating safe and effective vaccines that
meet the ultimate goal of preventing ill-
ness or death in the community.
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Integrating Safety and Efficacy Evaluation Throughout Vaccine Research and Development

George Curlin, Sarah Landry, Jessica Bernstein, Richard L. Gorman, Barbara Mulach, Charles J. Hackett, Stephanie Foster, Sarah E. Miers and Patricia Strickler-Dinglasan

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