appendix G

TABLE OF CONTENTS

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 present opportunities for the emergence of influenza A viruses that are antigenically novel to the human immune system. The emergence of such a virus that develops the ability for person-to-person transmission could lead to an influenza pandemic. Although exactly when and where the next influenza pandemic will occur is unknown, it is possible that the outcome will vary from serious to catastrophic. Expanding research on influenza before the next pandemic occurs will promote a better understanding of influenza and will lead to new strategies and products that could improve the effectiveness of a pandemic response and prevent disease and death.

Research on influenza is conducted by several HHS and other U.S. government agencies such as the Department of Defense, Department of Veteran's Affairs, and the Department of Agriculture. The largest proportion of influenza research is supported by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), primarily through investigator-initiated grants and contracts. These agreements support both basic and applied research on influenza virus biology, epidemiology, pathogenesis, and immunology, as well as the development of new and improved influenza diagnostics, antiviral drugs, and vaccines. Other influenza research is supported through the intramural program at NIH, including the Laboratory of Infectious Diseases (LID), which also has a strong focus 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 and/or advise on research on influenza vaccines and antivirals, respectively.

The Agency for Healthcare Research and Quality (AHRQ) supports research on surge capacity, the use of information systems for bed-tracking and syndromic surveillance in emergency departments, and primary care.

Expanding research on influenza before the next pandemic occurs will promote a better understanding of influenza and will lead to new strategies and products that could improve the effectiveness of a pandemic response and prevent disease and death.

The intent of the NRP is to reduce America's vulnerability to terrorism, major disasters, and other emergencies; to minimize the damage resulting from these emergencies; and to facilitate recovery.

In April 2005, the Institute of Medicine (IOM) convened The John R LaMontagne Memorial Symposium on Pandemic Influenza Research to address the current state of the research and outline future priorities of scientific research for pandemic influenza. HHS will consider these recommendations, as well as other outside expert opinion, as the basis for scientific research in influenza in the near future. The combined efforts of HHS agencies including NIH, CDC, and FDA, as well as the private sector, will be needed to develop and implement this research agenda.

Research has provided the underpinning of many of the tools HHS currently has to combat influenza and will be the basis of those that are developed in the future. This document will summarize critical HHS influenza research activities. As much of the research on influenza A is applicable to both interpandemic (H3N2 & H1N1) and pandemic influenza, this document will cover both.

A. Critical basic research foundation

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 and contribute to pandemic preparedness.

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 understanding of virus-host range restriction, viral replication, and pathogenicity in order to speed the production of inactivated and live-viral vaccine candidates.

Through NIH and private sector-supported applied research programs, new vaccine candidates are being developed and clinically tested.

An increasing number of materials and reagents are being made available through the NIAID Influenza Reference Repository, the CDC WHO Collaborating Center, and FDA/CBER, 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.

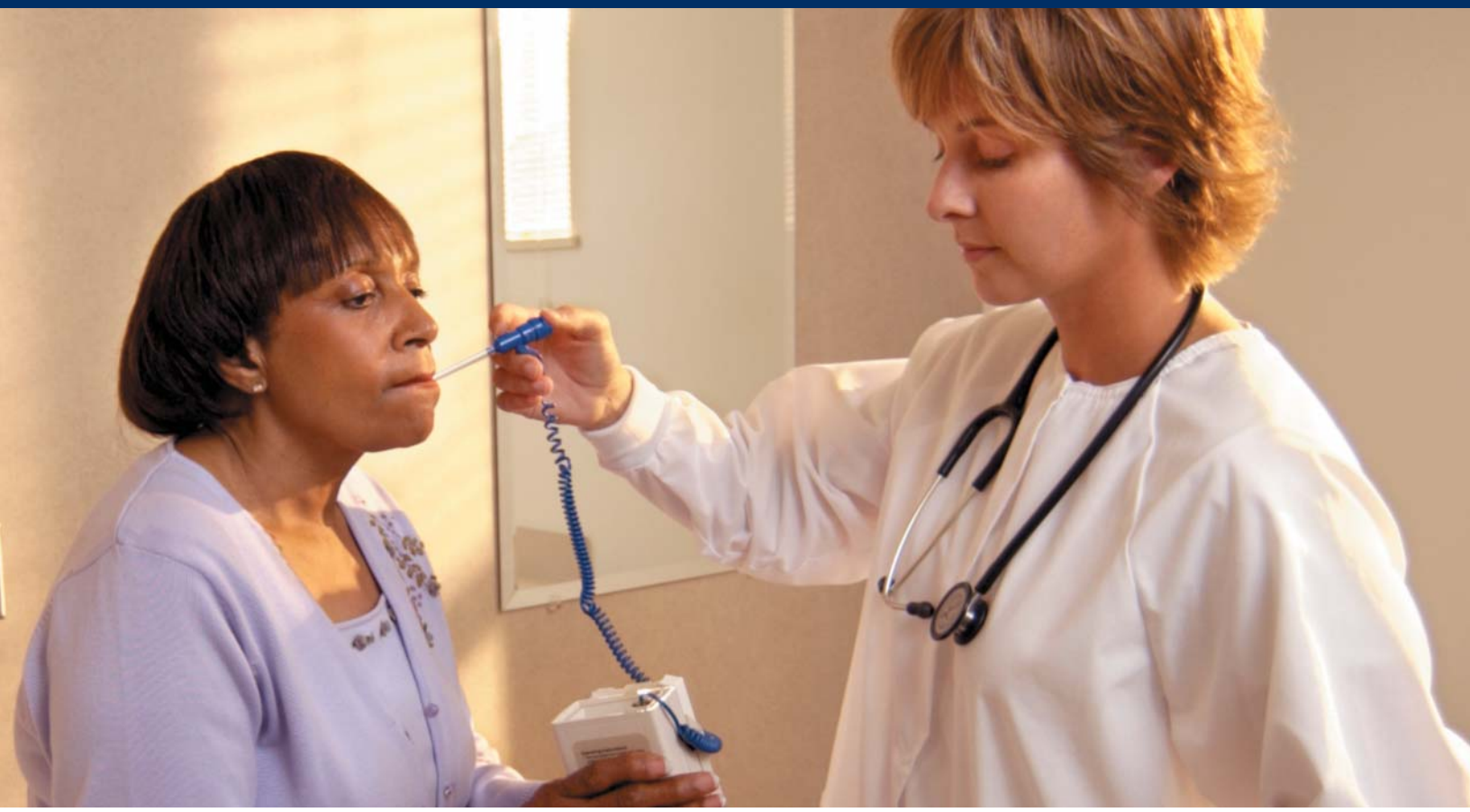
B. The transition to applied research

The plasticity of the influenza genome facilitates the virus's adaptability and its ability to escape the specific host immune responses, leading to the need for annual vaccination with 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 by the FDA 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 are being 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 on 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.

The NIAID Biodefense Partnership and Challenge Grant Programs provide support to private sector companies 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.



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 capacity 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 identifying and tracking disease before and during a pandemic, and to providing public health and health care providers the information needed to make optimal decisions.

Another component of applied research relates to the AHRQ support for research on health system preparedness. This work has focused on the use of real-time information systems to track hospital bed capacity, including emergency department and ventilator beds. In addition, a mass prophylaxis and vaccination program is currently part of the Cities' Readiness Initiative and the Strategic National Stockpile training activities.

In addition, epidemiological, programmatic, and behavioral research results lead to new understanding of influenza infections including their consequences and who is at risk, strategies to improve vaccination delivery and help eliminate racial and ethnic disparities, and effective communications messages and tools that will be vital to a pandemic response.

This appendix identifies ongoing HHS research activities for influenza, as well as highlights future research priorities that will allow the U.S. to prepare, respond, and reduce the overall morbidity and mortality associated with pandemic influenza.

II. U.S. PANDEMIC INFLUENZA: RESEARCH ACTIVITIES AND NEEDS

A. Basic virology and molecular biology

Influenza viruses, members 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 co-circulate globally in humans (H1N1 and H3N2), at least 16 distinct antigenic subtypes of HAs (H1 to H16) and nine NAs (N1 to N9) have been identified in wild aquatic birds. In spite of the severity of influenza disease, little is known about the role of the viral proteins in the virus' pathogenicity or transmission.

Goals:

- Understand the mechanism(s) by which influenza viruses of any novel subtype emerge in humans and animals.
- Identify genetic mutations that correlate with antiviral resistance.

Ongoing HHS activities:

- Conducting 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 2004–2005 H5N1 viruses and the role of virulence factors and pathogenic determinants in disease
- Using the Influenza Genome Sequencing Project to put influenza sequence data rapidly in the hands of scientists, enabling them to further study how influenza viruses evolve, spread, and cause disease
- Establishing libraries of antigenically and genetically characterized human and animal influenza viruses
- Developing new rapid methods to detect antiviral resistance in clinical influenza isolates
- Studying viral evasion mechanisms to the innate immune response mechanism, and how influenza A and B viruses modulate the innate defenses of the host
- Examining the molecular basis of transmission of influenza viruses among animals and humans

Future priorities:

- 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 in antiviral drug resistance using a reverse genetics system to find viruses with specific mutations associated with drug resistant phenotypes.
- Examine the reason behind the high lethality of the 1918 influenza pandemic.
- Identify the pandemic influenza genes that have the greatest potential for interspecies transfer. Research the role of other viral proteins in the pathogenesis of influenza.

- Identify and characterize the intracellular trafficking of influenza virus proteins, nucleic acids and complexes in avian and mammalian systems.
- Research the structural diversity of sialosides expressed at the surface of airway epithelial cells in avian and mammalian species.
- Conduct comparative analysis of membrane fusion mechanisms by HA in avian and mammalian cells.
- Research interactions between HA and mucins from avian and mammalian airway.
- Optimize reverse genetic techniques to facilitate isolation of reassortant influenza viruses.
- Research the role of other viral proteins in the pathogenesis of influenza.
- Determine the molecular basis of virulence in humans and animals.
- Support studies on the evolution and emergence of influenza viruses, including the identification of factors that affect influenza host-range and virulence.

B. Animal surveillance

Animal surveillance of influenza is important for several reasons. Previous epidemics of human infection with influenza in 1957 and 1968 were preceded by circulation of these viruses in animals. This was likely true in 1918 also, though the specific source is not clear. In addition, outbreaks in animals can be associated with considerable economic costs due to culling of infected animals and reduction in trade.

Recent outbreaks in domestic poultry in Asia 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.

Recent outbreaks in domestic poultry in Asia associated with cases of human disease highlight the importance of coordinating surveillance activities.

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.

Surveillance in the U.S. for influenza A viruses in swine and horses is currently 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.

Goal:

- Understand the prevalence, ecology, and spread of influenza virus subtypes in animal reservoirs.

Ongoing HHS activities:

- Conducting an ongoing animal influenza surveillance program in Hong Kong and other parts of Asia in wild birds, live bird markets, and pigs
- Conducting an annual surveillance of influenza viruses in wild migrating birds in North America and collaborating with the Canadian Wildlife Service to isolate influenza viruses from migratory birds

In addition to the HHS activities, other agencies are also conducting animal research.

- 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 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 Animal Health Trust, Newmarket, U.K., has taken the lead in organizing a program for equine influenza surveillance and reporting.
- The U.S. Department of Agriculture (USDA) conducts influenza surveillance in domestic animals.
- 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.

Future priorities:

- Expand surveillance of influenza viruses in poultry, swine, and wild migratory birds in the U.S. and abroad.
- Sequence known human and animal influenza viruses to understand their molecular evolution.

Year-round influenza surveillance provides 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.

C. Human surveillance and epidemiology

The information regarding circulating influenza strains is used to monitor global influenza activity and to update the formulation of annual influenza vaccines. It is also used 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 focuses on collecting influenza viral isolates for testing, monitoring morbidity and mortality, and identifying unusual or severe influenza outbreaks (see Part 2, **Supplement 1**). 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 provides 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.

Goals:

- Understand the prevalence of disease in select populations or other groups.
- Understand the factors involved in transmission of influenza.
- Understand the efficacy of potential control measures.

Ongoing HHS activities:

- Partnering with the WHO through the Global Outbreak Alert and Response Network (GOARN) to assure overall improvements in global disease detection and control
- Providing additional support and assistance to foreign governments for the development or improvement of influenza surveillance networks
- Providing support for BioSense: a state-of-the-art, multi-jurisdictional, data-sharing program to facilitate surveillance of unusual patterns or clusters of disease activity around the country
- Conducting surveillance of pediatric influenza-associated deaths, using the national reportable disease list by the Council of State and Territorial Epidemiologists, to aid in the identification of high-risk groups and in formulating improved immunization policies

- Conducting surveillance through the New Vaccine Surveillance Network to detect all influenza cases among children <5 years old who are admitted to a hospital to evaluate the effectiveness of influenza vaccination and the costs associated with pediatric influenza illness
- Supporting Emerging Infections Program network sites, which characterize the burden of severe, laboratory-confirmed pediatric influenza in the U.S.
- Supporting the Models of Infectious Disease Agent Study (MIDAS), which develops computational models that are agent-based, taking account of how individual people interact in their daily lives and examining how a pandemic might spread under various approaches to intervention
- Conducting studies to obtain annual estimates of vaccine effectiveness against laboratory- confirmed influenza illness that are underway
- Making interagency agreements with DoD for support of Naval Medical Research Unit [NAMRU] 2 (Jakarta) & 3 (Cairo) for surveillance of influenza and emerging infectious diseases
- Evaluating 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

In addition, 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.

Future priorities:

- 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.
- Determine the impact of antiviral drugs and increasing social distance measures in annual influenza epidemics, including studying the evolution of resistance and describing the behavior of individuals during an outbreak.
- Develop further analytical and computational models to study the potential impact of strategies to prevent emergence, contain spread, reduce mortality and morbidity, and make good use of limited resources. Models need to examine the individual and combined impact of intervention strategies.
- Establish a database of influenza subtypes, including sequences, clinical information, and temporal and geographic data.
- Examine the transmission of influenza viruses specifically in healthcare settings, evaluating the use of different personal protective equipment devices to prevent spread and the impact of vaccinating health care workers.

D. Immune response parameters

Historical experience with influenza vaccines suggests that two doses of inactivated 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 could 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 investigation needs to be done to understand whether adjuvants will be useful in a pandemic situation.

Goals:

- Determine how to further enhance the immunogenicity of influenza vaccines through adjuvants or alternative delivery approaches.
- Optimize immunological assays.
- Define serologic correlates of immunity.

Ongoing HHS activities:

- Developing new adjuvants
- Identifying immunologic markers that might correlate to immunity
- Evaluating mechanisms of secondary infections after influenza infections
- Creating "Immune Modeling Centers" that simulate human innate immune responses to adjuvants or immune modulators
- tudying immune responses to influenza vaccination in special populations and defining the immune parameters responsible for vaccine failure/response

Future priorities:

- Defining further the immunological markers (such as cell mediated immunity, cytokine production) that might constitute correlates of protection and determine the role of humoral, cellular, and mucosal immunity in protection against influenza disease, with an emphasis on those populations at highest risk
- Developing serological assays to assess immune responses to help researchers determine the immune mechanisms responsible for strong vs. weak immune responses to influenza vaccines
- Developing and evaluating new adjuvants
- Evaluating established and new immunotherapies on infections caused by novel influenza viruses
- Evaluating innate immune effector molecules (such as surfactants, mannose binding lectins, defensins, etc.) in the treatment of influenza
- Evaluating innate immune activation molecules (TLR 3,4,7,8,9 agonist, NOD receptors, etc.) in the treatment of influenza
- Developing modulators of inflammatory cascades

Early detection of new influenza outbreaks is critical to limit the spread of infection and control its impact on human health.

E. Diagnostic tools 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. Novel diagnostic tools are needed in the detection of newly emerging influenza strains and 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.

Goal:

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

Ongoing HHS activities:

- Developing new rapid antigen detection methods
- Developing subtype specific reference antisera for use in the rapid identification of novel influenza viruses
- Standardizing molecular techniques for the identification of influenza virus types and subtypes, including those normally circulating in human populations (H1, H3) and recent avian subtypes of interest (H5, H7 and H9)
- Developing a diagnostic microarray for influenza A (the "Flu Chip") that will provide information as to whether or not an individual is infected with influenza as well as provide both type and antigenic subtype characterization of the virus
- Developing new diagnostics that can discriminate between several different causes of respiratory diseases, including avian influenza and SARS
- Developing techniques for identifying host-response profiles for early pre-symptomatic infections

Future priorities:

- Develop more 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 patients infected with a novel influenza.
- Develop new rapid methods to detect antiviral resistance in clinical influenza isolate.
- Develop techniques for identifying host-response profiles for early detection of pre-symptomatic infections.

F. Antiviral drug development

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 of 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 anti-influenza drugs with broad activity and diminished risks of resistance emergence is of great importance.

Goals:

- Partner with industry, academia, and other interested parties to develop new influenza antiviral agents that can that can provide an option for therapy and chemoprophylaxis if strains that are resistant to currently available agents emerge and spread.
- Examine various treatment strategies to guide decision-making around the use of limited antiviral supplies.

Ongoing HHS activities:

- Evaluating monotherapy vs. combination therapy in the treatment of novel influenza infections
- Developing novel long-acting neuraminidase inhibitors
- Developing novel therapeutics using inhibitors of fusion proteins that may be capable of blocking infections by all strains of influenza viruses
- Investigating RNA interference of influenza virus infection as a new way of preventing and treating influenza infection
- Supporting "Immune Modeling Centers" which develop computational models to screen novel compounds for future clinical applications against influenza infection
- Supporting a clinical trial infrastructure (e.g., networks of potential sites with appropriate communication, documentation, and collaboration) to evaluate new influenza antiviral drugs

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 of the pandemic.

Future priorities:

- 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.
- Conduct clinical trials of potentially resource-sparing approaches such as dose reduction and shortened treatment courses that might contribute to the testing of new public health strategies.
- Develop inhaled antibodies for immunoprophylaxis against influenza.
- Support continued development of other agents with activity against influenza including hemagglutinin inhibitors, polymerase inhibitors, and protease inhibitors.
- Study antiviral drug efficacy in severely ill hospitalized patients (including treatment started late in disease course).
- Study antiviral drug effects on severe influenza complications.
- Evaluate safety and dosing in infants with influenza, and alternative dosing regimens/formulations for infants and young children.
- Establish a pregnancy registry to prospectively collect data on exposures and outcomes.

G. Vaccine development

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. Vaccination offers one of the most effective measures for minimizing the morbidity and mortality of influenza. 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. 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. A live, attenuated vaccine against influenza was licensed in 2003 for use in individuals 5 to 49 years of age. During a pandemic with a novel influenza virus, public health officials will be confronted with making critical decisions about the vaccine dosage level and immunization regimen for various populations.

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. Currently available influenza vaccines are produced by growing influenza viruses in embryonated chicken eggs, and take from 6 to 9 months to prepare. The rapid production and clinical evaluation of investigational lots of pandemic vaccines is an urgent global public health priority.

Goals:

- Increase availability of safe, effective, licensed pandemic influenza vaccines.
- Expand the repository of available vaccines, including those with varying potencies.

Ongoing HHS activities:

- Preparing of reference viruses of pandemic potential
- Preparing candidate vaccine reassortant strains for inactivated and live attenuated vaccines

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.

- Supporting preclinical and clinical studies of pandemic (e.g., H5N1, H9N2) inactivated and live attenuated vaccines
- Establishing small clinical trial networks in Southeast Asia in collaboration with WHO and others
- Developing alternatives to egg-based vaccine manufacturing technologies, which include cell culture-based systems, recombinant proteins, DNA-based platforms
- Developing common antigen vaccines, which could offer protection from multiple influenza viruses, including M2 Peptide-based vaccines
- Developing alternative mechanisms of vaccine administration, including nasal gel, topical patches, and self-administered vaccines
- Developing antigen-sparing strategies
- Supporting "Immune Modeling Centers" that use computational models to predict human immune responses to influenza and to test novel vaccine strategies
- Investigating genetic characteristics of influenza A and B viruses that influence virus yield in eggs and tissue culture

Future priorities:

- Evaluate strategies to enhance the yield of production of influenza vaccine using current manufacturing processes.
- Support the production and evaluation of investigational lots of pandemic vaccines, including those likely to be of greatest risk, to assess safety and immunogenicity in various populations.
- Continue development of new influenza vaccines, including those that may provide longer-term and/or broader protection.
- 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 vaccine.
- Develop gene-based vaccines against influenza.
- Assess the potential contribution of cellular immunity and broader cross-protection that may be provided by vaccination.
- Monitor the long-term sequelae of vaccination, including the possible protective role of vaccination against non-infectious diseases such as cardiovascular, neurological, and other diseases.
- Develop mass vaccination/delivery techniques.
- Develop common protein vaccines.
- Develop investigational live attenuated influenza virus vaccine candidates for all 16 antigenic subtypes of HAs (H1 to H16).

Performing clinical research during a pandemic offers a unique opportunity for gaining critical information about novel influenza infections.

H. 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.

Goals:

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

Ongoing HHS activities:

- Preparing antibodies and reference antigens to avian influenza viruses considered to be of high pandemic potential
- Development of diagnostic tests such as real-time PCR for rapid diagnosis of potential pandemic viruses
- Training of Public Health Laboratories in detection and characterization of potential pandemic viruses (courses and bench training of national and international laboratorians)
- Conducting animal influenza surveillance training courses in Asia
- Supporting the Influenza Genome Sequencing Project to determine the complete genetic sequences of thousands of influenza virus isolates and to rapidly provide these sequence data to the scientific community

Future priorities:

- Produce purified reference antigens to each of the 16 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 mechanisms that facilitate collaboration among international laboratories, which could result in the sharing of reagents, virus strains, data, new technologic advances, and training of laboratory personnel.

I. Research priorities during a pandemic

In the face of novel infections including novel influenza viruses, the optimal treatment and public health management is not clear. In the absence of clinical trials evaluating a pandemic strain, anecdotal experience is often extrapolated to mandates on standards of care, even if the intervention has no proven utility and may be harmful. Performing clinical research during a pandemic offers a unique opportunity for gaining critical information about novel influenza infections. The information gained may help minimize the impact of future epidemics.

Goals:

- Provide public health policy-makers with data to guide a pandemic response.
- Provide clinicians with scientific data to justify recommended treatments, vaccines, or other interventions.

Future priorities:

- Evaluate change in natural history of disease and effect of antiviral drugs (including possible dosing changes, resistance emergence, adverse events and risk/benefit assessment, etc.) in management of pandemic strain compared to previously circulating strains.
- Evaluate the safety and immunogenicity of different doses of pandemic influenza vaccines in various populations.
- Assess risk factors for infection and person-to-person transmission.
- Evaluate the population impact of outbreaks early in the development of a pandemic.
- Evaluate the effect of interventions such as travel restrictions or school closings during outbreaks early in the development of a pandemic.
- Evaluate the effect of early use of antiviral drugs in high-risk patients.
- Evaluate the efficacy of the pandemic vaccine.
- Evaluate the impact of vaccination on pathogenesis and transmission.
- Evaluate the characteristics of diagnostic tests.
- Continue other ongoing research priorities (discussed in previous sections) to the extent compatible with the pandemic situation.
- Evaluate infection control measures to prevent or minimize the spread of pandemic influenza within healthcare settings.

J. Research priorities after a pandemic

Since influenza is a global infection affecting multiple species, it is unlikely that influenza can ever be eradicated. It is likely that future pandemics that occur will continue to affect people. Therefore, critical examination of plans, responses, and outcomes of the pandemic may afford information that could affect planning and minimize impact of future pandemics.

Goal:

- Evaluate the effectiveness of policies and procedures used in the pandemic.

Future priorities:

- Detail the "natural history" of the pandemic.
- Compare the effectiveness of different infection control policies.
- Determine the factors that influenced vaccination strategies.
- Compare different vaccine delivery systems for mass vaccination.
- Determine the different rates and risk factors for adverse events to pandemic strain of influenza vaccine.
- Evaluate antiviral and vaccination strategies.
- Assess adverse events related to antivirals and vaccines.
- Evaluate the most effective disease surveillance strategies.