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DRAFT

I. Introduction

Influenza is not a disease that can be eradicated. Wild birds and domestic animals harbor influenza A viruses, which have the potential for direct transmission to man and for genetic recombination with human influenza A strains. As a result, animal reservoirs provide an ever-present opportunity for the emergence of influenza A viruses that are antigenically novel to the human immune system. If the virus that emerges is also able to spread readily from person-to-person, chances are greater that a pandemic will occur. Although exactly when and where the next influenza virus with pandemic potential will emerge is not known, it is likely that the outcome will vary from serious to catastrophic. Expanding focused research on specific areas of influenza before the next pandemic occurs can lead to new understandings, products, and strategies that will improve the effectiveness of a pandemic response and prevent disease and death. The development and implementation of a U.S. Pandemic Influenza Research Agenda during the current inter-pandemic period will provide a framework for such high priority research activities.

Research on influenza is conducted by several HHS agencies and by the Department of Agriculture and Department of Defense. The largest body of influenza research is supported by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), through investigator-initiated grants and contracts. These agreements support both basic and applied research on influenza virus biology, epidemiology, pathogenesis, immunology, and the development of new and improved influenza diagnostics, antiviral drugs, and vaccines. The intramural program at NIH, the Laboratory of Infectious Diseases (LID) also has a strong focus on influenza research, particularly in new vaccine development. The Centers for Disease Control and Prevention (CDC) through the National Center for Infectious Diseases and the National Immunization Program supports a broad intramural and collaborative influenza research portfolio including studies on influenza epidemiology, immunology, vaccines, and vaccination programs. The Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER), conduct research on influenza vaccines and antivirals, respectively.

In 1995, NIAID convened an international workshop entitled: *Pandemic Influenza: Confronting a Re-Emergent Threat*. Meeting participants were asked to assess gaps in scientific understanding and define a research agenda that would focus on the activities necessary to improve preparedness for the next pandemic. The recommendations that resulted from this workshop were subsequently published (*JID 1997; 176 [Suppl 1]*) and formed the basis for this pandemic research agenda. This document highlights key research activities that can contribute to a new U.S. Pandemic Influenza Research Agenda, and builds on the successes of previous research activities, new technologies, and new developments in influenza epidemiology and disease. For example, it has become clear since 1997 that highly pathogenic H5N1 and H7N7 avian influenza viruses as well as low pathogenic H9N2, H7N2 and H7N3 avian influenza viruses can directly transmit from infected poultry to humans. Although the 1997 H5N1 influenza outbreak in Hong Kong did not spread to other countries, it and the large outbreak of H5N1 in

poultry in Asia in 2004 clearly illustrates the potential hazards of avian-to-human transmission of influenza virus. Genomic testing research at Shantou University Medical School in China and at Hong Kong University indicates that H5NI is now endemic in domesticated ducks in southern China, which could potentially spark a pandemic in humans. As a result, there has been a significant emphasis placed on understanding the basis for emergence and pathogenesis of avian influenza viruses and their use in the production and clinical testing of investigational vaccines for influenza A viruses with pandemic potential.

A. Critical Basic Research Foundation

Research has provided the underpinning of many of the tools we currently have to combat influenza and will be the basis of those that are developed in the future. Basic research on influenza facilitates new ways of detecting and rapidly characterizing these viruses as they emerge. Most Federal funds currently available for influenza research are provided through NIH in the form of grant support for scientists to study fundamental issues related to basic biology, virology, immunology, pathogenesis, and the development of new diagnostics, antiviral agents, and vaccines. In addition, NIAID supports centralized research resources such as contracts to screen new drugs, develop new animal models, and establish a reagent repository. These resources are available to research scientists around the world.

Basic research on the virus and its structure, the factors that contribute to its virulence and its ability to evade the immune system, and an understanding of the genetic changes that permit an influenza virus to suddenly acquire the ability to transmit between species provide important information for fighting pandemic influenza. The development of new systems for manipulating influenza genes to create strains (referred to as “reverse genetics”) provides researchers with the opportunity to systematically uncover the function and interactions of each gene in the influenza virus genome. The application of this technology has already begun to expand our understanding of virus-host range restriction, viral replication and pathogenicity and to speed the production of inactivated and live-viral vaccine candidates. NIAID has recently initiated an influenza genomics program to fully sequence large numbers of human and avian influenza viruses and make this sequence information available to the public. This program will provide important information on the overall molecular evolution of influenza viruses and genetic correlates of virulence and severe disease.

In addition to grants, government contracts that support basic research also contribute to pandemic preparedness. A multi-year NIH contract on "Influenza Pandemic Preparedness in Asia," was awarded in part, to support the establishment of an animal influenza surveillance center at Hong Kong University. The monitoring of influenza viruses in waterfowl, poultry, and swine in Hong Kong has detected the reemergence of H5 avian influenza viruses in 2001 and 2002 and resulted in public health authorities taking preemptive steps to stop further spread of the virus. These contract activities supplement other surveillance systems to identify viruses that might be needed in future vaccines and also provide critical clues into the dynamics of influenza virus evolution and emergence that are likely occurring throughout the world. An increasing number of

materials and reagents are being made available through the NIAID Influenza Reference Repository, the CDC WHO Collaborating Center, and CBER/FDA, including antibodies and reference antigens to a number of avian influenza viruses considered to be of high pandemic potential. Updating the reagents in this library and making them available to research scientists around the world, remains an area of high priority.

B. The Transition to Applied Research

The plasticity of the influenza genome facilitates the virus' adaptability and its escape from specific host immune systems, leading to the need for annual vaccination with an often-updated vaccine. Through NIH and private sector-supported applied research programs, new vaccine candidates are being developed and clinically tested. One successful public-private partnership has been the government's long-standing involvement in the development of the live-attenuated influenza virus vaccine, which was licensed in the U.S. in 2003. Efforts are also underway to enhance the immunogenicity of inactivated influenza vaccines (especially for very young and very old individuals) by administering them using new delivery systems, providing them in higher doses, or by combining them with adjuvants or supplemental proteins. Vaccines that contain common protein epitopes from influenza viruses may provide generic protection against a wide range of influenza viruses and should continue to be aggressively pursued. While the exact subtype of influenza virus that will cause the next pandemic is not known, producing prototypic vaccine reference strains that can be used in developing vaccine candidates is essential for preparedness and is being supported by the CDC, FDA, the NIH, and other international laboratories. Production and clinical testing of investigational lots of vaccines made with these reference strains should be supported as they become available.

In addition to vaccine related research, the NIH supports several programs focused on supporting the development of new antiviral agents against influenza. These programs range from target identification to the support of clinical trials. *In vivo* and *in vitro* screening programs to identify promising drug candidates provided by private sector companies and academic laboratories are also ongoing. Through the NIAID Biodefense Partnership and Challenge Grant Programs, private sector companies are being supported to develop new vaccines against influenza, including non-egg based vaccine platforms, new antiviral drugs against influenza, and genomics-based diagnostic assays against a number of acute respiratory viruses, including influenza (<http://www2.niaid.nih.gov/biodefense/research/funding.htm>)

Applied research also leads to the development of tools, and to refinement of strategies that are critical to effective surveillance and pandemic response programs. Improved influenza rapid diagnostic tests, development of more sensitive and rapid laboratory assays for detecting and subtyping influenza viruses, and new high throughput methods to test influenza virus strains for susceptibility to antiviral drugs – and their implementation at CDC, public health, and hospital laboratories – all are key to identify and track disease before and during a pandemic, and to provide public health and health care providers the information needed to make optimal decisions. In addition, epidemiological, programmatic, and behavioral research results lead to new

understanding of risk groups for and consequences of influenza infections, strategies to improve vaccination delivery and eliminate racial and ethnic disparities, and effective communications messages and tools that will be vital to a pandemic response.

II. U.S. Pandemic Influenza: Research Needs

One of the highest priorities for pandemic preparedness and control must be a focused basic and applied research program that has the promise to further the development of new and improved diagnostics, antiviral drugs, and vaccines. Developing and implementing a research agenda will take the combined efforts of HHS agencies including NIH, CDC and FDA and the private sector. This annex identifies high priority research that will allow the U.S. to prepare, respond, and reduce the overall morbidity and mortality associated with pandemic influenza.

A. Basic Virology and Molecular Biology

Influenza viruses, a member of the family Orthomyxoviridae, are classified into three types; A, B, and C, with influenza A causing the most severe disease in humans and the most likely to trigger a pandemic. While a number of structural proteins have been identified in influenza A viruses, the two surface proteins, the hemagglutinin (HA) and neuraminidase (NA), play key roles in the pathogenesis of the virus and the host's immune response. Although only two influenza A subtypes currently cocirculate globally in humans (H1N1 and H3N2), at least 15 distinct antigenic subtypes of HAs (H1 to H15) and nine NAs (N1 to N9) have been identified in wild aquatic birds. Numerous influenza viral genomes have been completely sequenced and the sequences for 5 genes from the deadly 1918 strain have recently been reported. In spite of the severity of influenza disease, little is known about the role of the viral proteins in the virus' pathogenicity or transmission.

Goal: To understand the mechanism(s) by which highly pathogenic influenza viruses emerge in humans and animals and to identify genetic mutations that correlate with antiviral resistance.

Priority Actions:

- Conduct studies to examine the molecular biology and epidemiology of pathogenic viruses in avian reservoirs, with a focus on defining the molecular basis of virulence for avian viruses such as the 1997 and 2004 H5N1 viruses and the role of virulence factors and pathogenic determinants in disease.
- Determine the compatibility of gene segments derived from human and animal influenza viruses to reassort—an event that may result in the emergence and interspecies transmission of novel influenza viruses.
- Evaluate the role of mutations and constellations of mutations on antiviral drug resistance using a reverse genetics system to find viruses with specific mutations associated with drug resistant phenotypes.

B. Animal Surveillance

While no organized WHO program currently exists to support global surveillance in animals, the WHO has initiated limited systematic influenza surveillance in swine and recent avian outbreaks caused by highly pathogenic influenza strains are likely to lead to new avian surveillance activities.

The NIH supports an animal influenza surveillance program in Hong Kong and is expanding coverage into Mainland China and other parts of Asia. This program conducts ongoing influenza surveillance in wild birds, live bird markets, and pigs. In addition, researchers are examining the molecular basis of transmission of influenza viruses among animals and humans, studying why avian influenza viruses in Asia are becoming more lethal, and identifying avian influenza viruses that may be suitable for use in developing vaccines.

The Office International des Epizooties (OIE) has established reference laboratories for avian and equine influenza. These laboratories provide diagnostic testing including virus characterization, reagents, and training. The OIE member countries report outbreaks of avian, equine and swine influenza, and the OIE prepares a yearly summary of these reports.

The U.S. Department of Agriculture (USDA) conducts influenza surveillance in domestic animals. Recent outbreaks in domestic poultry in Asia and Europe associated with cases of human disease highlight the importance of coordinating surveillance activities. Surveillance for influenza A viruses in poultry in the U.S. has increased since the outbreak of highly pathogenic avian influenza (HPAI) in Pennsylvania and surrounding states in 1983 and 1984. Investigations may be conducted by state animal health officials, USDA-accredited veterinarians, university personnel, or members of the poultry industry. Samples from affected flocks are routinely submitted to state laboratories for diagnosis. If importation of HPAI is suspected, a Foreign Animal Disease Diagnostician will conduct an investigation and submit samples directly to the National Veterinary Services Laboratories (NVSL) in Ames, Iowa.

Other sources of surveillance samples from poultry come from monitoring for serum and egg yolk antibodies at processing plants, routine testing of game birds, qualifying birds for export, and testing ratites prior to interstate movement. In addition, the USDA's Animal and Plant Health Inspection Service (APHIS) has been monitoring live bird markets in the northeastern region of the U.S. since 1986 for the presence of avian influenza viruses that may pose a threat to commercial poultry.

Most birds submitted for entry into the United States must be quarantined in USDA approved quarantine facilities. During quarantine, avian influenza virus isolation is attempted on samples collected from all dead birds and some live birds.

Several programs exist for surveillance in wild birds in North America. NIH supports annual surveillance of influenza viruses in wild migrating birds in North America and collaborations with the Canadian Wildlife Service to isolate influenza viruses from

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migratory birds. Results obtained after analysis of the virus isolates from wild birds are published periodically.

Surveillance in the U.S. for influenza A viruses in swine and horses is less systematic than in poultry. While no requirement exists for USDA notification when cases or outbreaks of influenza occur in these animals, considerable interest exists in understanding the viruses that are circulating among them. In general, only outbreaks in swine of unusual severity or duration are likely to be investigated and reported. On the other hand, surveillance for influenza viruses causing disease in horses has practical utility because data generated from analysis of equine influenza viruses can be used to guide equine influenza vaccine formulation. The Animal Health Trust, Newmarket, U.K. has taken the lead in organizing a program for equine influenza surveillance and reporting, primarily in Europe and the United States. Based on this surveillance an annual report is published.

Goal: To understand the prevalence, ecology, and spread of influenza virus subtypes in animal reservoirs.

Priority Actions:

- Support international surveillance of influenza viruses in animals particularly in Asia and the Pacific Rim. This includes aquatic birds, live bird markets, pig farms and slaughterhouses, and other settings that provide enhanced opportunity for the reassortment of influenza virus subtypes.
- Expand surveillance of influenza viruses in poultry, swine, and wild migratory birds in the U.S. and abroad, and include seroepidemiological studies on poultry workers.
- Establish and maintain libraries of antigenically and genetically characterized animal influenza viruses that might be needed for vaccine development.
- Sequence known human and animal influenza viruses to understand their molecular evolution.
- Assess the antigenic diversity within each HA subtype.

C. Human Surveillance and Epidemiology (See also Annex 2: Surveillance)

The World Health Organization (WHO) supports an international laboratory-based surveillance network for influenza to detect the emergence and spread of new antigenic variants of influenza. The information regarding circulating influenza strains is used to monitor global influenza activity; to update the formulation of annual influenza vaccines; and to detect novel influenza strains (i.e., influenza A subtypes that have not recently circulated among people) that infect humans leading to the implementation of control measures and providing early warning of a possible pandemic.

CDC conducts and coordinates influenza surveillance in the United States. Surveillance foci include collecting influenza viral isolates for testing, monitoring morbidity and mortality, and identifying unusual or severe influenza outbreaks. The U.S. national influenza surveillance system includes: laboratory surveillance, outpatient influenza-like illness (ILI) surveillance, pneumonia and influenza (P&I) related mortality surveillance, and an assessment of influenza activity at the state level. Traditionally, U.S. influenza surveillance has been conducted from October through mid-May but is now being conducted year-round. Year-round influenza surveillance will provide information on the baseline level of influenza activity during the summer, and these data have the potential to become an important component of early detection for a pandemic.

Several activities to enhance influenza surveillance currently are underway:

- On a multinational level, the CDC is partnering with the WHO through the Global Outbreak Alert and Response Network (GOARN) to assure overall improvements in global disease detection and control. This network has demonstrated the value of novel and unconventional surveillance systems based on news media reports to quickly identify potential outbreaks.
- CDC is also providing additional support and assistance to foreign governments for the development or improvement of influenza surveillance networks. These networks focus on the systematic collection of virological and epidemiological information for influenza. The goal of this assistance and support are to 1) establish or enhance an active influenza surveillance network that uses standardized data collection instruments, operation definitions, and laboratory diagnostic tests to enhance surveillance for influenza; 2) expand existing surveillance systems; 3) improve local laboratory diagnostic capabilities; 4) develop educational and training opportunities for local public health practitioners; and, 5) improve communications and data exchange between laboratories and epidemiologists in the global influenza surveillance network.
- CDC's BioSense project is a state-of-the-art, multi-jurisdictional data-sharing program to facilitate surveillance of unusual patterns or clusters around the country. It could enhance the nation's capabilities to rapidly detect and quantify public health emergencies by enabling rapid access to, and analysis of, diagnostic and pre-diagnostic health data and establish the capability for rapid, around-the-clock electronic transmission of data to local, state and federal public health agencies from national, regional and local health data sources such as clinical laboratories, hospital systems, health plans, DoD and VA medical treatment

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facilities, and pharmacy chains. Therefore, it could facilitate appropriate public health investigation and follow-up by public health authorities.

- Studies have documented that children are major contributors to the spread of influenza within the community. In addition, there is increasing awareness that influenza is associated with significant morbidity and mortality among children. In order to better understand the dynamics of influenza in children, pediatric influenza-associated deaths have been added to the national reportable disease list by the Council of State and Territorial Epidemiologists. Implementing this surveillance will aid in the identification of high-risk groups and in formulating improved immunization policies.
- In three metropolitan areas included in the New Vaccine Surveillance Network, active-surveillance is ongoing to detect all influenza cases among children less than 5 years old who are admitted to hospital. Key features of this system are that it includes all hospitals that admit children from the surveillance counties; laboratory testing is done to detect which children admitted with febrile or respiratory illness actually have influenza; and data are being collected to characterize the clinical and epidemiological features of influenza in children. Based on influenza cases detected in children, studies are being done to evaluate the effectiveness of influenza vaccination and the costs associated with pediatric influenza illness.
- In nine Emerging Infections Program network sites, an investigation to characterize the burden of severe, laboratory-confirmed pediatric influenza in the U.S. was initiated during the 2003-2004 influenza season. Specific objectives include: 1) determining the age-specific rates of laboratory confirmed influenza-associated hospitalization among children aged <18 years in the surveillance areas during the 2003-2004 influenza season; 2) determining the rate of serious influenza-associated complications, such as secondary bacterial infections and the need for ICU admission/mechanical ventilation; and 3) describing clinical and epidemiologic characteristics of pediatric case-patients requiring hospitalization for influenza infection. Ongoing surveillance for severe influenza infections in children in the EIP sites is planned.
- Efforts continue to increase the number of regularly reporting sentinel provider sites in each state to 1 per 250,000 population or at least 10 in states with small population.
- Efforts to develop studies to obtain annual estimates of vaccine effectiveness against laboratory confirmed influenza illness is underway. Case-control studies in adult, and possibly pediatric populations, are being established and vaccine effectiveness estimates for laboratory confirmed disease will be reported to CDC on an ongoing basis during the study, with final results at the end of each influenza season.

Goal: To understand the factors involved in transmission of influenza and the efficacy of potential control measures.

Priority Actions:

- Conduct serological studies of humans who are in close contact with animal reservoirs to assess both cross-species transmission and subsequent human-to-human transmission.
- Determine population effects of vaccines by studying the impact of vaccination on annual influenza epidemics, developing models for predicting the impact of annual vaccination on a future pandemic, and establishing the cost savings of different vaccination programs.
- Evaluate the role of children as vectors for the transmission of influenza infection within a community and the impact/use of vaccines to reduce spread and potentially alter the course of an epidemic.

D. Diagnostic Development

Early detection of new influenza outbreaks is critical to limit the spread of infection and control its impact on human health. The influenza diagnostic tests that are currently available have limited sensitivity and specificity and are not able to discriminate between viral subtypes. The NIH is currently supporting the research and development of new ultra sensitive, genomics-based portable diagnostic devices that will be able to discriminate influenza viruses from other acute respiratory pathogens in clinical samples. These novel diagnostic tools will allow the rapid detection of newly emerging influenza strains and will be able to discriminate between different influenza subtypes.

The ability to test new diagnostic technologies in public health laboratory settings is also being enhanced through the distribution of standardized protocols for lab methods, by introducing new techniques, such as multiplex PCR and by expanding the role for use of molecular techniques to rapidly diagnose respiratory agents including influenza types and subtypes.

CDC, in collaboration with the Association of Public Health Laboratories, has planned and will be conducting training for state public health laboratory personnel in order to promote standard molecular techniques for the identification of influenza virus types and subtypes including those normally circulating in human populations, H1 and H3 and recent avian subtypes of interest, H5 and H7. The incorporation of these data into the surveillance reporting system will increase information on the circulation of influenza viruses and help develop a better understanding of the impact of specific viral subtypes. NIH supports diagnostic development for emerging infectious agents through the NIAID Biodefense Partnership and Challenge Grant Programs.

Goal: To support the development of rapid and reliable diagnostic tests for the identification and characterization of epidemic and pandemic influenza viruses.

Priority Actions:

- Support development of new technologies and platforms that allow for the detection and discrimination of newly emerging influenza virus subtypes.
- Develop new rapid antigen detection methods for use on clinical specimens obtained from influenza patients.
- Develop new rapid methods to detect antiviral resistance in clinical influenza isolates.
- Develop techniques for identifying host-response profiles for early detection of presymptomatic infections.

E. Antiviral Drug Development (*See also Annex 5: Antiviral Drugs and Strategies*)

In the event of a pandemic, antiviral drugs will be the first line of defense before a vaccine is available and could delay the spread on the pandemic particularly if the strain is not efficiently transmitted between humans. There are currently two classes of antiviral drugs against influenza, the neuraminidase inhibitors and the M2-ion channel blockers known as adamantanes. Studies have shown that neuraminidase inhibitors, in addition to being active against influenza A and B, may reduce complications of influenza in some individuals. H5N1 viruses isolated from poultry and humans in Asia in 2004 are known to be resistant to the adamantanes. The development of new broadly active anti-influenza drugs that do not induce the generation of drug resistant viral strains is essential. NIAID supported researchers are currently developing novel antiviral strategies against influenza. These efforts include the development of genomics based inhibitors of viral replication, compounds that block viral entry, and inhalable antibodies for immunoprophylaxis against influenza.

Goals: To develop new influenza antiviral agents that can provide an option for therapy and chemoprophylaxis if strains that are resistant to currently available agents emerge and spread. To examine various treatment strategies to guide decision-making around the use of limited antiviral supplies.

Priority Actions:

- Expand preclinical and clinical support for the development of new promising antiviral drugs against influenza.
- Monitor for the emergence of antiviral resistance.
- Conduct studies to improve programmatic feasibility of stockpiling antiviral drugs, for example by evaluating shelf life beyond current FDA licensed limits, and by assessing strategies for distribution of drugs from state health departments to points-of-care and end-users in field exercises.

- Explore public health strategies (i.e., dose reduction, shortened treatment courses) for maximal impact.

F. Vaccine Development (*See also Annex 3: Vaccine Development and Production*)

Inactivated influenza vaccines were developed more than 50 years ago, and since that time, annual vaccination with the inactivated vaccine has been the primary method by which the disease burden of influenza has been reduced. In 2003, a new intranasally administered live-attenuated influenza vaccine, FluMist®—developed in large part with research support by NIAID, was made available for vaccinating healthy individuals between the ages of 5 and 49 years. While influenza vaccines work well in the majority of people, they often do not work as well in the very young, the very old, or in patients with a compromised immune system. Currently available influenza vaccines are produced by growing influenza viruses in embryonated chickens eggs taking between 6 to 9 months to prepare.

Vaccines produced in the event of the emergence and spread of a new pandemic influenza strain must be safe, able to be produced in large quantities and delivered quickly, and protect the largest number of individuals possible. When the next influenza pandemic emerges, it will likely be caused by a type of influenza virus to which humans have little to no previous exposure. As a result, public health officials will be confronted with making critical decisions about the vaccine dosage level and immunization regimen for various populations. The production and clinical evaluation of investigational lots of pandemic vaccines is an urgent global public health priority. The NIAID supports a wide range of activities to develop and test pandemic influenza vaccines. These activities include supporting production of non-egg based vaccine technologies, strategies to improve the current inactivated vaccine by adding adjuvants, optimizing dose, and evaluating new routes of delivery and programs that support partnerships with industry to for the production and clinical evaluation of both inactivated and live-attenuated pandemic influenza vaccines.

Goal: To increase the speed of availability of safe, effective, licensed pandemic influenza vaccines. To expand the breadth and potency of existing vaccines.

Priority Actions:

- Prepare reference viruses that contain hemagglutinins (HAs) and neuraminidases (NAs) from avian influenza viruses with pandemic potential and genes from other well-characterized influenza strains (i.e., A/PR/8/34, A/Ann Arbor/6/60) that confer high-growth properties in eggs.
- Support the production and evaluation of investigational lots of pandemic vaccines to assess safety and immunogenicity of the vaccine in various populations, including those likely to be of greatest risk.
- Develop alternatives to egg-based vaccine manufacturing technologies, which include cell culture-based systems, recombinant proteins, DNA-based platforms.

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- Support new influenza vaccines, including those that may provide longer-term and/or broader protection.
- Assess the role of using the live-attenuated influenza vaccine in a pandemic.
- Encourage the development of strategies to enhance the yield of production of influenza vaccine using current manufacturing processes.
- Assess the potency of existing vaccines against combinations of traditional vaccine targets, e.g., HA and NA from different strains.
- Explore the potential of more highly conserved viral genes as targets of vaccination, and the efficacy of combination strain vaccines.
- Assess the potential contribution of cellular immunity to vaccine protection and expanded coverage.
- Monitor the long-term sequelae of vaccination, particularly the possible protective role of vaccination against non-infectious diseases such as cardiovascular, neurological, and other diseases, to understand the value of vaccination and possible indications for expanded vaccination in the future.

Development of Clinical and Research Protocols for Use During a Pandemic

Clinical trials of pandemic influenza vaccines sponsored by NIAID in response to the emergence of novel H1N1 influenza viruses in 1976 and 1977 provide valuable safety and immunogenicity data that was summarized in a supplement to *The Journal of Infectious Diseases* (Volume 176: supplement I; August 1997) and in articles by Paul D. Parkman et al (*The Journal of Infectious Diseases* 136:S341-S746;1977) & by John R. La Montagne et al (*Reviews of Infectious Diseases* 5: 723-764; 1983). Lessons learned from these trials and others conducted during previous pandemics and during the current inter-pandemic period serve as the basis of our current understanding of the safety, immunogenicity, and efficacy of pandemic vaccines.

Recent studies with H5N1 influenza viruses that have caused outbreaks in humans over the last seven years suggest that the immune response to different H5N1 isolates and other avian influenza virus subtypes are not likely to be predictable. In addition, each individual vaccine manufacturer produces influenza vaccines somewhat differently, and therefore efficacy for these different vaccines may not be generalizable. As a result of the needs to further clinically evaluate these products, the NIAID held a workshop in 2003 entitled Development of a Clinical Trial Plan for Pandemic Influenza Vaccines (<http://www.niaid.nih.gov/dmid/meetings/flu vaccine.htm>). Participants at this workshop identified critical questions that need to be addressed in future studies. These include:

- Does increasing the dose, the dosing interval or giving two doses increase the immune response?
- Are increasing dosages of vaccine associated with increased reactogenicity?

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- Do adjuvants truly augment the immune response?
- Do different aged populations respond differently to the same vaccine dose?
- Is a single higher dose as immunogenic as two smaller doses?
- While the current surrogate of protection is serum HAI antibody, are other surrogates such as antibody neutralization titers more appropriate?

Goal: Prepare clinical and research protocols that can be used to rapidly assess the safety, immunogenicity, and efficacy of pandemic influenza vaccines in a variety of population groups and provide public health policy-makers data to guide a pandemic response.

Priority Actions:

- Develop clinical protocols that evaluate the safety and immunogenicity of different doses of pandemic influenza vaccines in various populations.
- Develop and evaluate case control and case cohort study protocols that can be used in an outbreak setting where a novel virus with pandemic potential is causing an outbreak in order to assess risk factors for infection, detect person-to-person transmission, and assess vaccine effectiveness.
- Develop study protocols for rapid assessment of the population impact of outbreaks early during the development of a pandemic.
- Develop and evaluate study protocols for the measuring the effect of interventions such as travel restrictions or school closings during outbreaks early in the development of a pandemic.
- Develop study protocols for determining the effect of early use of antivirals in high-risk patients.

Immune Response Parameters

NIAID supports basic research to understand how the influenza virus evades the host immune response and identify the host immune factors that influence disease outcome. Other activities include the development and evaluation of novel adjuvants and delivery systems to enhance vaccine immunogenicity. NIAID is also supporting a large multi-component research project to compare the humoral, cellular, and innate immune responses in children and adults that are vaccinated with live-attenuated or inactivated vaccines or that are naturally infected.

Historical experience with influenza vaccines suggests that two doses of vaccine will be needed to induce adequate levels of immunity to a pandemic strain of influenza. Enhancing the immunogenicity of a pandemic vaccine so that a one dose course could be used would ultimately reduce the time and cost required to protect the population. This may require inclusion of an adjuvant – a substance included in vaccines to increase the strength of the immune response – in the formulation of a pandemic vaccine. Further

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investigation needs to be done to understand whether adjuvants will be useful in a pandemic situation.

Goal: To determine how to further enhance the immunogenicity of influenza vaccines through adjuvants or alternative delivery approaches. In addition, research is needed to optimize immunological assays and to define serologic correlates of immunity.

Priority Actions:

- Evaluate the immune response to dose ranging studies with multiple doses of licensed vaccines in various populations.
- Evaluate alternative strategies of vaccine administration that could reduce the dosage of the vaccine required to achieve an optimum immune response, including intranasal, intradermal administration, adjuvants, and transcutaneous patches.
- Determine the immunological markers (such as cell mediated immunity, cytokine production) that might constitute correlates of protection. Determine the role of humoral, cellular, and mucosal immunity in protection against influenza disease, with an emphasis on those populations at highest risk.
- Develop serological assays to assess immune responses. Improved techniques could help researchers determine the immune mechanisms responsible for strong versus weak immune responses to influenza vaccines.
- Develop new adjuvants.

G. Research Resources and Training

Supporting the availability of research resources is essential to facilitate advances in basic and translational research on influenza. These resources include providing research reagents and access to genomic and immunologic databases, animal models for preclinical drug and vaccine development, and biocontainment laboratories. NIAID has made substantial investments in the support of resources for the scientific community for biodefense and emerging infectious diseases, which includes research on pandemic influenza. Details about these resources can be found at <http://www.niaid.nih.gov/Biodefense/Research/resources.htm>. The NIAID has also supported, in collaboration with the WHO, animal influenza surveillance training courses in Asia. These courses are aimed at training individuals from Pacific Rim countries in the early detection of avian influenza viruses.

Goal: To regularly update and expand reagents and influenza virus sequence data available to the worldwide research community and to expand the number of well-trained investigators who have influenza research or surveillance as a primary focus.

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Priority Actions:

- Produce purified reference antigens to each of the 15 novel influenza virus hemagglutinins and to selected neuraminidase molecules.
- Prepare subtype specific reference antisera (monoclonal and/or polyclonal antibodies) to avian hemagglutinin and neuraminidase proteins for use in the rapid identification of novel viruses and vaccine standardization.
- Produce a series of oligonucleotide primers to conserved regions of influenza virus genomes. These primers would allow for the rapid sequencing, identification, and characterization of novel influenza virus strains.
- Establish and maintain an up-to-date database of human and animal influenza gene sequences that can be accessed by the research community.
- Establish mechanisms that facilitate collaboration among international laboratories, which will result in the sharing of reagents, virus strains, data, new technologic advances, and training of laboratory personnel.

H. Communication Strategies (See also Annex 7: Communication)

In the setting of an influenza pandemic, clear and reliable communication that provides information that allows an individual, stakeholders or an entire community to make the best possible decisions about their well being will be crucially important.

Goal: Identify provider and public concerns and information needs about pandemic influenza and annual influenza disease and response. Identify preferred formats for information and available methods for dissemination of that information.

Priority Actions:

- Measure provider and public knowledge and beliefs about influenza disease and health care options, including perceptions, vaccine benefits and risks, among providers.
- Assess provider and public understanding and reactions to different influenza information formats and content including:
 - Annual influenza season materials, for example: Vaccine Information Statements (VIS); ACIP statements, and influenza websites.
 - Pandemic influenza materials, for example: pandemic preparedness video, satellite broadcasts, webcasts, influenza disease fact sheets, and influenza vaccine fact sheets.
- Identify, develop, and test strategies for information dissemination to providers and the public, partner organizations and agencies, and the media.