National Institute of Allergy and Infectious Diseases

REPORT OF THE BLUE RIBBON PANEL ON INFLUENZA RESEARCH

September 11-12, 2006

Report of the Blue Ribbon Panel on Influenza Research

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I. EXECUTIVE SUMMARY

The National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH) of the Department of Health and Human Services (DHHS), has primary responsibility within the Federal government for basic and applied influenza research. In early 2006, NIAID undertook a comprehensive examination of its influenza portfolio to improve its planning and coordination in this area, and to take full advantage of recent scientific and technological advances. NIAID then convened a Blue Ribbon Panel on Influenza Research to identify areas of influenza research in which progress is needed.

The panel outlined several strategic principles that should guide the research and provided specific research recommendations in eight areas in which substantial progress is needed. Taken together, these principles and recommendations provide a framework to guide NIAID's influenza research activities in the years to come.

Guiding Principles

Five important principles regarding the conduct of influenza research emerged repeatedly during the panel's deliberations.

- Promote innovative multidisciplinary research.
- Integrate seasonal and pandemic influenza research activities.
- Balance investigator-initiated and targeted research.
- Maximize applicability of influenza research results to other fields.
- Enhance research coordination and collaboration within NIH, within DHHS (especially with the Centers for Disease Control and Prevention, CDC), across all Federal agencies, with private industry, and internationally.

These overarching, strategic principles are critical to the successful implementation of the recommendations that follow.

Research Recommendations

The panel identified eight specific aspects of influenza research in which there are substantial gaps in knowledge and outlined several key recommendations within each area which are essential for progress to be made:

Influenza at the Animal-Human Interface

Scientific understanding of how animal and human influenza viruses interact, including how influenza viruses circulate among various reservoirs and the evolutionary pressures that lead to the emergence and spread of new viral sub-types, could be improved.

- Elucidate patterns of influenza virus diversity and evolution.

- Define patterns of influenza virus transmission in and between human and animal populations.
- Examine interactions of diverse influenza viruses with various hosts.

Influenza in Individuals
Many aspects of human clinical and immune responses to influenza infection, such as the role innate and adaptive responses play in pathogenesis and the host genetic factors that lead to severe influenza outcomes, have not been fully described.

- Increase understanding of influenza pathology and pathogenesis in humans.
- Fully describe human cellular immune responses to influenza infection.
- Describe innate and mucosal immune mechanisms in influenza.
- Map genomics and proteomics of human responses to influenza viruses.
- Strengthen infrastructure for clinical influenza research.

Influenza in Human Populations
Many aspects of influenza epidemiology, including the relative importance of aerosol, droplet, and fomite transmission and the contribution of specific sub-populations such as schoolchildren to epidemic spread, are not adequately understood.

- Expand understanding of influenza viruses in different human populations.

Animal Models
Animal models, which are essential tools for virtually all aspects of influenza research, could be improved.

- Enhance the depth of understanding of commonly used models.
- Increase the range of options for animal models.
- Improve the availability of appropriate animals for use in influenza research.

Vaccines
Development of improved influenza vaccines is a key priority for the control of both seasonal and pandemic influenza.

- Define all correlates of immune protection from influenza.
- Facilitate studies that include challenge of human volunteers with live virus.
- Improve adjuvants and other dose-optimization technologies for influenza vaccines.
- Define evaluation criteria for vaccine efficacy testing.

Therapies
Expansion of the current repertoire of antiviral drugs and other therapies to reduce the severity of influenza outcomes would allow better control of both seasonal and pandemic influenza.

- Expand studies of currently licensed antiviral drugs.
- Develop new drugs and new drug targets for influenza.
- Investigate therapies for late-stage, severe influenza.

Assay Technologies

The advent of new technologies such as DNA microarrays has provided new opportunities to improve diagnostic and immunological assays relevant to influenza.

- Develop new point-of-care diagnostic assays.
- Improve and standardize assays for cellular immune responses to influenza.
- Improve methods for assaying immune responses in the respiratory tract.

Resources

- Expand the range of materials available to the research community.
- Increase services for researchers.
- Improve mechanisms for the exchange of information among researchers.

II. INTRODUCTION

A. Background

Influenza is a familiar but dangerous infectious disease. Historical records indicate that influenza epidemics have occurred among human populations for hundreds if not thousands of years. The virus was first isolated in the 1930s, and by the 1940s an influenza vaccine had been shown to be capable of preventing infection among young, healthy adults. Since the 1960s, U.S. public health authorities have recommended annual influenza vaccination for the elderly and other people at high risk for severe influenza outcomes.

Influenza, however, continues to impose a substantial annual burden of morbidity and mortality. An average of about 200,000 influenza-related hospitalizations and about 36,000 influenza-related deaths occur in a typical winter-seasonal epidemic in the United States; the majority of these severe outcomes occur among seniors aged 65 years and older.[1] The cumulative burden is even more striking: approximately 900,000 influenza-related deaths have occurred in the United States over the past 30 years,[2] making influenza one of the leading causes of death among vaccine-preventable infections.

Beyond the seasonal toll, however, influenza viruses have an as yet unpredictable ability to cause devastating pandemics. Influenza pandemics occur when a virus arises that causes illness, is one with which the population has no prior immunological experience, and is easily transmitted between individuals. Three influenza pandemics occurred in the 20th century. The pandemics of 1957 and 1968 were serious infectious disease events that killed approximately two million and 1 million people worldwide, respectively; the 1918 pandemic, however, was catastrophic, and caused an estimated 40 million deaths worldwide.[3]

The current global outbreak of H5N1 avian influenza among domestic and wild birds, as well as a growing awareness of the burden of seasonal influenza and the potential for another catastrophic pandemic, has refocused attention on the threat of influenza. As of June 6, 2007, 310 cases of human H5N1 influenza infection had been confirmed; of these, 189 had died as a consequence.[4] Although a few instances of human-to-human transmission have been documented, the virus has not acquired the ability to spread

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[1] Thompson WW, Shay DK, Weintraub E Brammer L, Cox N, Anderson LJ, and Fukuda K.. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 289:179 (2003).
[2] Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Impact of influenza vaccination on seasonal mortality in the U.S. elderly population. Arch Intern Med 165:265 (2005).
[3] WHO, Avian Influenza: Assessing the Pandemic Threat, January 2005. Available at http://www.who.int/csr/disease/influenza/H5N1-9reduit.pdf, accessed February 8, 2007.
[4] Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO, available at http://www.who.int/csr/disease/avian_influenza/country/en/, accessed February 5, 2007.

efficiently in the human population.[5] The vast majority of human cases are strongly linked to exposure to infected domestic fowl.

Within the Federal government, NIAID, a component of NIH and DHHS, has long held primary responsibility for both the conduct of scientific research in influenza and for carrying out applied research and clinical evaluation to foster development of drugs, vaccines, and diagnostic tools; this role was reconfirmed in the 2005 DHHS Pandemic Influenza Plan. Annual funding for influenza research at NIAID has increased from approximately $15 million in fiscal year 2001 to an estimated $212 million in fiscal year 2007.

Much has been learned, but many basic scientific topics must be more fully explored, and vaccines, drugs, and diagnostics for influenza need to be improved. Accomplishing these goals will help policy makers make the difficult choices involved in pandemic planning by arming them with better countermeasures and scientific information. Only continued basic and applied research can lay the foundation for development of new vaccines, therapies, and diagnostic tools that will allow society to cope effectively with the next influenza pandemic.

B. Planning and Assessment Process

To improve the planning and coordination of NIAID influenza research activities, to identify research gaps, and to ensure that these activities are structured to take full advantage of every avenue that recent scientific and technological advances have to offer, NIAID undertook a comprehensive examination of its influenza research portfolio. In February 2006, a one-day "NIAID Influenza Research Summit" of senior NIAID scientific staff was convened, at which the influenza research activities of the Institute were reviewed and specific gaps and opportunities identified.

NIAID then convened a 35-member Blue Ribbon Panel on Influenza Research to build on the results of the February meeting. Panel members were chosen from among scientists affiliated with academic research institutions, various U.S. government and international agencies, vaccine and pharmaceutical manufacturers, and non-governmental organizations. NIAID deliberately sought to create a panel of experts with broad experience and a wide variety of viewpoints and expertise.

The Blue Ribbon Panel met in Bethesda, MD, on September 11-12, 2006. The goal of the meeting was to provide guidance for NIAID's influenza research activities in the coming years. On the first day, participants separated into three groups for discussions. All three breakout groups were given the charge to review, comment on, and suggest additions to the report from the NIAID Influenza Research Summit, and to recommend approaches that NIAID could use to develop an innovative research agenda to guide its future influenza research program. They were also asked to identify barriers that must be overcome, partnerships that must be forged, and resources that must be provided to speed

[5]WHO, Basic health information on Human Avian Influenza A/H5N1. http://www.wpro.who.int/information_sources/databases/regional_statistics/rstat__Human_Avian_influenza.htm, accessed June 11, 2007.

research progress. Participants were urged to think broadly and for the long term, paying particular attention to how new technological advances in research could be applied for maximum effect. The entire panel reconvened on the second day for presentations from each breakout group, and for discussion of the issues raised.

This report presents a summary of the Panel's deliberations and recommendations. Section III, "Guiding Principles," presents five overarching, strategic approaches to the conduct of influenza research that emerged during the Panel's discussions. Section IV, "Research Recommendations," presents specific recommendations in eight areas of influenza research in which substantial progress is both needed and, with sufficient effort, will likely occur. Taken together, these principles and recommendations provide a framework to guide NIAID's influenza research activities in the years to come.

III. GUIDING PRINCIPLES

Throughout both the February NIAID Influenza Research Summit and the Blue Ribbon Panel meetings, several important themes regarding the conduct of influenza research emerged repeatedly and in multiple contexts. These themes are summarized here as five strategic principles to guide NIAID's influenza research program.

A. Promote innovative multidisciplinary research

Increasingly, a multidisciplinary approach that integrates individuals from diverse fields—both within and beyond the life sciences—is required to translate biomedical research advances into improved patient care. Indeed, well-integrated teams of individuals with different perspectives, approaches and expertise are needed to solve basic and applied research problems related to influenza. Laboratory-based scientists with expertise in, for example, virology, immunology, genomics, ecology, evolutionary biology and epidemiology, should work with clinical researchers with expertise in, for example, infectious diseases and pulmonology, to conduct both laboratory and clinical research. It is equally important that research teams include individuals drawn from non-biological disciplines as needed, such as physics, mathematics, engineering, and computer science. Integration of divergent fields, people and perspectives into a well-coordinated influenza research program will be essential in order to make rapid progress.

B. Integrate seasonal and pandemic influenza research activities

Seasonal and pandemic influenza differ mostly in virulence and the degree of immunity present in the human population. Increased basic understanding of seasonal influenza helps the development of vaccines and other countermeasures that could be used against the next influenza pandemic; and increased development of new vaccines, treatments, and diagnostics for seasonal influenza will strengthen our ability to respond adequately when the next pandemic influenza virus emerges. There is one caveat to this principle, however. Because a pandemic virus is by definition one with which scientists and physicians have little experience, specific plans, infrastructure and protocols that allow laboratory and clinical study of a pandemic influenza virus to proceed rapidly need to be developed before a pandemic virus emerges.

C. Balance investigator-initiated basic research with targeted research activities

Much contemporary research requires large-scale or multi-site collaborative projects that are beyond the reach of any single investigator. At the same time, however, investigator-initiated basic research projects, which have for decades been the foundation of NIH-funded research and the source of knowledge on which new medical interventions are based, will continue to be critically important. Thus, it is crucial that NIAID continue to support investigator-initiated studies in influenza.

D. Maximize broad applicability of influenza research results

Much of the knowledge gained as a result of the influenza research effort, as well as many of the product platforms developed, may be applicable to other infectious diseases. Influenza research activities should be structured to take full advantage of any

opportunities to collect data with broad uses and to create technology platforms and infrastructure applicable to other infectious diseases, and thereby capitalize on these opportunities to the greatest extent possible.

E. Enhance Research Coordination and Collaboration

Influenza research demands cooperation and collaboration across international and organizational boundaries, as well as across scientific disciplines and between public and private entities. At both the February and September meetings, however, a clear consensus emerged that collaboration and coordination in influenza research at all levels is at present imperfect and should be improved. The strong collaborative relationships that are necessary are found at many organizational levels, including:

- ***Within NIH.*** Although NIAID plays the lead role in influenza research, other institutes and centers, including the National Institute of Child Health and Human Development (NICHD), the Clinical Center (CC), the National Institute of General Medical Sciences (NIGMS), and the National Heart Lung and Blood Institute (NHLBI), play important roles as well.
- ***Within DHHS.*** DHHS is the parent agency of the CDC and the Food and Drug Administration (FDA) as well as the NIH. CDC is the lead U.S. agency for public health response and disease surveillance; CDC also carries out research in influenza epidemiology and molecular virology, and conducts development activities for vaccines and diagnostic tests. FDA regulates vaccines and therapies, and its Center for Biologics Evaluation and Research conducts influenza research.
- ***Across Federal Agencies***. Several agencies across the Federal government are involved in activities relevant to influenza research, including the U.S. Department of Agriculture (USDA), the Department of the Interior, the Department of Defense (DoD), the Department of State, and the U.S. Agency for International Development (USAID).
- ***With Private Industry.*** Both established pharmaceutical corporations and new start-up companies play a vital role in the development of new products and strategies for control of influenza. Efficient development of improved vaccines, therapeutics, and diagnostics therefore requires close collaboration with the private sector.
- ***Internationally.*** The World Health Organization (WHO) is responsible for coordinating global influenza surveillance and the global response to an emerging influenza pandemic. DHHS is the official point of contact between WHO and the U.S. government; CDC is a designated WHO Influenza Reference Center and thus has the most extensive relationship with the WHO influenza program.

Building these various collaborative relationships is not an easy task. Approaches that might help improve collaborations within NIH and with other Federal agencies include holding joint conferences to foster the exchange of information and to increase awareness of other agencies' activities, increased sharing of data such as genomic sequences, and providing funding and incentives for scientists and staff to establish collaborative relationships between agencies and organizations.

Improving international coordination and collaborations is more complex. Many U.S. government organizations are involved, especially in coordinating the response to an emerging influenza pandemic, and National governments are subject to a variety of conflicting pressures and incentives concerning the free movement of information, materials, and people involved in influenza research and pandemic response. The trend in international health research generally is to complement strategies that establish centralized clearinghouses for samples or information regarding a particular international health problem by increasing support for resource-poor countries' as they strive to improve their indigenous scientific, laboratory, and public health capacities. It is therefore important that NIAID and CDC collaborate closely as NIAID continues to build its international research portfolio in influenza and integrate its activities and resources more completely into international influenza research coordinated by WHO.

IV. RESEARCH RECOMMENDATIONS

The NIAID Influenza Research Summit report identified eight major aspects of influenza research in which there are substantial gaps in knowledge, and that therefore present opportunities for further research. The Blue Ribbon Panel reviewed this list, provided additional items, and discussed ways to answer the key questions. A summary of the findings and recommendations is presented here; unless specifically noted, these recommendations are intended to apply to both seasonal and pandemic influenza research. Each sub-section below begins with a brief statement of the research area identified, followed by specific recommendations for action.

A. Influenza at the Animal-Human Interface

Animal reservoirs play a central role in the emergence of new seasonal influenza viruses as well as of viruses with pandemic potential. However, it is not yet clear how the interactions of various animal influenza reservoirs with each other and with the human population affect the evolution of influenza viruses and their adaptation to humans. Highly-pathogenic H5N1 avian influenza (AI), for example, has been shown to infect at least 105 avian species as well as several mammalian species[6]. Although most human H5N1 infections have resulted from contact with infected chickens, other wild and domestic species could participate in the propagation of H5N1 AI to regions currently unaffected and cause new cases of human infection. Learning more about how influenza viruses circulate between animal reservoirs and about the evolutionary pressures that lead to the emergence and spread of new viral sub-types—especially the factors that favor transmission from animals to humans—are urgent research priorities.

Elucidate patterns of influenza virus diversity and evolution. Increased collection and sequencing of influenza viruses currently circulating in animal and human populations, as well as sequencing of viruses currently held in collections, would allow more complete comparative genomic studies to reveal patterns of viral diversity and evolution in various animal reservoirs. Although the number of influenza virus genome sequences available to the entire research community has grown substantially in the past two years, much more remains to be accomplished. Human and animal influenza virus sequences, combined with clinical data on the disease course and outcome, should be made available to the research community in an integrated database. Moreover, clinical samples from human hosts and samples of the virus should be made available to researchers when feasible.

Define patterns of influenza virus transmission in and between human and animal populations. Improved sero-surveillance studies in various influenza virus reservoirs, including humans, would help to define past patterns of influenza transmission in animal and human populations. For example, mapping the number and distribution of people in different regions whose sera indicate a past exposure to H5N1 influenza could reveal the degree to which the virus has been transmitted to humans in the recent past, which would

[6] Olsen B, Munster VJ, Wallensten A, Waldenström J Osterhaus ADME and Fouchier RAM. Global Patterns of Influenza A Virus in Wild Birds, Science 312:384 (2006).

in turn provide more direct evidence for the significance of the infections and deaths in the human populations affected thus far.

Examine interactions of diverse influenza viruses with various hosts. Expansion of comparative studies of the interaction of animal and human influenza viruses with their hosts, including studies of the interactions between viral proteins and host receptors, would help to elucidate the factors controlling viral emergence and evolution, and provide data that would complement genomic analyses.

B. Influenza in Individuals

Many fundamental aspects of human clinical and immune responses to infection by both seasonal and pandemic influenza viruses have not yet been fully described—for example, the role innate and adaptive responses play in pathogenesis, host genetic factors that may affect susceptibility to severe influenza outcomes, and how innate immune mechanisms prevent or slow infection or, conversely, exacerbate illness.

Increase understanding of influenza pathology and pathogenesis in humans. Expanded clinical study of seasonal influenza patients could provide insights into influenza disease pathology and pathogenesis, human immune responses to influenza infection (especially cytokine responses), and the effectiveness of treatments. These insights would in turn improve vaccines and therapeutics for seasonal and pandemic influenza alike.

Fully describe human cellular immune responses to influenza infection. Antibodies against hemagglutinin and neuraminidase have long been known to play a role in protective immunity. However, studies of protection elicited by live-attenuated influenza vaccines indicate that humoral antibody responses are not the only important correlates of immunity, and that cellular responses also play an important role in immune protection. There is thus a need to understand these cellular response more completely, such as by fully describing all CD4+ T-cell, CD8+ T-cell, and cytokine responses to influenza, and determining the factors that lead to robust generation and maintenance of T- and B-cell memory.

Describe innate and mucosal immune mechanisms in influenza. Innate immune responses are important in limiting progression in the early stages of influenza infection, and conversely, may contribute to the dysregulation of immune signaling that often accompanies severe outcomes. Moreover, a better understanding of innate immune responses to influenza may lead to new vaccine adjuvants, immune modulators, or other means of preventing infection. Mucosal immune mechanisms are important for preventing infection, both in the acute response to the virus and in long term protective immunity; for example, mucosal mechanisms are particularly important in protection provided by cold-adapted, live-attenuated influenza vaccines. A greater understanding of the important roles played by innate and mucosal immune responses in protecting against influenza is critical to efforts to develop new preventive measures.

Map genomics and proteomics of human responses to influenza viruses.
Comprehensive understanding of the host genes that activate in response to influenza

infection is lacking. Such clinical genomics studies could examine multiple sites within individuals—both the upper and lower respiratory tract as well as the blood, for example—to uncover host genetic factors associated with susceptibility to severe outcomes, and could facilitate early diagnosis and clinical management of influenza infection.

Strengthen infrastructure for clinical influenza research. Increasing the number of centers at which clinical influenza research is routinely conducted would help to fill current gaps concerning how influenza viruses interact with human patients to cause disease, and would speed the study of pandemic influenza patients when they soon after a pandemic is declared. Moreover, the establishment of uniform case criteria, definitions, case report forms, and standardized databases would improve the ability to compare data from different studies, speed communication of results, and facilitate collaborations between clinical and basic researchers.

C. Influenza in Human Populations

Many issues relevant to influenza epidemiology are not adequately understood. Examples include the relative importance of aerosol, droplet, and fomite transmission; the contribution of specific sub-populations such as schoolchildren to epidemic spread; and how growth in the immunosuppressed and elderly populations in recent decades might affect influenza transmission.

Expand understanding of influenza viruses in human populations. Expanded studies of influenza in human populations would help to elucidate the modes of viral transmission; population sub-groups that affect transmission (e.g., age, occupation, residential setting, heath status, immunodeficiency); risk factors for severe outcomes (e.g., age, specific genetic characteristics, co-morbidities); and dynamics of viral spread across geographic regions. Moreover, such studies would improve the evidence base for modeling studies of the potential effects of public health interventions and thereby help to guide pandemic influenza preparedness.

To accomplish this, one or more prospective, comprehensive cohort studies of people (including children and the elderly) with influenza could be undertaken; other respiratory illnesses might be covered by the study as well. Many of the available data about the epidemiology of influenza in U.S. communities were derived from prospective cohort studies conducted decades ago. These studies, such as the Cleveland Family Study, the Tecumseh Study of Respiratory Illness and others,[7,8,9] followed enrolled individuals and families over multiple years; illnesses were noted, and specimens taken for laboratory analysis. The goal was to increase understanding of the epidemiology, etiology, clinical

[7] Jordan WS Jr, Badger GF, Dingle JH. A study of illness in a group of Cleveland families. XVI. The epidemiology of influenza, 1948-1953. Am J Hyg. 68:169 (1958).
[8] Monto AS and Kioumehr F. The Tecumseh Study of Respiratory Illness. IX. Occurrence of influenza in the community, 1966—1971. Am J Epidemiol. 102:553 (1978).
[9] Glezen WP, Couch RB. Interpandemic influenza in the Houston area, 1974-76. N Engl J Med. 298:587 (1978).

manifestations and best treatments of influenza and other respiratory infections. New studies could be similar in structure but use newer scientific tools, including

- genomic analysis of both viruses and human hosts
- comprehensive, standardized assays of cellular, humoral, and innate immune responses.
- rapid identification of infected patients with the best available diagnostic technology
- storage of accessible specimens for later analysis in laboratory studies
- collection of clinical and virologic data in integrated databases
- less-invasive methods for obtaining information from the lower respiratory tract

Such cohort studies would help to illuminate the mechanisms and patterns of viral transmission in a modern setting; these may have changed from a generation ago, when child day care was less pervasive and people commuted to work over shorter distances. Such studies could also help to reveal the factors related to severe outcomes, including viral genomics, host HLA type, age, co-morbidities, and use of various treatment strategies. They could also shed light on the effectiveness of possible pandemic-control measures such as antiviral prophylaxis of close contacts, school closings, and other steps to limit transmission within a population, and would provide an opportunity to field-test and compare new point-of-care diagnostic assays.

In addition, existing cohorts assembled for the study of other diseases could be adapted for influenza research. This could be done retrospectively, by analysis of banked clinical samples and relevant data, or prospectively, by adding influenza data and sample collection to ongoing or planned protocols. For example, NIAID's Multi-Center AIDS Cohort Study (MACS), which has been following thousands of individuals since 1984, could be adapted to also collect information relevant to influenza; other NIAID-sponsored cohorts in the United States and overseas could similarly be adapted to answer questions in influenza research.

D. Animal Models

Animal models are essential tools for virtually all aspects of influenza research, from basic immunology and pathogenesis studies to testing and development of vaccines, antiviral drugs, and other countermeasures. Influenza researchers use a variety of inbred and outbred animal models—e.g., pigs, chickens, ducks, ferrets, non-human primates—to serve distinct research needs in areas such as transmission, pathogenesis, immunity, and vaccine development.

Enhance the depth of understanding of commonly-used models. Animal models such as mice and ferrets have been used widely in influenza research for many years. Enhancements would include adding further detail about the immunology, pathogenic mechanisms, and other aspects of the model's responses to influenza, and increasing knowledge of how those responses correlate to human immune responses. In addition, better standardization of assays and reagents used in animal studies would allow improved comparisons of results from different laboratories. Full genome sequencing of

animals used in influenza research such as ferrets would also be useful, as would the development of additional reagents to study host immune responses in other animals.

Increase the range of options for animal models. Some animal models that have been used only rarely or not at all for influenza could be further characterized and developed for influenza research. For example, the miniature pig, which has been used in a relatively small number of influenza studies, might be more widely used if more were known about its responses to infection and if standardized reagents were made available to researchers. A wider repertoire of avian species for influenza models would be helpful, and humanized mice for use in influenza research should be developed and made available. And while non-human primates can be infected with influenza, they are rarely used as experimental models because they have not been reported to reliably develop influenza symptoms; it would be useful to systematically re-evaluate selected non-human primates as models for influenza.

Improve the availability of appropriate animals for use in influenza research. Because they are convenient and inexpensive to use, mice are used for most animal studies of influenza. However, mice do not always mimic human immune responses. Steps to increase the availability of ferrets, humanized mice, and perhaps other models would speed research.

E. Vaccines

Development of improved influenza vaccines and related manufacturing technology is an important priority. Influenza vaccines currently used in the United States must be cultured in fertilized chicken eggs, which would make it difficult to rapidly scale up production in response to the surge in demand for vaccine that would accompany a pandemic. Current vaccines must also be reformulated every year on the basis of predictions about the strains most likely to circulate in the coming season; live-attenuated vaccines may offer a greater degree of heterosubtypic protection but are not as yet used in a large proportion of the population. Inactivated virus vaccines effectively prevent infection in adults and children; however, while these vaccines are recommended for use by people over age 65, this population does not in general respond as vigorously as young adults. Promising new technologies for new influenza vaccine platforms and production methods, some of which are currently used in licensed vaccines for other diseases, are now under development.

Define all correlates of immune protection from influenza. High titers of hemagglutination inhibiting antibodies against well-matched strains are correlated with both protection and also with neutralizing antibody titers. Other (non–HA) protective immune responses have not been as thoroughly described. For example, cell-mediated responses to influenza antigens other than hemagglutinin and neuraminidase could be important to protection, especially against divergent viral subtypes (heterosubtypic protection). Similarly, innate immune responses to influenza, which keep the virus in check until adaptive immune responses become active, are not thoroughly understood. Passive immunization to protect individuals, either by itself or in combination with an active vaccination strategy, must also be evaluated. Comprehensive description of all protective mechanisms and the interdependent roles they play in immune protection

might better inform decisions on which vaccine candidates should proceed to large scale efficacy trials.

Facilitate studies that include challenge of human volunteers with live virus. In order to assess potential efficacy more completely than with surrogate measures alone, protocols for studies in which human volunteers are challenged with live influenza virus under controlled conditions must be developed, and regulatory issues must be resolved. Such studies could involve either wild-type virus or live-attenuated strains, and would also be useful for increasing knowledge of the entire set of human immune responses to influenza. In addition, these studies would be facilitated by the provision of well-characterized strains of influenza virus, including live-attenuated strains of H5N1 AI, for use in challenge studies.

Improve adjuvants and other dose-optimization technologies for influenza vaccines. Currently, influenza vaccines administered in the US do not contain adjuvants. Evaluation of seasonal vaccine preparations containing adjuvants is a priority, especially for use in populations in which vaccine response may be reduced. Development of new adjuvants and other dose-optimization techniques for use in a pandemic, when vaccine will be in short supply, is also needed and is best addressed now.

Define evaluation criteria for vaccine efficacy testing. Many vaccine candidates—both new seasonal vaccines and vaccines against H5N1 AI—are now undergoing preclinical studies and, in some cases, Phase I clinical trials, but not all of these candidates can be tested in large efficacy trials. It is therefore important to carefully define the criteria that will be used to identify the most promising candidates to evaluate for efficacy. To allow comparison of assay results from different laboratories, it is imperative to standardize assays and reagents not only for well characterized correlates of protection such as virus neutralization, but for less well-defined correlates such as cellular and innate immune responses.

F. Therapies

Antiviral drugs and other therapies to reduce the severity of influenza outcomes have the potential to be important tools for controlling both seasonal and pandemic influenza epidemics.

Expand studies of currently licensed antiviral drugs. Currently licensed influenza antivirals have been shown to modestly speed recovery from disease if given shortly after symptoms first appear. However, further study is required to clarify whether these drugs can be effective when administered to patients hospitalized with severe influenza, including patients with H5N1 AI; if so, dosing regimens would have to be optimized. Moreover, the mechanisms that result in resistance to these drugs should be explored further.

Develop new drugs and new drug targets for influenza. Preclinical research, such as identifying new protein targets for antiviral therapy, should be pursued vigorously. Candidate compounds that do not directly block a viral protein but act indirectly, such as

by preventing the virus from disabling innate immune responses or by preventing aberrant cytokine signaling, should also be investigated. Clinical activities, including determining the optimal timing and dosing of antiviral candidates should follow as soon as feasible. Protocols and preparations for testing of candidate therapeutic interventions for pandemic influenza should occur in advance of need.

Investigate therapies for late-stage, severe influenza. In many patients with severe influenza, disruptions of cytokine signaling occur days after viral titer has reached its peak. Such dysregulation is thought to be linked to severe influenza outcomes, but very little is known about how it occurs. Immunomodulatory and other therapies for use in patients with severe influenza or secondary infections should be explored.

G. Assay Technologies

New technologies for detecting and quantifying biomolecules such as DNA microarrays—chip-based arrays that can detect the presence of small concentrations of specific nucleotide sequences—are in the process of being converted from research tools into clinically useful products. Activities to speed development of new assay technologies for influenza should therefore be pursued.

Develop new point-of-care diagnostic assays. During the Severe Acute Respiratory Syndrome (SARS) crisis, the lack of diagnostic assays capable of quickly and accurately identifying infected individuals soon after infection was keenly felt by public health authorities. Tools to rapidly and definitively identify people infected with a pandemic influenza virus would help to both slow the spread of the virus and maximize the effectiveness of stockpiled antivirals. Use of improved diagnostics during seasonal epidemics, especially those capable of diagnosing other common respiratory infections, would allow physicians to prescribe influenza drugs only for people who are actually infected, and would permit rapid identification of potential participants for clinical studies of influenza.

Improve and standardize assays for cellular immune responses to influenza. Assays of specific T-cell responses, innate immune responses, and cytokine responses to influenza infection or vaccination are not as widely conducted or standardized as are antibody assays; indeed, many of the important cellular responses to influenza have yet to be fully described. But in order to facilitate measurement of these responses in a large number of influenza patients, the technology of the immune-function assays themselves must be improved. Improvements would include standardization to allow more valid comparison of results from different studies, decreased sample size requirements, automation, and improved access to necessary reagents. Currently available assays are too expensive for large-scale applications. Thus, it is important to develop technologies based on nanotechnology and microfluidics, which would use smaller volumes and could reduce costs. Moreover, if possible these assays should be adapted to allow physicians to predict more accurately which patients diagnosed with influenza are at highest risk for severe outcomes.

Improve methods for assaying immune responses in the respiratory tract. Current methods for obtaining samples from deep within the lungs, either to look for the evidence of infection or to assay specific immune responses for research purposes are highly invasive and not suitable for routine use. Other technologies, such as exhaled-breath analysis or advanced imaging, should be developed that would allow researchers to take samples or otherwise probe deep in the lungs of patients with influenza infection. Involvement of individuals with expertise in pulmonology would likely prove to be useful in this area.

H. Resources

NIAID currently provides many resources to the global influenza research community. Influenza research would benefit significantly from an expansion of resources provided by NIAID and other organizations.

Expand the range of materials available to the research community. The range of materials pertinent to influenza which NIAID currently makes available to the research community could be expanded to include different virus strains (including strains suitable for use in human challenge studies), cDNAs, peptide arrays, monoclonal and polyclonal antibodies, purified proteins, and clinical specimens; if necessary, a scientific advisory committee could be established to determine priorities for access to limited materials in this reagent repository.

Increase services for researchers. NIAID supports sequencing of influenza viral genomes in order to expand the availability of these sequences in publicly available databases, and provides in vitro and in vivo screening of compounds for antiviral activity. The establishment of a central laboratory at which samples relevant to clinical studies could be analyzed for a variety of immunologic responses would be a valuable addition to those services currently available.

Improve mechanisms for the exchange of information among researchers. Mechanisms for the exchange of information and data among influenza researchers should be improved. Establishing accessible, integrated databases that combine clinical and genomic data from influenza patients, and encouraging adoption of standardized database architectures to permit appropriate data comparisons would be useful in this regard. In addition, NIAID could facilitate researchers' access to the resources and services by consolidating information about all that it offers to influenza researchers at a single portal on the NIAID Web site.

V. APPENDICES

A. Membership Roster of the Blue Ribbon Panel on Influenza Research

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Claire Fraser-Liggett, Ph.D.
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Bruce Gellin, M.D., M.P.H.
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Jesse Goodman, M.D., M.P.H.
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Larry Granger, D.V.M.
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Robert A. Lamb, Ph.D., Sc.D.
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James W. Le Duc, Ph.D.
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B. NIAID Attendees of the Meeting of the Blue Ribbon Panel on Influenza Research

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John McGowan, Ph.D.
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Hillery Harvey, Ph.D.
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Carole Hudgings, Ph.D.
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Robert J. Taylor, Ph.D.[*]
Analyst[*]

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Karl Western, M.D.
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C. Summary of Major NIAID Influenza Research Activities, by Division

EXTRAMURAL RESEARCH ACTIVITIES

Division of Microbiology and Infectious Diseases (DMID)

DMID is the lead NIAID Division for influenza research, and supports a large portfolio of influenza research projects that will lead to more effective approaches to control influenza virus infections. These projects include

- Basic research on virus structure and function, viral pathogenesis, and host responses to infection
- Epidemiologic studies on the natural history and ecology of influenza viruses among birds and other animals
- Vaccine development and evaluation
- Improved vaccine delivery
- Drug discovery and evaluation
- Development of diagnostic technologies

Taken together, DMID activities constitute the major portion of the overall NIAID influenza research effort.

Biology of the Virus and Host Response. DMID-funded basic research projects in influenza cover a comprehensive array of studies of the biology of influenza virus and the host response to it, including topics in virology, pathogenesis, immunology, and genomics. The DMID portfolio of basic research grants in influenza has expanded substantially in recent years to more than 100 grants. This expansion has been due in large measure to specific requests for applications and other solicitations DMID has issued, and the resurgence of interest in influenza since the first human cases of H5N1 AI in 1997.

Much of this research is funded through grants to individual investigators at academic institutions and in industry; such grant applications are evaluated by a variety of study sections. Topics include

- Structure/function studies, including binding of inhibitors, role of M1 motifs in viral budding, viral fusion
- Viral replication, including factors that allow viral entry into host cells, viral RNA synthesis and virus particle assembly
- Viral evolution, including molecular modeling to predict antigenic drift, emergence
- Identification of virulence factors
- Evaluation of role of immunomodulators (e.g., TGFβ) in virulence
- Factors leading to interspecies adaptation and drug resistance
- Characterization of strain-specific binding properties and host range
- Genomic and proteomic analysis of host genes following infection
- Innate immune responses
- Monocyte and dendritic cell processing of influenza antigens

- Cellular immune responses, including CD8+ and CD4+ response and regulation, T-cell epitopes of core proteins, generation of memory CD8+ cells
- Humoral immune responses, including induction, generation, and maintenance of influenza-specific B cell subsets

NIAID funds a center on "Influenza Immunity: Protective Mechanisms against a Pandemic Respiratory Virus" under the Cooperative Centers for Translational Research on Human Immunology and Biodefense program. This center studies both vaccine-induced and naturally acquired immune responses to influenza A in children and adults. Specific topics studied at this center encompass innate, natural killer cell responses to influenza and the acquisition of adaptive immunity.

In addition to grant support, some DMID research is conducted under contract. For example, DMID has a long-standing "Pandemic Preparedness in Asia" contract with St. Jude Children's Research Hospital (Robert Webster, PI) not only to conduct surveillance for viruses with pandemic potential in China and other countries in Southeast Asia, but also to carry out research on the viral, host, and other factors that affect the evolution of influenza viruses in animal and human populations, to supply reagents for influenza research to the broader research community, and to conduct training to build research capacity abroad.

DMID has expanded the number of contract influenza research centers from one to six. These new "Centers of Excellence for Influenza Research and Surveillance" will conduct surveillance in animals for influenza viruses with pandemic potential and carry out research into the factors that influence the properties of influenza viruses and host immune responses.

DMID also supports the "Influenza Genome Sequencing Project" in collaboration with the National Center for Biotechnology Information and The Institute for Genomic Research (TIGR). The project is intended to increase the number of influenza genomic sequences in the public domain by supporting determination of complete genome sequences of influenza viruses submitted by domestic and international researchers. All sequence data generated by this initiative are released immediately to the public domain, so that they can be independently analyzed by researchers throughout the world.

Targeted Development of New Products. DMID supports many efforts intended to accelerate the development of influenza vaccines, antiviral drugs, and diagnostics. These activities are funded by grants, cooperative agreements, and contracts. They are directed toward all stages of the development process, from the earliest proof-of-concept studies for a new influenza vaccine strategy to the purchase of doses for clinical trials of candidate vaccines and vaccine adjuvants for use against H5N1 and other influenza strains with pandemic potential.

Representative examples of DMID research support intended to accelerate development of new influenza vaccines, therapeutics, and diagnostics include

- *Vaccines*
  - An inactivated nasal powder vaccine (Delsite Biotechnologies)
  - Novel cell-culture derived split influenza vaccine (ID Biomedical)
  - Replication-Defective Adenovirus-Vectored Pandemic Influenza (Vaxin)
  - M2 peptide-based "universal" vaccines against influenza (Washington University)
- *Therapeutics*
  - Ion Channel Assay for Identifying Influenza Therapeutics (Integral Molecular)
  - Development of siRNAs to Prevent and Treat Influenza Infection (Galenea)
  - Identifying Broad-Spectrum Influenza Virus Inhibitors (Nexbio)
  - Inhalable IgG Synthesis For Influenza Immuno-prophylaxis (Aktiv-Dry)
- *Diagnostics*
  - DNA/RNA Multiplex Platform for Detection and Sub-typing (U. Colorado)
  - Multiplex Immunoassay Platform for Respiratory Viruses (Lawrence Livermore)
  - New DNA genotyping chip-based technology (TIGR)

Clinical Testing. DMID also supports clinical testing of new and currently-licensed influenza vaccines and antivirals through its clinical networks. Examples of these studies include

- Safety and immunogenicity trials of inactivated H5N1 vaccines with and without adjuvants and alternate routes of administration
- Safety and immunogenicity trial of inactivated H9N2 vaccine with adjuvant
- Efficacy of combination oseltamivir and rimantadine for seasonal influenza
- Oseltamivir in infants

Influenza Research Resources. DMID supports three programs that provide resources and services relevant to influenza research.

- Antimicrobial Acquisition and Coordinating Facility (AACF). This facility screens compounds for activity against a variety of viruses, including influenza. After a simple application process, compounds are first screened in vitro; to date, more than 3500 compounds submitted by more than 80 different organizations have been screened in vitro for activity against influenza viruses. If results warrant, compounds can also be tested in mice by AACF, and in ferrets through a separate DMID contract mechanism.
- Vaccine and Treatment Evaluation Units (VTEUs). DMID supports a network of sites at university research hospitals across the United States to conduct Phase I and II clinical trials of candidate vaccines and treatments for infectious diseases, including influenza. Candidate H5N1 AI inactivated vaccines have already been tested through the VTEUs, and trials of other H5N1 candidates, including adjuvanted formulations, are under way or planned.

- Biodefense & Emerging Infections Research Resources Repository. This repository provides many reagents relevant to influenza research, including purified influenza proteins; monoclonal antibodies (including antibodies that bind H5 antigens), human sera, viral isolates (including influenza vaccine strains), and peptides for epitope mapping.

Division of Allergy, Immunology, and Transplantation (DAIT)

DAIT research focuses on the role of the immune system in health and disease. In that role, DAIT supports some research specific to influenza, as well as many other basic studies that are relevant to understanding influenza pathogenesis and immunology, and to the development of new vaccines, vaccine adjuvants, and immune-based therapies.

Biology of the Host Immune Response. DAIT-funded basic research projects cover a comprehensive array of studies of the host immune response to influenza. Much of this research is funded through grants to individual investigators at academic institutions and in industry; such grant applications are evaluated by a variety of study sections. Topics include

- Studies of B-cell and T-cell responses to influenza infection
- B-cell and T-cell immune memory following influenza infection or vaccination
- The role of the influenza NS1 protein in evasion of the immune response
- Processing and presentation of influenza antigens to immune cells
- Innate immune responses to influenza

In addition to unsolicited research projects, solicited programs that encompass influenza research include

- Cooperative Centers for Translational Research on Human Immunology and Biodefense, some of which study H5N1 adaptive immunity
- Innate Immune Receptors and Adjuvant Discovery, with studies on new adjuvants for influenza vaccines
- Immunity and Biodefense in Children, Elderly, and Immunocompromised Populations, with studies of immune responses to influenza vaccination in children, pregnant women, the elderly, and patients on immunosuppressive therapies for autoimmune disease or organ or tissue transplant
- Modeling Immunity for Biodefense, including the mathematical modeling of innate and adaptive immune responses to influenza infection, validated through direct laboratory experimentation in animal systems and vaccinated humans
- Epitope Discovery Program, to map CD4 and CD8 T-cell epitopes for influenza
- Asthma and Allergy Centers, with studies on influenza-induced airway inflammation
- Population Genetics Analysis Program: Immunity to Vaccines/Infections, including a study on immune response gene variations associated with outcomes of influenza infection

Influenza Research Resources. DAIT also supports programs that provide resources and reagents to the research community, including influenza researchers. These programs include

- The Immune Epitope Database and Analysis Program, which maintains a comprehensive database of antibody and T-cell epitopes and provides tools for the analysis of antibody and T-cell epitopes from many pathogens, including numerous strains of influenza
- The NIH Tetramer Facility, which produces MHC-peptide tetramers from many pathogens, including 5 pre-made MHC class II-influenza peptide tetramers and custom-made MHC class I and class II tetramers for detection of influenza-specific T-cells
- The Systems Approach to Innate Immunity Program, which provides tools to characterize innate immune responses to influenza infection, such as antibodies, protein expression vectors, data analysis tools, and genetically-engineered mice

Animal resources that could be used more extensively for influenza research include the National Swine Research and Resource Center, specific-pathogen-free (SPF) Macaque Breeding Colonies, and the Nonhuman Primate Reagent Resource Development program.

Division of Acquired Immune Deficiency Syndrome (DAIDS)

Because DAIDS focuses on HIV/AIDS, it has not supported a great deal of influenza research. However, DAIDS is currently expanding its activities relevant to influenza:

- DAIDS is adapting long-running cohorts studies, including the Women's Interagency Cohort Study (WIHS) and the Multi-center Aids Cohort Study (MACS), to study the effects of influenza in HIV-positive populations; protocols being prepared to make use of these cohorts will help to elucidate the consequences of both seasonal and pandemic influenza in people with HIV infection, as well as provide information relevant to influenza epidemiology in the population as a whole.
- DAIDS is preparing its research infrastructure in China and elsewhere in South East Asia to help monitor for the emergence of influenza strains with pandemic potential. Similar efforts could be undertaken at DAIDS-supported research facilities in Africa as well.
- A DAIDS master contract with Chiron was adapted to fund the manufacture of adjuvanted inactivated H5N1 influenza vaccines.

INTRAMURAL RESEARCH ACTIVITIES

Division of Intramural Research (DIR)

DIR researchers are studying the basic biology of influenza, including its pathogenesis, immunogenicity and genetic variability; investigating host immune responses to the virus in animal models and in humans; and developing vaccines to prevent influenza, especially strains with pandemic potential.

Influenza is a primary research focus of four DIR laboratories:

- The Respiratory Viruses Section of the Laboratory of Infectious Diseases (LID) is focused on pandemic influenza vaccine development. This section conducted the fundamental research that led to the development of the live-attenuated influenza vaccine manufactured by MedImmune. Currently, under a Cooperative Research and Development Agreement (CRADA), LID and MedImmune scientists are generating candidate, live-attenuated vaccines for a broad range of influenza subtypes with pandemic potential and evaluating them in preclinical studies and clinical trials. Analysis of data from a phase I trial of a live-attenuated H9N2 vaccine is nearing completion, and a trial of a similar H5N1 vaccine began in June, 2006. The LID Respiratory Viruses Section also conducts studies of the basic biology of influenza virus, including the factors that influence virulence, immunogenicity, transmissibility, and susceptibility of various host species.
- The Molecular Pathogenesis and Epidemiology of Influenza Section in LID was established in June 2006 when Jeffery Taubenberger, formerly of the Department of Molecular Pathology at the Armed Forces Institute of Pathology (AFIP) in Rockville, MD joined LID. This section will study the pathogenesis of influenza in diverse host species; influenza virus evolution and adaptation, especially the factors that lead to the emergence of pandemic strains; and the molecular basis for virulence of highly pathogenic influenza viruses, including the 1918 pandemic strain and H5N1 viruses.
- The Cellular Biology and Viral Immunology Sections of the Laboratory of Viral Diseases (LVD) investigate basic aspects of the interaction of influenza A viruses with the host immune system to enable rational design of vaccines capable of eliciting optimal immunity. Specific topics include the cell biology of viral peptide generation and presentation to T-cells, the induction and regulation of T-cell anti-viral responses, the mechanism of antigenic drift in viral glycoproteins and the contribution of the accessory protein PB1-F2 to viral pathogenesis.
- The Epidemiology Unit of the Office of Global Affairs joined the Epidemiology Section of the Laboratory of Infectious Diseases in June 2006. This group has studied historic patterns of pandemic and seasonal influenza mortality worldwide; the epidemiology of influenza vaccines, including efficacy in the elderly and the generation of herd immunity; and population-level trends in circulating influenza viruses such as the emergence and spread of antiviral resistance.

Division of Clinical Research (DCR)

The Division of Clinical Research (DCR) conducts clinical studies within NIAID's Division of Intramural Research (DIR) and collaborates with clinical trial networks

worldwide to develop vaccines, therapeutics and diagnostics. DCR influenza research activities center on two international networks:

- DCR recently initiated a multilateral collaborative program with the Wellcome Trust, Oxford University, WHO and researchers in Thailand, Vietnam, and Indonesia to establish the South East Asia (SEA) Influenza Clinical Research Network. The initial focus of the network is influenza, with a strong emphasis on building independent clinical research capacity in the region. A clinical trial to evaluate high-dose oseltamivir compared to standard dose against severe influenza is under way, and pharmacokinetic studies of intravenous Zanamivir, with and without Oseltamivir, are being planned.
- The Department of Defense (DoD) maintains a large network of domestic and international sites for the clinical study of emerging infectious diseases. In September 2005 NIAID signed an Inter-agency Agreement (IAA) with Uniformed Services University of the Health Sciences (USUHS) to establish a NIAID/DOD Emerging Infectious Disease clinical research program. DCR is currently collaborating with DoD to develop an influenza research agenda that uses the DoD network.

Vaccine Research Center (VRC)

The primary focus of activities at the VRC remains the development of an effective HIV/AIDS vaccine. Over the last several years the VRC research program has also expanded its programs to include vaccine development for Ebola, SARS, West Nile Virus and Influenza. VRC scientific approaches and technology platforms have a time horizon of 1 to 5 years, and include development of novel vaccine platforms as well as basic research questions related to the breadth of neutralizing antibodies, heterosubtypic immunity, the strengths of different vaccine platforms, and the relative contributions to protection of cellular and humoral immunity. This work builds on VRC capabilities in immunology, structural biology, and vaccine production. VRC contributions to the NIAID influenza program include

- Development of novel gene-based and recombinant protein-based platforms
- Identification of shared epitopes/serotypes
- Generation of antiviral compounds and monoclonal antibodies
- Evaluation of breadth and structural diversity of neutralizing antibodies, and assessment of the role of cellular immunity in cross-strain immunity

Three new vaccines have been developed at the VRC, each composed of a single plasmid DNA encoding hemagglutinin (HA) protein from H1N1, H3N2 and H5N1 subtypes isolated from recent human outbreaks of influenza. In future, the list of targeted genes may increase to include all common variants of hemagglutinin, neuraminidase, and ion channel genes (HA, NA, and M2). AVRC H5 subtype DNA vaccine candidate entered Phase I clinical trials in December 2006.