



part 1

Strategic Plan



strategic plan

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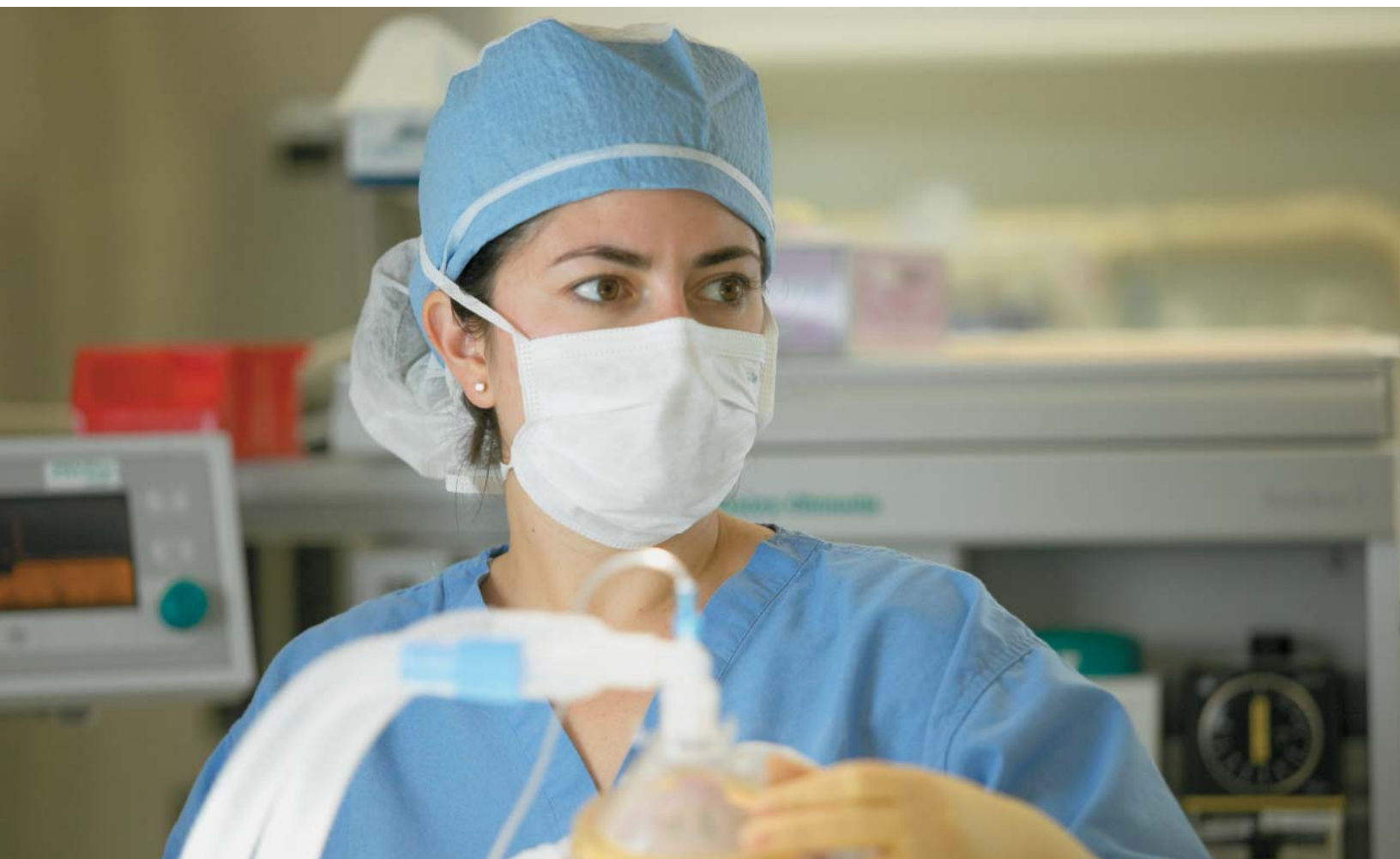
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the pandemic influenza threat

Influenza A viruses have infected many different animals including ducks, chickens, pigs, whales, horses, and seals. Influenza A viruses normally seen in one species can sometimes cross over and cause illness in another species. This creates the possibility that a new virus will develop, either through mutation or mixing of individual viruses, in turn creating the possibility for new viral strains that can be highly infective, readily transmissible, and highly lethal in humans. When a pandemic virus strain emerges, 25% to 35% of the population could develop clinical disease, and a substantial fraction of these individuals could die. The direct and indirect health costs alone (not including disruptions in trade and other costs to business and industry) have been estimated to approach \$181 billion for a moderate pandemic (similar to those in 1957 and 1968) with no interventions. Faced with such a threat, the U.S. and its international partners will need to respond quickly and forcefully to reduce the scope and magnitude of the potentially catastrophic consequences.

Such a threat currently exists in the form of the H5N1 virus, which is spreading widely and rapidly in domestic and migratory fowl across Asia and Europe. As of October 2005, this strain has infected more than 115 humans, killing approximately 50% of those known to be infected. The virus is now endemic in many bird species so that elimination of the virus is not feasible. If this virus mutates in such a way that it becomes capable of spreading efficiently from person to person, the feared pandemic could become a reality. (Additional background information is provided in Appendix B.)



When a pandemic virus strain emerges, 25% to 35% of the population could develop clinical disease, and a substantial fraction of these individuals could die.

Emergence of a human influenza virus with pandemic potential presents a formidable response challenge. If such a strain emerged in one or a few isolated communities abroad or within the U.S. and was detected quickly, containment of the outbreak(s), though very difficult, might be feasible, thereby preventing or significantly retarding the spread of disease to other communities. Containment attempts would require stringent infection-control measures such as bans on large public gatherings, isolation of symptomatic individuals, prophylaxis of the entire community with antiviral drugs, and various forms of movement restrictions—possibly even including a quarantine.

The resources required for such vigorous containment would almost certainly exceed those available in the affected community(ies). Thus, if a containment attempt is to have a chance of succeeding, the response must employ the assets of multiple partners in a well coordinated way. For isolated outbreaks outside the U.S., this means effective multinational cooperation in executing containment protocols designed and exercised well in advance. For isolated outbreaks within the U.S., this would require effective integration of the response assets of local, state, and federal governments and those of the private sector.

The National Response Plan (NRP), based on the principles of incident management, provides an appropriate conceptual and operational framework for a multi-party response to an outbreak of a potential influenza pandemic in one or a few U.S. communities. In particular, the NRP is designed to engage the response assets of multiple public and private partners and bring them to bear in a coordinated way at one or a few incident sites. (Appendix A provides additional information regarding the NRP.)

If efforts to contain isolated outbreaks within the U.S. were unsuccessful and influenza spread quickly to affect many more communities either simultaneously or in quick succession—the hallmark of a pandemic—response assets at all levels of government and the private sector would be taxed severely. Communities would need to direct all their influenza response assets to their own needs and would have little to spare for the needs of others. Moreover, as the number of affected communities grows, their collective need would spread the response assets of states and the federal government ever thinner. In the extreme, until a vaccine against the pandemic virus would become available in sufficient quantity to have a significant impact on protecting public health, thousands of communities could be countering influenza simultaneously with little or no assistance from adjacent communities, the state, or the federal government. Preparedness planning for pandemic influenza response must take this prospect into account.



planning assumptions

Pandemic preparedness planning is based on assumptions regarding the evolution and impacts of a pandemic. Defining the potential magnitude of a pandemic is difficult because of the large differences in severity for the three 20th-century pandemics. While the 1918 pandemic resulted in an estimated 500,000 deaths in the U.S., the 1968 pandemic caused an estimated 34,000 U.S. deaths. This difference is largely related to the severity of infections and the virulence of the influenza viruses that caused the pandemics. The 20th century pandemics have also shared similar characteristics. In each pandemic, about 30% of the U.S. population developed illness, with about half seeking medical care. Children have tended to have the highest rates of illness, though not of severe disease and death. Geographical spread in each pandemic was rapid and virtually all communities experienced outbreaks.

Pandemic planning is based on the following assumptions about pandemic disease:

- Susceptibility to the pandemic influenza subtype will be universal.
- The clinical disease attack rate will be 30% in the overall population. Illness rates will be highest among school-aged children (about 40%) and decline with age. Among working adults, an average of 20% will become ill during a community outbreak.
- Of those who become ill with influenza, 50% will seek outpatient medical care.
- The number of hospitalizations and deaths will depend on the virulence of the pandemic virus. Estimates differ about 10-fold between more and less severe scenarios. Because the virulence of the influenza virus that causes the next pandemic cannot be predicted, two scenarios are presented based on extrapolation of past pandemic experience (Table 1).

Table 1. Number of Episodes of Illness, Healthcare Utilization, and Death Associated with Moderate and Severe Pandemic Influenza Scenarios*

Characteristic	Moderate (1958/68-like)	Severe (1918-like)
Illness	90 million (30%)	90 million (30%)
Outpatient medical care	45 million (50%)	45 million (50%)
Hospitalization	865,000	9,900,000
ICU care	128,750	1,485,000
Mechanical ventilation	64,875	742,500
Deaths	209,000	1,903,000

*Estimates based on extrapolation from past pandemics in the United States. Note that these estimates do not include the potential impact of interventions not available during the 20th century pandemics.

Risk groups for severe and fatal infections cannot be predicted with certainty.

- Risk groups for severe and fatal infections cannot be predicted with certainty. During annual fall and winter influenza season, infants and the elderly, persons with chronic illnesses, and pregnant women are usually at higher risk of complications from influenza infections. In contrast, in the 1918 pandemic, most deaths occurred among young, previously healthy adults.
- The typical incubation period (the time between acquiring the infection until becoming ill), for influenza averages 2 days. We assume this would be the same for a novel strain that is transmitted between people by respiratory secretions.
- Persons who become ill may shed virus and can transmit infection for one-half to one day before the onset of illness. Viral shedding and the risk for transmission will be greatest during the first 2 days of illness. Children will shed the greatest amount of virus and, therefore are likely to pose the greatest risk for transmission.
- On average about 2 secondary infections will occur as a result of transmission from someone who is ill. Some estimates from past pandemics have been higher, with up to about 3 secondary infections per primary case.
- In an affected community, a pandemic outbreak will last about 6 to 8 weeks. At least two pandemic disease waves are likely. Following the pandemic, the new viral subtype is likely to continue circulating and to contribute to seasonal influenza.
- The seasonality of a pandemic cannot be predicted with certainty. The largest waves in the U.S. during 20th century pandemics occurred in the fall and winter. Experience from the 1957 pandemic may be instructive in that the first U.S. cases occurred in June but no community outbreaks occurred until August and the first wave of illness peaked in October.

*In an affected community, a pandemic outbreak will last about 6 to 8 weeks.
At least two pandemic disease waves are likely.*



doctrine for a pandemic

HHS will be guided by the following principles in initiating and directing its response activities:

- 1) In advance of an influenza pandemic, HHS will work with federal, state, and local government partners and the private sector to coordinate pandemic influenza preparedness activities and to achieve interoperable response capabilities.²
- 2) In advance of an influenza pandemic, HHS will encourage all Americans to be active partners in preparing their states, local communities, workplaces, and homes for pandemic influenza and will emphasize that a pandemic will require Americans to make difficult choices. An informed and responsive public is essential to minimizing the health effects of a pandemic and the resulting consequences to society.
- 3) In advance of an influenza pandemic, HHS, in concert with federal partners, will work with the pharmaceutical industry to develop domestic vaccine production capacity sufficient to provide vaccine for the entire U.S. population as soon as possible after the onset of a pandemic and, during the pre-pandemic period, to produce up to 20 million courses of vaccine against each circulating influenza virus with pandemic potential and to expand seasonal influenza domestic vaccine production to cover all Americans for whom vaccine is recommended through normal commercial transactions.
- 4) In advance of an influenza pandemic, HHS, in concert with federal partners and in collaboration with the States, will procure sufficient quantities of antiviral drugs to treat 25% of the U.S. population and, in so doing, stimulate development of expanded domestic production capacity sufficient to accommodate subsequent needs through normal commercial transactions. HHS will stockpile antiviral medications in the Strategic National Stockpile, and states will create and maintain local stockpiles.
- 5) Sustained human-to-human transmission anywhere in the world will be the triggering event to initiate a pandemic response by the United States. Because we live in a global community, a human outbreak anywhere means risk everywhere.
- 6) The US will attempt to prevent an influenza pandemic or delay its emergence by striving to arrest isolated outbreaks of a novel influenza wherever circumstances suggest that such an attempt might be successful, acting in concert with WHO and other nations as appropriate. At the core of this strategy will be basic public health measures to reduce person-to-person transmission.

² Throughout this document, the term "state and local" is inclusive of municipal, county, territorial, and tribal governments and health authorities.

In advance of an influenza pandemic, HHS will encourage all Americans to be active partners in preparing their states, local communities, workplaces, and homes for pandemic influenza and will emphasize that a pandemic will require Americans to make difficult choices.

- 7) At the onset of an influenza pandemic, HHS, in concert with federal partners, will work with the pharmaceutical industry to procure vaccine directed against the pandemic strain and to distribute vaccine to state and local public health departments for pre-determined priority groups based on pre-approved state plans.
- 8) At the onset of an influenza pandemic, HHS, in collaboration with the states, will begin to distribute and deliver antiviral drugs from public stockpiles to healthcare facilities and others with direct patient care responsibility for administration to pre-determined priority groups.





key pandemic influenza response

An influenza pandemic will place extraordinary and sustained demands on public health and healthcare systems and on providers of essential community services across the U.S. and throughout the world. The nature and scope of these demands will vary over the course of the pandemic. Table 2 lists key pandemic response actions that public health, medical, and other government authorities at all levels must be prepared to take to mitigate the potentially catastrophic consequences of a pandemic. A more detailed list of HHS-specific response actions categorized by WHO pandemic phase is shown in Tables 4 through 9.

Pandemic influenza preparedness is a process, not an isolated event. To most effectively implement key pandemic response actions, specific capabilities must be developed through preparedness activities implemented before the pandemic occurs. For each key pandemic response activity, Table 2 summarizes capabilities needed for implementation of an effective response.

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Table 2. Key Pandemic Response Elements and Key Capabilities for their Effective Implementation

Key Pandemic Response Actions	Key Capabilities Needed for Implementation of an Effective Response
Surveillance, Investigation, and Protective Public Health Measures	
<p>1. Increase international surveillance and collaborate in outbreak investigation to track the emerging epidemiological patterns and impacts of disease caused by the novel influenza virus subtype.</p>	<p>1. Agreements with international partners, including international organizations, and other U.S. government agencies, to improve the capability and capacity of local public health systems in countries where a potential pandemic virus strain is likely to emerge so that accurate and timely influenza surveillance information can be obtained.</p>
<p>2. Determine feasibility of containing the initial outbreak of a potential pandemic, working in consultation with international partners, and if feasible, implement containment activities.</p>	<p>2. Assets (people, facilities, equipment, supplies, and exercised procedures), deployed at home and abroad, to investigate, and if feasible, mount an immediate emergency response.</p>
<p>3. Obtain samples of the potential pandemic virus from infected people and distribute them to laboratories for genetic, antigenic, and antiviral resistance analysis. Prepare reference strains for distribution to vaccine manufacturers. Assess cross-protection of stockpiled vaccine, if available, against the pandemic virus.</p>	<p>3. Laboratory assets to characterize the novel influenza virus strain (genetic and antigenic characteristics and antiviral resistance) and rapidly develop a vaccine reference strain for distribution to manufacturers. Agreements with international partners to quickly obtain samples.</p>
<p>4. Implement surveillance and control measures (e.g., isolation of cases, quarantine of contacts, antiviral drug treatment and prophylaxis) at points-of-entry to decrease introduction and spread of the pandemic virus in the U.S.</p>	<p>4. Quarantine stations and related protections at all major U.S. ports of entry to limit the introduction of pandemic influenza, isolate cases, and trace contacts.</p>
<p>5. Enhance domestic surveillance to detect pandemic outbreaks, track the spread of virus in near real-time, and assess impacts on health and infrastructure.</p>	<p>5. Real-time or near real-time electronic connectivity with major domestic healthcare institutions and public health departments across the U.S. to obtain daily influenza disease and resource availability information.</p> <p>Widely available, reliable, rapid, sensitive, and accurate diagnostic tests.</p>
<p>6. Implement public health measures to limit the spread of infection (e.g., canceling public gatherings) as well as individual measures to decrease the risk of acquiring or spreading infection (e.g., personal hygiene, isolation of ill persons).</p>	<p>6. Assets (people, facilities, equipment, supplies, and exercised procedures) to effect wide-spread individual and community-based infection control measures and educate individuals on personal protection strategies.</p>
<p>7. Monitor pandemic response actions and assess their effectiveness.</p>	<p>7. Assets (people, facilities, equipment, supplies, and exercised procedures) to analyze data continually during the course of the pandemic to guide response activities and to assess the safety and efficacy of interventions.</p>

Table 2. (Continued)

Key Pandemic Response Actions	Key Capabilities Needed for Implementation of an Effective Response
Vaccines and Antiviral Drugs	
<p>1. Consider administration of pre-pandemic stockpiled vaccine, if available, to pre-defined groups critical to the pandemic response. This could provide partial immune protection and/or prime the immune system for a protective response once a targeted pandemic vaccine becomes available.</p>	<p>1. A national stockpile of 40 million doses (2 doses per person) of vaccine against influenza virus subtypes considered to pose a substantial pandemic risk (currently avian H5N1).</p>
<p>2. In conjunction with other parties, manufacture, test, license, and produce vaccine against the specific pandemic virus strain.</p>	<p>2. Domestic influenza vaccine manufacturing capacity to produce sufficient pandemic vaccine for the U.S. population within 6 months of the onset of an influenza pandemic.</p> <p>Consider liability concerns vaccine manufacturers.</p> <p>A library of reference strains and reagents for novel influenza subtypes; clinical trials of candidate pandemic influenza vaccines in the U.S. and affected areas.</p>
<p>3. Allocate and administer pandemic vaccine to pre-defined priority groups. Ensure security for protection of scarce vaccines.</p>	<p>3. State and local vaccine distribution plans, guided by recommendations for use of pandemic vaccine when supply is short, that are specific, implementable, and which have been practiced in tabletop and field exercises.</p>
<p>4. Monitor vaccine coverage and track vaccine use so persons who receive initial pandemic vaccine can return for a second dose, if required. Monitor for adverse events following vaccination and conduct studies to assess vaccine safety and effectiveness.</p>	<p>4. Assets (people, facilities, equipment, supplies, and exercised procedures) to monitor vaccine coverage, adverse events, and effectiveness.</p>
<p>5. Allocate stockpiled antiviral drugs for use in pre-defined high-risk and critical infrastructure populations.</p>	<p>5. Availability of at least 81 million treatment courses of approved antiviral drugs—enough for treatment of approximately 25% of the U.S. population and 6 million additional treatment courses in reserve for domestic containment.</p> <p>State and local antiviral drug distribution plans, guided by recommendations for use of pandemic vaccine when supply is short, that are specific, implementable, and have been practiced in tabletop and field exercises.</p> <p>Increased U.S.-based antiviral drug manufacturing.</p>

Table 2. (Continued)

Key Pandemic Response Actions	Key Capabilities Needed for Implementation of an Effective Response
Vaccines and Antiviral Drugs (Continued)	
<p>6. Monitor antiviral drug distribution and adverse events, and conduct studies to further assess safety and effectiveness.</p>	<p>6. Assets (people, facilities, equipment, supplies, and exercised procedures) to monitor antiviral distribution, adverse events, and effectiveness.</p>
Healthcare and Emergency Response	
<p>1. Distribute stockpiled ventilators and other medical material needed to treat and care for infected individuals to health departments and federal agencies that provide direct patient care.</p>	<p>1. Equipment and supplies maintained in the Strategic National Stockpile and state stockpiles sufficient to enhance medical surge capacity.</p>
<p>2. Deploy Federal Medical Stations, as available, to provide healthcare surge capacity in hardest hit areas.</p>	<p>2. Federal Medical Stations and healthcare assets (people, facilities, equipment, supplies, and exercised procedures) to enhance medical surge capacity.</p>
<p>3. Test patient specimens using highly accurate (sensitive and specific) rapid diagnostic tests to identify pandemic outbreaks in communities and contribute to management decisions.</p>	<p>3. Widely available accurate rapid diagnostic methods to detect and characterize influenza viruses.</p>
<p>4. Assist communities with surge mortuary services to accommodate a large number of expected fatalities.</p>	<p>4. Assets (people, facilities, equipment, supplies, and exercised procedures) for the timely, safe, and respectful disposition of the deceased.</p>
<p>5. Provide psychosocial support to responders and affected communities.</p>	<p>5. Institutionalization of psychosocial support services and development of workforce resiliency programs.</p>
Communications and Outreach	
<p>1. Public education and information campaign to 1) communicate measures the public can implement to minimize risk and decrease the spread of infection; 2) provide honest, accurate, understandable and timely information; and 3) counter confusion and panic.</p>	<p>1. Pre-tested risk communication materials that provide the public easy-to-understand information regarding pandemic influenza and how individuals can protect themselves and help others during an influenza pandemic, and appropriate use of vaccines and antiviral drugs.</p> <p>Pre-tested procedures through which public authorities within each community will provide information and guidance to the public (including marginalized, disadvantaged, and foreign-language populations) during an influenza pandemic.</p>



roles and responsibilities of HHS agencies and offices

Table 3 provides a summary of the roles and responsibilities assigned to select HHS officials, agencies, and divisions.



Table 3. Summary of Major Pandemic Response Roles of HHS Officials, Agencies, and Divisions

HHS Official, Agency, or Division	Roles
Secretary of Health and Human Services	<ul style="list-style-type: none"> ■ Directs all HHS pandemic response activities
Assistant Secretary for Public Health Emergency Preparedness (ASPHEP)	<ul style="list-style-type: none"> ■ Coordinates HHS pandemic response activities ■ Monitors effectiveness of response activities and modifies strategies, as needed ■ Coordinates and communicates with other federal departments and agencies
Assistant Secretary for Health (ASH)	<ul style="list-style-type: none"> ■ Directs the Office of the Surgeon General in deployment of U.S. Public Health Service Commissioned Corps assets ■ Directs Regional Health Administrators who will be members of Secretary's Emergency Response Teams (SERTs) in their regions ■ Advises Secretary on Public Health and Science as he directs HHS pandemic response activities ■ Coordinates operations planning efforts of HHS agencies, operational divisions and offices ■ Assists with public communications and coordination with state and local public health partners ■ Directs the National Vaccine Program Office (NVPO) in pandemic preparedness and response
Director of Office of Intergovernmental Affairs	<ul style="list-style-type: none"> ■ Advises and coordinates outreach and communications to state, local and tribal officials and national intergovernmental organizations
Assistant Secretary for Legislation (ASL)	<ul style="list-style-type: none"> ■ Coordinates Congressional outreach and communications
Office of the Surgeon General (OSG)	<ul style="list-style-type: none"> ■ Deploys U.S. Public Health Service Commissioned Corps assets (upon approval of the Assistant Secretary for Health) ■ Assists with public communication and education ■ Assists and coordinate pandemic planning with partner federal health service providers, specifically the Indian Health Service, The Federal Bureau of Prisons and the Coast Guard
Assistant Secretary for Public Affairs (ASPA)	<ul style="list-style-type: none"> ■ Coordinates public information and communications
National Vaccine Program Office (NVPO)	<ul style="list-style-type: none"> ■ Chairs Secretary's Task Force on Influenza Preparedness ■ Coordinates communication between vaccine and antiviral drug manufacturers and HHS agencies ■ Coordinates development of after-action report and lessons learned ■ Maintains close communication with drug and vaccine manufacturers

Table 3. (Continued)

HHS Official, Agency, or Division	Roles
Office of the General Counsel (OGC)	<ul style="list-style-type: none"> ■ Advises on legal issues and authorities related to key pandemic response activities
Director of the Office of Global Health Affairs (OGHA)	<ul style="list-style-type: none"> ■ Coordinates interactions with health authorities in other governments and international organizations in coordination with the Department of State
Centers for Disease Control and Prevention (CDC)	<ul style="list-style-type: none"> ■ Conducts and supports clinical and virological influenza surveillance ■ Monitors pandemic health impacts ■ Implements travel-related and community containment measures as necessary to prevent the introduction, transmission, and spread of pandemic disease from foreign countries into the US, from state to state or in the event of inadequate local control ■ Coordinates pandemic response activities with state, local and tribal public health agencies ■ Investigates epidemiology and clinical characteristics of pandemic disease ■ Assists in vaccination program implementation and in monitoring and investigating vaccine adverse events ■ Assesses vaccine effectiveness in population-based studies ■ Coordinates antiviral and other drug delivery from the Strategic National Stockpile ■ Monitors antiviral drug use, effectiveness, safety, and resistance ■ Monitors the implementation/effectiveness of protective public health measures ■ Recommends and evaluates community measures to prevent and control disease ■ Makes recommendations on diagnosis and management of influenza illness ■ Makes recommendations on appropriate infection control recommendations ■ Communicates with state and local health departments and other public health partners ■ Communicates information on pandemic health impacts as directed by the ASPA ■ Maintains close communication with drug and vaccine manufacturers
Centers for Medicare and Medicaid	<ul style="list-style-type: none"> ■ Provides streamlined payment mechanisms and works with prescription drug plans and Medicare managed care plans, as necessary to ensure ready access to pandemic influenza vaccine and antiviral prescription drugs for Medicare’s population ■ Communicates specific guidance and supports pandemic flu response activities of the nation’s hospitals, home health agencies, skilled nursing facilities and other health care providers, suppliers and practitioners that participate in Medicare and Medicaid

Table 3. (Continued)

HHS Official, Agency, or Division	Roles
Food and Drug Administration (FDA)	<ul style="list-style-type: none"> ■ Communicates influenza pandemic related information through existing outreach networks to Medicare beneficiary populations ■ Supports tracking and surveillance of Medicare patients, including high-risk and vulnerable patients who have received pandemic influenza vaccine and antiviral prescription drugs, including review of Medicare claims and quality data ■ Supplies “real time” intelligence to other Federal health care agencies on the status of local, regional and national pandemic flu response provider activities through stakeholder association meetings and open door forums ■ Prepares reference strains appropriate for vaccine manufacturing <ul style="list-style-type: none"> ■ Regulates manufacturing process ■ Evaluates and licenses pandemic vaccines ■ Evaluates and approves antiviral drugs for influenza ■ Facilitates the development, evaluation and clearance or approval of diagnostic tests and devices ■ Prepares reagents to standardize potency of inactivated influenza vaccines ■ Prepares reference strains appropriate for vaccine manufacturing ■ Reviews antiviral drug and pandemic vaccine supply issues ■ Evaluates and issues Emergency Use Authorizations when appropriate ■ Monitors vaccine adverse events ■ Monitors antiviral drug adverse events ■ Maintains close communication with drug and vaccine manufacturers ■ Evaluates investigational new drug applications (INDs) and investigational device exemptions (IDEs) for medical products that diagnose, treat, prevent or mitigate influenza ■ Evaluates new manufacturing sites and processes for antiviral drugs ■ Makes necessary changes in prescribing and patient information, including dosing, target populations, and other direction for use, for antiviral drugs and pandemic vaccines based on research and adverse events ■ Evaluates long-term stability of stockpiled antiviral drugs for purposes of shelf life extension ■ Monitors to protect against the distribution of counterfeit antiviral drugs and pandemic vaccines

Table 3. (Continued)

HHS Official, Agency, or Division	Roles
National Institutes of Health (NIH)	<ul style="list-style-type: none"> ■ Develops improved drugs against influenza ■ Supports basic research, including structure/function studies of influenza virus proteins with the goal of identifying new therapeutic targets ■ Develops and clinically evaluates novel influenza vaccines and vaccination strategies (e.g., adjuvants, delivery systems) ■ Develops sensitive, specific, and rapid diagnostic tests for influenza ■ Evaluates the immune response to infection and vaccination ■ Determines the molecular basis of virulence in humans and animals ■ Evaluates the molecular and/or environmental factors that influence the transmission of influenza viruses, including drug-resistant strains ■ Studies the evolution and emergence of influenza viruses including the identification of factors that affect influenza host-range and virulence ■ Supports virologic and serologic surveillance studies of the distribution of influenza viruses with pandemic potential in animals ■ Maintains close communication with drug and vaccine manufacturers ■ Prepares reference strains appropriate for vaccine manufacturing
Agency for Healthcare Research and Quality (AHRQ)	<ul style="list-style-type: none"> ■ Communicates with and supports federal, state, and local public health partners on mass vaccination and surge capacity healthcare delivery plans
Health Resources and Services Administration (HRSA)	<ul style="list-style-type: none"> ■ Communicates with and provides technical assistance to support pandemic response activities of state primary care associations, health centers, and other community-based providers ■ Promotes coordination with the National Hospital Bioterrorism Preparedness Program for surge capacity plans
Substance Abuse and Mental Health Services Administration (SAMHSA)	<ul style="list-style-type: none"> ■ Communicates with and supports pandemic response activities of state, local, and tribal mental health and substance abuse agencies ■ Communicates information on behavioral health issues, including stress and anxiety as a result of pandemic health impacts, as directed by the ASPA
Administration for Children and Families (ACF)	<ul style="list-style-type: none"> ■ Communicates with and supports pandemic response activities of state, local, tribal, and nonprofit (including faith-based and community) human services organizations ■ Communicates information on child and family well-being, including the importance and availability of vaccinations and antiviral drugs, as well as proper hygienic practices, to treat pandemic influenza and prevent its spread

Table 3. (Continued)

HHS Official, Agency, or Division	Roles
	<ul style="list-style-type: none"> ■ Encourages the participation of human services providers (e.g., Head Start centers, child care centers, family resource centers, community action agencies, runaway and homeless youth shelters, and shelters for unaccompanied alien children) in making vaccines and antiviral drugs available to vulnerable populations ■ Assists in medium- and long-term social adjustment of individuals, families, and communities following the pandemic
Indian Health Service (IHS)	<ul style="list-style-type: none"> ■ Communicates with and supports state, local, and tribal pandemic response activities at HHS, tribal, and urban Indian sites serving American Indian and Alaska Native populations





HHS actions for pandemic influenza preparedness and response

HHS will follow the WHO published guidance for national pandemic planning, which defines pandemic activities in six phases. WHO Phases 1 and 2 are the Interpandemic Period, which includes phases where no new influenza virus subtypes have been detected in humans.

The Pandemic Alert Period includes a phase when human infection with a novel influenza strain has been identified but no evidence has been found of transmission between people or at most rare instances of spread to a close contact (WHO Phase 3) and includes phases where person-to-person transmission is occurring in clusters with limited human-to-human transmission (WHO Phases 4 and 5). WHO Phase 6 is the Pandemic Period, in which there is increased and sustained transmission in the general population. (Appendix C describes the WHO pandemic phases in detail.)

Each pandemic phase is associated with a range of preparedness and response activities directed by the Secretary of Health and Human Services, after consultation with international authorities and others, as necessary. Given that an influenza pandemic may not unfold in a completely predictable way, decision-makers must regularly reassess their strategies and actions and make adjustments as necessary. This section highlights critical pandemic preparedness and response activities to be implemented by HHS.



Given that an influenza pandemic may not unfold in a completely predictable way, decision-makers must regularly reassess their strategies and actions and make adjustments as necessary.

Table 4: WHO Pandemic Phases 1 and 2: HHS Actions

WHO Phases 1 and 2: Interpandemic Phase Actions	
Planning and Coordination	<ul style="list-style-type: none"> ■ Assess preparedness status and identify actions needed to fill gaps. ■ Coordinate with Federal, state and local, tribal, and private-sector authorities and organizations, and with media and the public. ■ Develop and conduct tabletop and field exercises to evaluate and improve preparedness plans and response capabilities. ■ Coordinate completion of pandemic preparedness and response plans at Federal, state local, tribal, and private-sector levels. ■ Update HHS Pandemic Influenza Plan as needed. ■ Consider indemnification and liability protection issues for affected entities, including pandemic vaccine manufacturers, pandemic vaccine distributors, and healthcare providers who administer pandemic vaccines.
Surveillance, Investigation, and Protective Public Health Measures	<ul style="list-style-type: none"> ■ Prepare reagents for identification of new influenza strains in animals and other strains with pandemic potential. ■ Assist in domestic and international influenza outbreak investigations. ■ Develop strategies to enhance domestic surveillance and collaborate with international organizations to improve global surveillance to allow earlier detection of novel influenza viruses. ■ Enhance collaborations with international organizations and governments to facilitate surveillance and reporting and the ability to investigate disease outbreaks and implement containment measures that could prevent a pandemic. ■ Develop guidance for outbreak control measures in healthcare settings and other institutions such as long-term care facilities. ■ Develop strategies to prevent spread of infection to or within the U.S. from affected areas (e.g., travel advisories or precautions, assessment of travelers returning from affected areas). ■ Assess pathogenicity, antiviral susceptibility, and other characteristics of novel influenza strains.
Vaccines and Antiviral Drugs	<ul style="list-style-type: none"> ■ Develop strategies to increase uptake of annual influenza vaccine. ■ Expand U.S.-based influenza vaccine manufacturing capacity, diversifying vaccine production methods and suppliers. ■ Ensure capacity exists to produce adequate doses of influenza vaccine year-round. ■ Support development, evaluation, and U.S.-based production of an influenza vaccine produced in cell culture. ■ Support development, evaluation and U.S.-based production of antiviral drugs. ■ Develop vaccine reference strain and reagents for influenza strains with pandemic potential.

Table 4. (Continued)

WHO Phases 1 and 2: Interpandemic Phase Actions	
	<ul style="list-style-type: none"> ■ Obtain investigational lots of candidate vaccine for novel influenza strains and conduct clinical testing. ■ Develop strategies for rapid administration of vaccines to priority populations and mechanisms to monitor vaccine effectiveness and safety. ■ Support efforts to make antiviral drugs available to treat priority populations and to support containment, outbreak response, and protection of priority populations involved in pandemic response activities and maintenance of critical services and infrastructures.
Healthcare and Emergency Response	<ul style="list-style-type: none"> ■ Assess surge capacity of medical (including inpatient, outpatient, and long-term care facilities) and emergency response systems (e.g. beds, ventilators, etc.) to meet expected needs during a pandemic. ■ Assess surge capacity of federal medical assets (e.g. IHS, VA, DOD).
Communications and Outreach	<ul style="list-style-type: none"> ■ Coordinate communication activities across federal departments and with state, local and international partners. ■ Inform and educate the public about influenza. ■ Communicate with state and local health departments. ■ Develop educational materials for healthcare and human services providers, the media, and the public on pandemic influenza preparedness and response, including facilities, vaccine, and antiviral drugs in short supply. ■ Develop strategies and materials to support a pandemic response and to promote public trust and decrease fear and anxiety.
Research	<ul style="list-style-type: none"> ■ Conduct research to develop and manufacture new influenza vaccines and antiviral drugs. ■ Conduct research to decrease time needed to develop, evaluate, and produce pandemic vaccine. ■ Conduct research to decrease time needed to develop, evaluate, and produce antiviral drugs. ■ Conduct research on effective protective health measures.

Table 5: WHO Pandemic Phase 3: HHS Actions

WHO Phase 3: Pandemic Alert Phase Actions (No person-to-person transmission)	
Planning and Coordination	<ul style="list-style-type: none"> ■ Assess preparedness status and identify actions needed to fill gaps. ■ Collaborate with international partners to respond to pandemic alert. ■ Inform government officials (including Congress and state health departments) and legislators of pandemic alert status.
Surveillance, Investigation, and Protective Public Health Measures	<ul style="list-style-type: none"> ■ Distribute reagents to state public health laboratories and WHO National Influenza Centers for detection of the new strain. ■ Assist in international influenza outbreak investigations and characterize disease epidemiology and antigenic and genetic characteristics of the virus. ■ Implement strategies to enhance domestic surveillance and to identify suspect cases in the U.S. in coordination with state and local health authorities. ■ Provide guidance to implement outbreak control measures in healthcare settings and other institutions, such as long-term care facilities, as needed. ■ Implement strategies to prevent the spread of infection to or within the U.S. from affected areas, in coordination with state and local health authorities.
Vaccines and Antiviral Drugs	<ul style="list-style-type: none"> ■ Develop vaccine reference strain to the novel influenza virus and distribute to manufacturers. ■ Develop reagents for evaluation of candidate vaccines to the novel strain. ■ Test investigational lots of vaccine to the new strain. ■ Develop a tracking system that will ensure that individuals obtain subsequent doses of vaccine and will report and monitor for adverse events. ■ Develop a tracking system to report and monitor for adverse events in individuals given antiviral therapies. ■ Assess status of available antiviral drugs and strategies for use. ■ Evaluate antiviral susceptibilities of the novel strain.
Healthcare and Emergency Response	<ul style="list-style-type: none"> ■ Assess capacity of medical and emergency response systems to meet expected needs during a pandemic. ■ Enhance surge capacity of federal medical systems.
Communications and Outreach	<ul style="list-style-type: none"> ■ Update state and local health departments, other stakeholders, and the media on status of pandemic. ■ Enhance healthcare provider awareness of the potential for a pandemic and the importance of diagnosis and viral identification for persons with influenza-like illness, especially from potentially affected areas. ■ Implement strategies and disseminate materials to support a pandemic response and to promote public trust and decrease fear and anxiety.

Table 6: WHO Pandemic Phases 4 and 5: HHS Actions

WHO Phases 4 and 5: Pandemic Alert Phase Actions – Limited human-to-human transmission	
Planning and Coordination	<ul style="list-style-type: none"> ■ Assess preparedness status and identify immediate actions needed to fill gaps. ■ Establish coordination of response activities through the Secretary’s Operations Center. ■ Coordinate with the WHO and foreign governments. ■ Notify government officials (including Congress and state health departments) and legislators of pandemic status.
Surveillance, Investigation, and Protective Public Health Measures	<ul style="list-style-type: none"> ■ Assist in international containment efforts, if appropriate. ■ Assist in international influenza outbreak investigations and characterize disease epidemiology and antigenic and genetic characteristics of the virus. ■ Distribute reagents to state public health laboratories for detection of the novel strain. ■ Continue enhanced national surveillance; identify suspect cases and/or introduction of a novel virus into the U.S. ■ Provide education to travelers, including refugees being resettled in the U.S., and issue travel advisories, precautions, or restrictions if warranted by disease epidemiology; investigate illness among travelers returning from affected areas and implement isolation and quarantine, as needed.
Vaccines and Antiviral drugs	<ul style="list-style-type: none"> ■ Develop vaccine reference strain (if not already done) and distribute to manufacturers. ■ Develop and test investigational lots of vaccine to the new strain. ■ Develop reagents for formulation and potency testing of pandemic vaccine. ■ Contract with manufacturers to develop pilot lots of pandemic vaccine for clinical testing. ■ Initiate rapid clinical studies of pandemic vaccine safety, immunogenicity, and schedule. ■ Determine susceptibility of the novel influenza strain to antiviral drugs (if not already done). ■ Assess supply, distribution, and production capacity of antiviral drug manufacturers. ■ Contract with manufacturers for production of additional antiviral drugs. ■ Ready process for investigational new drug (IND) or Emergency Use Authorization (EUA) applications for experimental vaccines and antiviral drugs available for use under EUA or IND.

Table 6. (Continued)

WHO Phases 4 and 5: Pandemic Alert Phase Actions – Limited human-to-human transmission	
Healthcare and Emergency Response	<ul style="list-style-type: none"> ■ Assess capacity of medical and emergency response systems to meet expected needs during a pandemic. ■ Provide updated guidance, if indicated, to healthcare providers on clinical management and infection control.
Communications and Outreach	<ul style="list-style-type: none"> ■ Update Congress; state, local, and tribal health departments; local officials, other stakeholders, and the media. ■ Implement public education on the potential for a pandemic and the actions to be taken to reduce risk.

Table 7: WHO Pandemic Phase 6, No U.S. Cases: HHS Actions

WHO Phase 6: Pandemic Period Actions (no cases in the U.S.)	
Planning and Coordination	<ul style="list-style-type: none"> ■ Update government officials (including Congress and state health departments) and legislators on pandemic status. ■ Coordinate information sharing with other federal agencies, including DHS, Department of State, DOD, the WHO, and other countries.
Surveillance, Investigation, and Protective Public Health Measures	<ul style="list-style-type: none"> ■ Collaborate with international organizations to assess epidemiology of disease outbreaks and efficiency of person-to-person transmission, and to obtain parameter estimates to support real-time mathematical modeling. ■ Implement travel advisories, precautions, or restrictions, as appropriate. ■ Investigate illness among travelers returning from affected areas; implement isolation and quarantine, as needed. ■ Assist states, as needed, in investigating potential cases of pandemic influenza. ■ Continue activities to enhance detection of U.S. cases of influenza at borders, hospitals, and outpatient settings. ■ Ensure availability of diagnostic reagents for pandemic influenza strain at state and local public health laboratories. ■ Provide reference laboratory support to test clinical specimens for influenza and identify novel strain. ■ Develop and evaluate diagnostic tests for the novel strain.

Table 7. (Continued)

WHO Phase 6: Pandemic Period Actions (no cases in the U.S.)	
Vaccines and Antiviral drugs	<ul style="list-style-type: none"> ■ Contract with manufacturers for production of pandemic vaccine. ■ Assess candidate vaccines for licensure. ■ Review and revise, as needed, priority groups and strategies for antiviral drug use and vaccination. ■ Continue ongoing assessment of antiviral resistance of the pandemic strain.
Healthcare and Emergency Response	<ul style="list-style-type: none"> ■ Review and revise, as needed, plans for healthcare delivery and community support. ■ Assess availability of federal personnel, supplies, and materials for infection control and clinical care of infected patients. ■ Provide guidance to healthcare providers on infection control guidelines for hospitals, long-term care facilities, and outpatient settings.
Communications and Outreach	<ul style="list-style-type: none"> ■ Update stakeholders and the media through regular briefings. ■ Educate healthcare providers through satellite broadcasts, webcasts, and other communications channels. ■ Continue public education activities.

Table 8: WHO Pandemic Phase 6, U.S. Cases: HHS Actions

WHO Phase 6: Pandemic Period Actions (cases in the U.S.)	
Planning and Coordination	<ul style="list-style-type: none"> ■ Make determination of pandemic disease in the U.S. ■ Assess need for funding for costs associated with pandemic response. ■ Coordinate with international organizations and foreign governments as well as state and local governments.
Surveillance, Investigation, and Protective Public Health Measures	<ul style="list-style-type: none"> ■ Investigate initial cases and outbreaks; consider/implement interventions to decrease disease spread. ■ Implement studies of spread in communities and families; identify risk factors for infection and adverse health outcomes. ■ Reassess containment strategies such as travel advisories and restrictions. ■ Provide laboratory support to health departments in affected areas. ■ Initiate active reporting of enhanced surveillance for mortality and severe morbidity in affected areas. ■ Assist state and local health agencies in responding to outbreaks.

Table 8. (Continued)

WHO Phase 6: Pandemic Period Actions (cases in the U.S.)	
	<ul style="list-style-type: none"> ■ Consult with state and local public health agencies on implementation of strategies to control disease spread and decrease infection rates in communities, as needed. ■ Assess impacts of community control strategies. ■ Assess the effectiveness of public health measures and outbreak control.
Vaccines and Antiviral drugs	<ul style="list-style-type: none"> ■ Review/revise priority populations for vaccination and antiviral drug use. ■ Negotiate production and purchase of pandemic vaccine from manufacturers. ■ Begin distribution of pandemic vaccine, if available, and immunization of target groups. ■ Assist in providing resources and personnel for vaccine administration. ■ Monitor vaccine coverage and vaccine adverse events. ■ Conduct studies of vaccine effectiveness; re-evaluate vaccine dose and schedule. ■ Implement distribution of the antiviral stockpile. ■ Monitor antiviral drug distribution and adverse events. ■ Conduct studies of antiviral drug impacts. ■ Review and approve, as appropriate, IND or EUA applications.
Healthcare and Emergency Response	<ul style="list-style-type: none"> ■ Advise states and localities to activate plans to coordinate healthcare delivery and community response. ■ Deploy medical personnel, equipment, and supplies to augment local healthcare capacity in affected areas. ■ Evaluate clinical outcomes and define optimal treatment strategies.
Communications and Outreach	<ul style="list-style-type: none"> ■ Activate pandemic communications plan. ■ Reinforce education on care seeking and home care. ■ Communicate lessons learned to healthcare providers and public health agencies on effectiveness of clinical and public health responses.
Research	<ul style="list-style-type: none"> ■ Evaluate effectiveness of vaccine, antiviral drugs, and other interventions.

Table 9: WHO Pandemic Phase 6, Between Pandemic Waves or Pandemic Subsided in the U.S: HHS Actions

WHO Phase 6: Pandemic Period Actions (between pandemic waves or pandemic subsided in the U.S.)	
Planning and Coordination	<ul style="list-style-type: none"> ■ Assess coordination during period of pandemic disease and revise response plans, as needed. ■ Implement after-action review of pandemic response activities. ■ Assess resources and authorities that may be needed for subsequent pandemic waves.
Surveillance, Investigation, and Protective Public Health Measures	<ul style="list-style-type: none"> ■ Estimate overall pandemic health impacts including mortality and severe morbidity. ■ Continue enhanced domestic and international surveillance to detect further pandemic waves.
Vaccines and Antiviral drugs	<ul style="list-style-type: none"> ■ Assess vaccine coverage, effectiveness of targeting to priority groups, and efficiency of distribution and administration; determine number of persons who remain unprotected. ■ Assess vaccine efficacy, safety, and impact during the pandemic. ■ Determine potential vaccine formulation changes to improve efficacy or supply. ■ Monitor continued administration of vaccine to persons not previously protected. ■ Assess antiviral effectiveness and safety. ■ Evaluate need to expand vaccine and antiviral production capacity.
Healthcare and Emergency Response	<ul style="list-style-type: none"> ■ Assess effectiveness of federal healthcare and service delivery during prior pandemic phases and revise plans, as needed.
Communications and Outreach	<ul style="list-style-type: none"> ■ Assess effectiveness of communications during prior pandemic phases and revise plans, as needed. ■ Communicate with healthcare providers, the media, and the public about the likely next pandemic wave.
Research	<ul style="list-style-type: none"> ■ Evaluate effectiveness of vaccine, antiviral drugs, and other interventions.



appendices



appendices

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appendix A: national response plan

An influenza pandemic may require activation of the National Response Plan (NRP), especially if the first appearance of the disease in the United States occurs in one or a few isolated communities and an intense multi-party containment effort led by the federal government seems feasible. The Department of Homeland Security (DHS), in collaboration with HHS and other response partners, developed the NRP and the associated National Incident Management System (NIMS) pursuant to the requirements of Homeland Security Presidential Directive (HSPD) #5 – Management of Domestic Incidents. Full descriptions of the NRP and the NIMS, respectively, are available at www.dhs.gov/interweb/assetlibrary/NRP_FullText.pdf and www.fema.gov/nims/nims_compliance.shtm#nimsdocument.

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. The NIMS aligns the special-purpose incident management and emergency response plans of federal government agencies into a unitary structure. Together, the NRP and the NIMS provide a conceptual and operational framework to integrate the capabilities and resources of various governmental jurisdictions, incident management and emergency response disciplines, nongovernmental organizations (NGOs), and the private sector into a cohesive, coordinated, and seamless national framework for domestic incident management. The federal government can invoke the NRP partially or fully in the context of a threat, anticipation of a significant event, or the response to a significant event.

Emergency support functions

The NRP applies a functional approach that groups the capabilities of federal government departments and agencies and the American Red Cross into Emergency Support Functions (ESFs) to provide the planning, support, resources, program implementation, and emergency services that are most likely to be needed. The HHS has primary responsibility for implementing ESF #8 – Public Health and Medical Services, which provides the mechanism for coordinated federal government assistance to supplement state, local, and tribal resources in response to public health and medical care needs (to include veterinary and/or animal issues when appropriate) in the face of a potential or actual large-scale public health and medical emergency.



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.

The full set of Emergency Support Functions is as follows:

ESF1	Transportation
ESF2	Communications
ESF3	Public Works and Engineering
ESF4	Firefighting
ESF5	Emergency Management
ESF6	Mass Care, Housing, Human Services
ESF7	Resource Support
ESF8	Public Health and Medical Services
ESF9	Urban Search and Rescue
ESF10	Oil and Hazardous Materials Response
ESF11	Agriculture and Natural Resources
ESF12	Energy
ESF13	Public Safety and Security
ESF14	Long-Term Community Recovery and Mitigation
ESF15	External Affairs

ESF #8 provides for supplemental assistance to state, local, and tribal governments in identifying and meeting the public health and medical needs in core functional areas that include assessment of public health and medical needs (including behavioral health); public health surveillance; medical care personnel; fatality management; and medical equipment and supplies. Management of response activities under ESF #8 occurs through the National Response Coordination Center (NRCC), the Interagency Incident Management Group (IIMG), and the Joint Information Center (JIC). Medical response assets internal to HHS (e.g., the U.S. Public Health Service Commissioned Corps) and through ESF #8 supporting organizations (e.g., the Department of Homeland Security's National Disaster Medical System [NDMS]) may be deployed along with assets from the Strategic National Stockpile (SNS). A complete description of ESF #8 actions and authorities is included in the Public Health and Medical Services annex of the NRP.

The Secretary of HHS directs and oversees HHS activities under ESF-8 through the Assistant Secretary for Public Health Emergency Preparedness (ASPHEP). These activities generally include activation of the Incident Management Team (IMT) within the Secretary's Operation Center (SOC), which serves as the focal point for coordination and communication within HHS and with the DHS and other departments and independent agencies. The ASPHEP serves as the Incident Manager. If warranted, the ASPHEP requests HHS Operating Divisions (OPDIVs) to provide individuals to serve on the IMT. OPDIV Emergency Operations Centers (EOCs) are activated in accordance with the magnitude of the response.

The scope and pace of an influenza pandemic may defy accurate prediction. **The disease may appear in many different parts of the Nation almost simultaneously, or disease may occur in only one or a few communities, and if not contained there, proceed to affect other communities.** In either case, the Secretary of HHS may have reason to exercise his authority under the Public Health Service Act to declare a Public Health Emergency prior to or essentially coincident with activation of the NRP.



appendix B: pandemic influenza background

Pandemics of influenza are extreme infectious disease outbreaks. Although many infectious disease outbreaks (e.g. Severe Acute Respiratory Syndrome [SARS], Ebola, HIV, or West Nile Virus) can cause devastation, these infections are typically limited in their spread to either localized areas or regions, or to at-risk populations. Pandemic influenza, by contrast, is an explosive global event in which most, if not all, populations worldwide are at risk for infection and illness. In past pandemics, influenza viruses have spread worldwide within months and are expected to spread even more quickly today given modern travel patterns.

It is the sheer scope of influenza pandemics, with their potential to rapidly spread and overwhelm societies and cause illnesses and deaths among all age groups, which distinguishes pandemic influenza from other emerging infectious disease threats and makes pandemic influenza one of the most feared emerging infectious disease threats.

A. Influenza viruses

The agent of pandemic influenza is the influenza virus, which is also responsible for causing seasonal influenza, known by most persons as the flu. Seasonal influenza, a common disease characterized by symptoms such as fever, fatigue, body pain, headache, dry cough, and sore throat, affects large numbers of people each year. Although most people infected with flu recover, it is still responsible for approximately 36,000 deaths and 226,000 hospitalizations each year in the U.S.

Influenza viruses are negative-stranded RNA viruses that have been classified taxonomically as orthomyxoviruses; they are divided into two types: "A" and "B" viruses. Influenza type C is not known to cause disease in humans and so is not applicable to this discussion. The remarkable variation of influenza strains—particularly type A—and their ability to cause annual epidemics of respiratory illness of varying intensity and severity, continue to be the focus of intense investigation. Only type A viruses are known to cause pandemics. Type A viruses are further divided into subtypes based on the specific hemagglutinin (H) and neuraminidase (N) proteins on the virus surface. Currently, two subtypes of A viruses are in worldwide circulation in humans: H3N2 and H1N1. The emergence of both of these subtypes in the 20th century led to separate pandemics. For example, the 1918 pandemic resulted from the emergence and spread of the H1N1 virus while the 1968 pandemic was associated with the H3N2 virus. The 1957 pandemic was associated with the emergence and spread of the H2N2 virus; however, this virus subtype stopped circulating in 1968. **Influenza pandemics are believed to have occurred for at least 300 years at unpredictable intervals.**

Pandemic influenza ... is an explosive global event in which most, if not all, populations worldwide are at risk for infection and illness.

B. Why influenza pandemics occur

1. Drift and shift

An important feature of influenza viruses that helps to explain much of their epidemiological patterns is the ability and propensity of these viruses to modify (drift) or replace (shift) two key viral proteins, hemagglutinin and neuraminidase, on the viral surface. Because these proteins are the main targets for the immune system, changes in these proteins can have minor to profound effects on the antigenicity of influenza viruses.

a) Drift

Influenza viruses can change through antigenic drift, which is a process in which mutations to the virus genome produce changes in the viral H or N. Drift is a continuous ongoing process that results in the emergence of new strain variants. The amount of change can be subtle or dramatic, but eventually one of the new variant strains becomes dominant, usually for a few years, until a new variant emerges and replaces it. In essence, drift affects the influenza viruses that are already in worldwide circulation. This process allows influenza viruses to change and re-infect people repeatedly through their lifetime and is the reason the influenza virus strains in vaccine must be updated each year.

b) Shift

In contrast to drift, pandemic viruses arise through a process known as antigenic shift. In this process, the surface existing viral H and N proteins are not modified, but are replaced by significantly different H and Ns. Since influenza A viruses that bear new (or novel) H or H/N combinations are perceived by immune systems as new, most people do not have pre-existing antibody protection to these novel viruses. This is one of the reasons that pandemic viruses can have such severe impact on the health of populations.

C. Animal reservoirs

Novel influenza viruses occasionally emerge among humans as part of the natural ecology and biology of influenza viruses. Wild birds are considered the reservoir for influenza viruses because more influenza A subtypes (15) circulate among wild birds than humans or other animal species. Normally, animal influenza viruses do not infect humans. However, avian influenza viruses can sometimes cross this barrier and directly infect humans. This was demonstrated in 1997, when an outbreak of avian influenza A (H5N1) viruses infected both domestic poultry and humans in Hong Kong, leading to 18 hospitalizations and 6 deaths. Since then, other outbreaks of avian viruses (such as H9N2 in 1999, H7N2 in 2002, H7N7 in 2003, and H5N1 again in 2004) have occurred and been found to directly infect people. Fortunately, these avian viruses lacked the ability to spread easily from person-to-person and therefore did not precipitate larger outbreaks or a pandemic.

Pandemic viruses can also arise when some of the genes from animal influenza viruses mix or reassort with some of the genes from human influenza viruses to create a new hybrid influenza virus. This can occur when a single animal (for example, a pig or possibly a person) is simultaneously co-infected by both a human influenza virus and an avian influenza virus. In this situation, genes from the human and avian viruses can reassort and create a virus with the surface proteins derived from the avian virus (hence, creating a new subtype) and the internal proteins derived from the human virus, enhancing the transmissibility of the hybrid virus. The process of reassortment is not theoretical. Reassorted viruses have been frequently identified and are thought to have been responsible for the 1957 and 1968 pandemic viruses.

D. Distinguishing pandemic from seasonal influenza

Several epidemiological features distinguish pandemic influenza from seasonal influenza. Pandemics of influenza are unusual events and their timing cannot be predicted. For example, only three pandemics occurred in the 20th century (1918, 1957, and 1968). The infrequency and unpredictable timing of these events is explained by the fact that influenza pandemics occur only when a new (or novel) influenza A virus emerges and spreads globally. By definition, most people have never been exposed to these viruses and therefore are susceptible to infection by them. In contrast, seasonal influenza virus strain variants are modified versions of influenza A viruses that are already in widespread circulation. Therefore, there is usually some level of pre-existing immunity to strain variants. Because of the frequent appearance of new variants, virus strains contained in seasonal interpandemic trivalent influenza vaccines must be updated annually.



Influenza pandemics occur only when a new (or novel) influenza A virus emerges and spreads globally.

It is clear that pandemic influenza has the potential to pose disease control challenges unmatched by any other natural or intentional infectious disease event.

E. Impact of influenza and influenza pandemics

An annual influenza season in the U.S., on average, results in approximately 36,000 deaths, 226,000 hospitalizations, and between \$1 billion and \$3 billion in direct costs for medical care. This impact occurs because influenza infections result in secondary complications such as pneumonia, dehydration, and worsening of chronic lung and heart problems. Despite the severity of influenza epidemics, it is sobering to understand that the effects of seasonal influenza are moderated because most individuals have some underlying degree of immunity to recently circulating influenza viruses either from previous infections or from vaccination.

It is clear that pandemic influenza has the potential to pose disease control challenges unmatched by any other natural or intentional infectious disease event. Pandemic influenza viruses have demonstrated their ability to spread worldwide within months, or weeks, and to cause infections in all age groups. While the ultimate number of infections, illnesses, and deaths is unpredictable, and could vary tremendously depending on multiple factors, it is nonetheless certain that without adequate planning and preparations, an influenza pandemic in the 21st century has the potential to cause enough illnesses to overwhelm current public health and medical care capacities at all levels, despite the vast improvements made in medical technology during the 20th century.

Certain modern trends could increase the potential for pandemics to cause more illnesses and deaths than occurred in earlier pandemics:

- First, the global population is larger and increasingly urbanized, allowing viruses to be transmitted within populations more easily.
- Second, levels of international travel are much greater than in the past, allowing viruses to spread globally more quickly than in the past.
- Third, populations in many countries consist of increasing numbers of elderly persons and those with chronic medical conditions, thus increasing the potential for more complicated illnesses and deaths to occur.

This combination of factors suggests that the next pandemic may lead to more illnesses occurring more quickly than in the past, overwhelming countries and health systems that are not adequately prepared.

The 1957 pandemic, during an era with much less globalization, spread to the U.S. within 4–5 months of its detection in China, and the 1968 pandemic spread to the U.S. from Hong Kong within 2–3 months. As was amply demonstrated by the SARS outbreak, modern travel patterns may significantly reduce the time needed for pandemic influenza viruses to spread globally to a few months or even weeks. The major implication of such rapid spread of an infectious disease is that many, if not most, countries will have minimal time to implement preparations and responses once pandemic viruses have begun to spread. While SARS infections spread quickly to multiple countries, the epidemiology and transmission modes of the SARS virus greatly helped to contain the spread of this infection in 2003, along with quarantine, isolation, and other control measures. Fortunately, no widespread community transmission took place. By contrast, because influenza spreads more rapidly between

Table B-1: Effects of Past Pandemics on the U.S.

Pandemic	Estimated U.S. Deaths	Influenza A Strain	Populations at greatest risk
1918-1919	500,000	H1N1	Young, healthy adults
1957-1958	70,000	H2N2	Infants, elderly
1968-1969	34,000	H3N2	Infants, elderly

people and can be transmitted by those who are infected but do not yet have symptoms, the spread of pandemic influenza to multiple countries is expected to lead to the near simultaneous occurrence of multiple community outbreaks in an escalating fashion. No other infectious disease threat, whether natural or engineered, poses the same current threat for causing increases in infections, illnesses, and deaths so quickly in the U.S. and worldwide.

F. H5N1 avian influenza

Although it is unpredictable when the next pandemic will occur and what strain may cause it, the continued and expanded spread of a highly pathogenic—and now endemic—avian H5N1 virus across much of eastern Asia, Russia, and eastern Europe represents a significant pandemic threat. Human avian H5N1 influenza infection was first recognized in 1997 when it infected 18 people in Hong Kong, causing 6 deaths. Concern has increased in recent years as avian H5N1 infections have killed poultry flocks in countries throughout Asia and in parts of Europe. Since 2003, over 100 human H5N1 cases have been diagnosed in Thailand, Vietnam, Cambodia, and Indonesia. The H5N1 virus circulating in Asia has raised concerns about the potential for a pandemic because:

- The avian H5N1 virus is widespread and endemic in much of Asia with spread to Russia and Europe.
- The avian H5N1 virus is becoming more deadly in a growing number of bird species and mammals.
- Wild birds and domestic ducks may be infected asymptotically, providing a reservoir for infection of other domestic poultry species.
- The virus is able to transmit directly from birds to some mammals and in some circumstances to people.
- There is sporadic spread directly from animals to humans with suspected human-to-human transmission in rare instances.
- Genetic studies confirm that H5N1, like other influenza viruses, is continuing to change and evolve.

While H5N1 is the greatest current pandemic threat, other avian influenza subtypes have also infected people in recent years. In 1999, H9N2 infections were identified in Hong Kong; in 2003, H7N7 infections occurred in the Netherlands; and in 2004, H7N3 infections occurred in Canada. Such outbreaks have the potential to give rise to the next pandemic, reinforcing the need for continued surveillance and ongoing vaccine development efforts against these strains.



appendix C: WHO pandemic phases

In 1999, the World Health Organization (WHO) Secretariat published guidance for pandemic influenza and defined the phases of a pandemic. Updated guidance was published in 2005 to redefine these phases. This schema is designed to provide guidance to the international community and to national governments on preparedness and response for pandemic threats and pandemic disease. Compared with the 1999 phases, the new definitions place more emphasis on pre-pandemic phases when pandemic threats may exist in animals or when new influenza virus subtypes infect people but do not spread efficiently. Recognizing that distinctions between the two interpandemic phases and the three pandemic alert phases may be unclear, the WHO Secretariat proposes to base classification on assessment of risk based on a range of scientific and epidemiological data.

Table C-1: Summary of WHO Global Pandemic Phases (WHO Global Influenza Preparedness Plan, 2005)

Interpandemic Period

- Phase 1.** No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered to be low
- Phase 2.** No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease

Pandemic Alert Period

- Phase 3.** Human infection(s) with a new subtype but no human-to-human spread or at most rare instances of spread to a close contact
- Phase 4.** Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans
- Phase 5.** Larger cluster(s) but human-to-human spread is still localized, suggesting that the virus is becoming increasingly better adapted to humans but may not yet be fully transmissible (substantial pandemic risk)

Pandemic Period

- Phase 6.** Pandemic phase: increased and sustained transmission in the general population

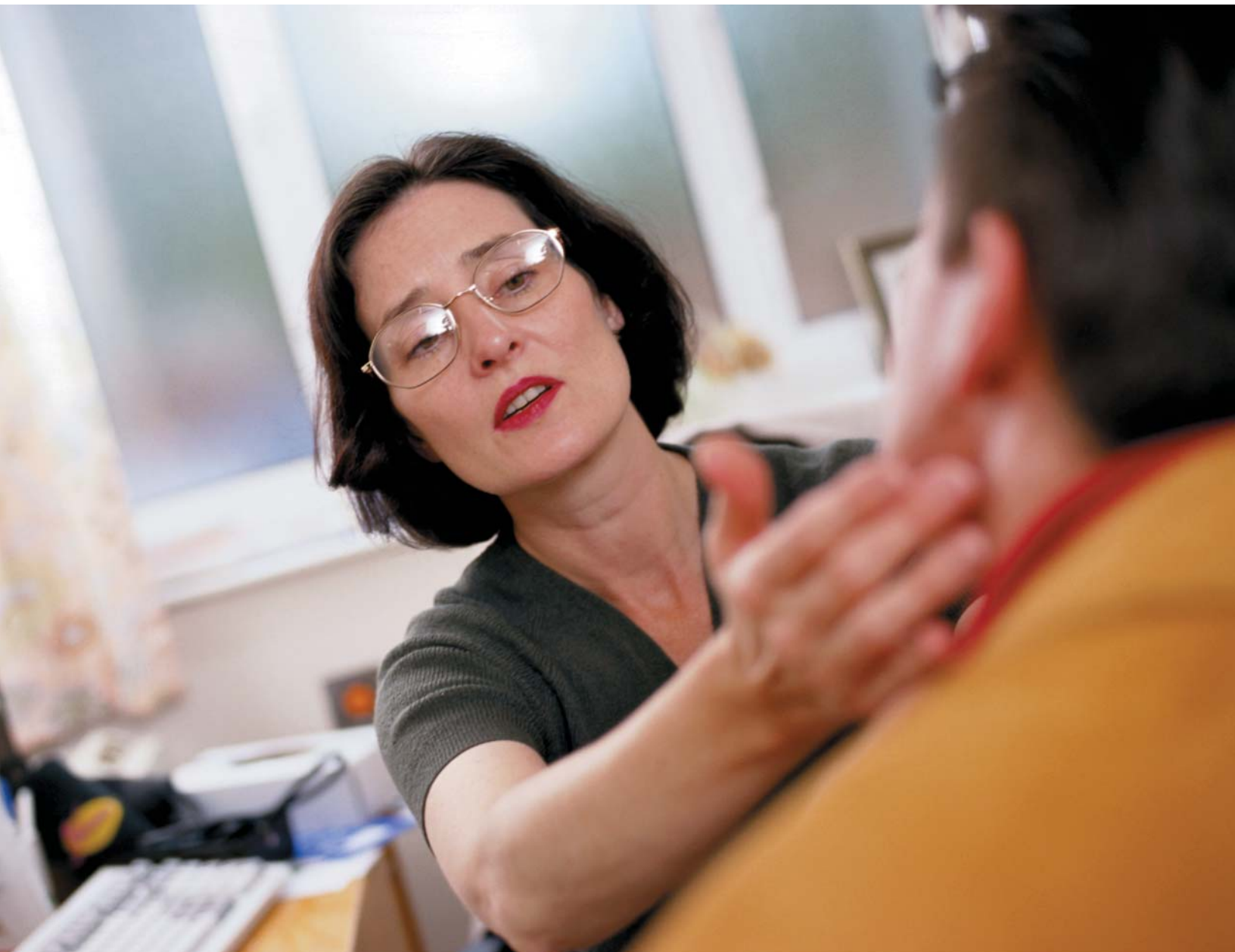
Postpandemic Period

Return to the Interpandemic Period (Phase 1)

¹ <http://www.who.int/csr/resources/publications/influenza/whocdscsredc991.pdf>

² http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf

Recognizing that at any pandemic phase, national situations will differ based on whether a country is affected or not affected by the novel influenza subtype, the WHO Secretariat recommends "national subdivisions" of phases based on whether a country is experiencing disease or has extensive trade and travel links with an affected country. National subdivisions of phases will be designated by national authorities. In the United States, pandemic phases will be defined based on the global phase and determined by the Secretary of Health and Human Services. During the pandemic phase, additional subdivisions may be defined based on the extent of disease. In actual practice, the distinction between the various phases of pandemic influenza may be blurred or occur in a matter of hours, again underscoring the need for flexibility.





appendix D: NVAC/ACIP recommendations for prioritization of pandemic influenza vaccine and NVAC recommendations on pandemic antiviral drug use

Advisory Committee recommendations ... provide guidance for planning purposes and form the basis for further discussion of how to equitably allocate medical countermeasures that will be in short supply early in an influenza pandemic.

Advisory Committee recommendations are presented in this report to provide guidance for planning purposes and to form the basis for further discussion of how to equitably allocate medical countermeasures that will be in short supply early in an influenza pandemic.

Two federal advisory committees, the Advisory Committee on Immunization Practices (ACIP) and the National Vaccine Advisory Committee (NVAC), provided recommendations to the Department of Health and Human Services on the use of vaccines and antiviral drugs in an influenza pandemic.

Although the advisory committees considered potential priority groups broadly, the main expertise of the members was in health and public health. The primary goal of a pandemic response considered was to decrease health impacts including severe morbidity and death; secondary pandemic response goals included minimizing societal and economic impacts. However, as other sectors are increasingly engaged in pandemic planning, additional considerations may arise. The advisory committee reports explicitly acknowledge the importance of this, for example highlighting the priority for protecting critical components of the military. Finally, HHS has recently initiated outreach to engage the public and obtain a broader perspective into decisions on priority groups for pandemic vaccine and antiviral drugs. Though findings of the outreach are preliminary, a theme that has emerged is the importance of limiting the effects of a pandemic on society by preserving essential societal functions.

Based on this guidance, state, local, and tribal implementation plans should be developed to 1) include more specific definitions of the priority groups (e.g., which functions are indeed critical to maintaining continuity) and their size; 2) define how persons in these groups will be identified; and 3) establish strategies for effectively and equitably delivering vaccines and antiviral drugs to these populations. The committees acknowledged that further work is needed, in particular, to identify the functions that must be preserved to maintain effective services and critical infrastructures and to identify the groups that should be protected to achieve this goal. The committees also acknowledge that the specific composition of some priority groups may differ between states or localities based on their needs and that priority groups should be reconsidered when a pandemic occurs and information is obtained on its epidemiology and impacts.



On July 19, 2005, ACIP and NVAC voted unanimously in favor of the vaccine priority recommendations summarized in Table D-1. These votes followed deliberations of a joint Working Group of the two committees, which included as consultants representatives of public and private sector stakeholder organizations and academic experts. There was limited staff level participation from DoD, DHS, and VA. Several ethicists also served as consultants to the Working Group.

A. Critical assumptions

The recommendations summarized in Table D-1 were based on the following critical assumptions:

- **Morbidity and mortality.** The greatest risk of hospitalization and death—as during the 1957 and 1968 pandemics and annual influenza—will be in infants, the elderly, and those with underlying health conditions. In the 1918 pandemic, most deaths occurred in young adults, highlighting the need to reconsider the recommendations at the time of the pandemic based on the epidemiology of disease.
- **Healthcare system.** The healthcare system will be severely taxed if not overwhelmed due to the large number of illnesses and complications from influenza requiring hospitalization and critical care. CDC models estimate increases in hospitalization and intensive care unit demand of more than 25% even in a moderate pandemic.
- **Workforce.** During a pandemic wave in a community, between 25% and 30% of persons will become ill during a 6 to 8 week outbreak. Among working-aged adults, illness attack rates will be lower than in the community as a whole. A CDC model suggests that at the peak of pandemic disease, about 10% of the workforce will be absent due to illness or caring for an ill family member. Impacts will likely vary between communities and work sites and may be greater if significant absenteeism occurs because persons stay home due to fear of becoming infected.
- **Critical infrastructure.** Only limited information was available from which to assess potential impacts on critical infrastructure sectors such as transportation and utility services. Because of changes in business practices and the complexity of networks, information from prior pandemics was not considered applicable.
- **Vaccine production capacity.** The U.S.-based vaccine production capacity was assumed at 3 to 5 million 15µg doses per week with 3 to 6 months needed before the first doses are produced. Two doses per person were assumed to be required for protection. Subsequent results of an NIH clinical trial of influenza A (H5N1) vaccine suggest that higher doses of antigen will be needed to elicit a good immune response; thus, the assumptions made by the committee could potentially substantially exceed the amount of vaccine that would be produced.

Table D-1: Vaccine Priority Group Recommendations*

Tier	Subtier	Population	Rationale
1	A	<ul style="list-style-type: none"> ■ Vaccine and antiviral manufacturers and others essential to manufacturing and critical support (~40,000) ■ Medical workers and public health workers³ who are involved in direct patient contact, other support services essential for direct patient care, and vaccinators (8-9 million) 	<ul style="list-style-type: none"> ■ Need to assure maximum production of vaccine and antiviral drugs ■ Healthcare workers are required for quality medical care (studies show outcome is associated with staff-to-patient ratios). There is little surge capacity among healthcare sector personnel to meet increased demand.
	B	<ul style="list-style-type: none"> ■ Persons ≥ 65 years with 1 or more influenza high-risk conditions, not including essential hypertension (approximately 18.2 million) ■ Persons 6 months to 64 years with 2 or more influenza high-risk conditions, not including essential hypertension (approximately 6.9 million) ■ Persons 6 months or older with history of hospitalization for pneumonia or influenza or other influenza high-risk condition in the past year (740,000) 	<ul style="list-style-type: none"> ■ These groups are at high risk of hospitalization and death. Excludes elderly in nursing homes and those who are immunocompromised and would not likely be protected by vaccination
	C	<ul style="list-style-type: none"> ■ Pregnant women (approximately 3.0 million) ■ Household contacts of severely immunocompromised persons who would not be vaccinated due to likely poor response to vaccine (1.95 million with transplants, AIDS, and incident cancer x 1.4 household contacts per person = 2.7 million persons) ■ Household contacts of children <6 month olds (5.0 million) 	<ul style="list-style-type: none"> ■ In past pandemics and for annual influenza, pregnant women have been at high risk; vaccination will also protect the infant who cannot receive vaccine. ■ Vaccination of household contacts of immunocompromised and young infants will decrease risk of exposure and infection among those who cannot be directly protected by vaccination.
	D	<ul style="list-style-type: none"> ■ Public health emergency response workers critical to pandemic response (assumed one-third of estimated public health workforce=150,000) ■ Key government leaders 	<ul style="list-style-type: none"> ■ Critical to implement pandemic response such as providing vaccinations and managing/monitoring response activities ■ Preserving decision-making capacity also critical for managing and implementing a response

³ This is inclusive of federal healthcare providers to Indian nations and tribes.

Table D-1. Continued

Tier	Subtier	Population	Rationale
2	A	<ul style="list-style-type: none"> ■ Healthy 65 years and older (17.7 million) ■ 6 months to 64 years with 1 high-risk condition (35.8 million) ■ 6-23 months old, healthy (5.6 million) 	<ul style="list-style-type: none"> ■ Groups that are also at increased risk but not as high risk as population in Tier 1B
	B	<ul style="list-style-type: none"> ■ Other public health emergency responders (300,000 = remaining two-thirds of public health work force) ■ Public safety workers including police, fire, 911 dispatchers, and correctional facility staff (2.99 million) ■ Utility workers essential for maintenance of power, water, and sewage system functioning (364,000) ■ Transportation workers transporting fuel, water, food, and medical supplies as well as public ground public transportation (3.8 million) ■ Telecommunications/IT for essential network operations and maintenance (1.08 million) 	<ul style="list-style-type: none"> ■ Includes critical infrastructure groups that have impact on maintaining health (e.g., public safety or transportation of medical supplies and food); implementing a pandemic response; and on maintaining societal functions
3		<ul style="list-style-type: none"> ■ Other key government health decision-makers (estimated number not yet determined) ■ Funeral directors/embalmers (62,000) 	<ul style="list-style-type: none"> ■ Other important societal groups for a pandemic response but of lower priority
4		<ul style="list-style-type: none"> ■ Healthy persons 2-64 years not included in above categories (179.3 million) 	<ul style="list-style-type: none"> ■ All persons not included in other groups based on objective to vaccinate all those who want protection

*The committee focused its deliberations on the U.S. civilian population. ACIP and NVAC recognize that Department of Defense needs should be highly prioritized. DoD Health Affairs indicates that 1.5 million service members would require immunization to continue current combat operations and preserve critical components of the military medical system. Should the military be called upon to support civil authorities domestically, immunization of a greater proportion of the total force will become necessary. These factors should be considered in the designation of a proportion of the initial vaccine supply for the military.

Other groups also were not explicitly considered in these deliberations on prioritization. These include American citizens living overseas, non-citizens in the U.S., and other groups providing national security services such as the border patrol and customs service.

B. Definitions and rationales for priority groups

1. Healthcare workers and essential healthcare support staff

a) Definition

Healthcare workers (HCW) with direct patient contact (including acute-care hospitals, nursing homes, skilled nursing facilities, urgent care centers, physician's offices, clinics, home care, blood collection centers, and EMS) and a proportion of persons working in essential healthcare support services needed to maintain healthcare services (e.g. dietary, housekeeping, admissions, blood collection center staff, etc.). Also included are healthcare workers in public health with direct patient contact, including those who may administer vaccine or distribute influenza antiviral medications, and essential public health support staff for these workers.

b) Rationale

The pandemic is expected to have substantial impact on the healthcare system with large increases in demand for healthcare services placed on top of existing demand. HCW will be treating influenza-infected patients and will be at risk of repeated exposures. Further, surge capacity in this sector is low. To encourage continued work in a high-exposure setting and to help lessen the risk of healthcare workers transmitting influenza to other patients and HCW family members, this group was highly prioritized. In addition, increases in bed/nurse ratios have been associated with increases in overall patient mortality. Thus, substantial absenteeism may affect overall patient care and outcomes.

2. Groups at high risk of influenza complications

a) Definition

Persons 2–64 years with a medical condition for which influenza vaccine is recommended and all persons 6–23 months and 65 years and older. Excludes nursing home residents and severely immunocompromised persons who would not be expected to respond well to vaccination.

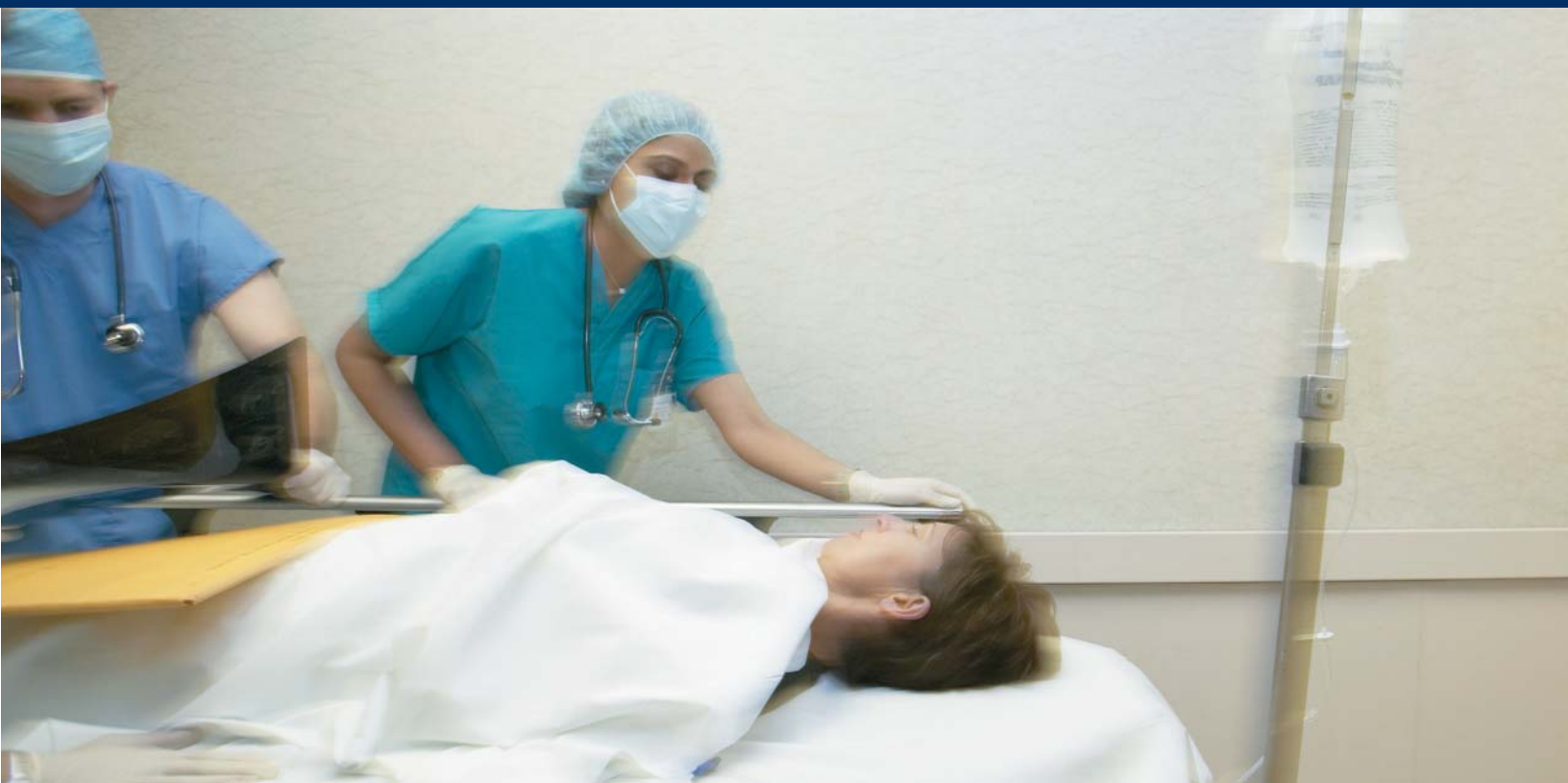
b) Rationale

These groups were prioritized based on their risk of influenza-related hospitalization and death and also their likelihood of vaccine response. Information from prior pandemics was used whenever possible, but information from interpandemic years was also considered. Nursing home residents and severely immunocompromised persons would be prioritized for antiviral treatment and/or prophylaxis and vaccination of healthcare workers and household contacts who are most likely to transmit influenza to these high risk groups.

3. Critical infrastructure

a) Definitions and rationale

Those critical infrastructure sectors that fulfill one or more of the following criteria: have increased demand placed on them during a pandemic, directly support reduction in deaths and hospitalization; function is critical to support the healthcare sector and other emergency services, and/or supply basic



necessities and services critical to support of life and healthcare or emergency services. Groups included in critical infrastructure are needed to respond to a pandemic and to minimize morbidity and mortality, and include the following sectors:

- Persons directly involved with influenza vaccine and antiviral medication manufacturing and distribution and essential support services and suppliers (e.g., growers of pathogen-free eggs for growth of vaccine virus) production activities
- Key government leaders and health decision-makers who will be needed to quickly move policy forward on pandemic prevention and control efforts
- Public safety workers (firefighters, police, and correctional facility staff, including dispatchers) are critical to maintaining social functioning and order and will contribute to a pandemic response, for example by ensuring order at vaccination clinics and responding to medical emergencies
- Utility service workers (water, power, and sewage management) are prioritized as the services they provide are also essential to the healthcare system as well as to preventing additional illnesses from lack of these services unrelated to a pandemic.
- Transportation workers who maintain critical supplies of food, water, fuel, and medical equipment and who provide public transportation, which is essential for provision of medical care and transportation of healthcare workers to work and transportation of ill persons for care
- Telecommunication and information technology services critical for maintenance and repairs of these systems are also essential as these systems are now critical for accessing and delivering medical care and in support of all other critical infrastructure.
- Mortuary services will be substantially impacted due to the increased numbers of deaths from a pandemic and the fact that impact will be high in the elderly, a growing segment of the population

4. Public health emergency response workers

a) Definition

This group includes persons who do not have direct patient care duties, but who are essential for surveillance for influenza, assessment of the pandemic impact, allocation of public health resources for the pandemic response, development and implementation of public health policy as part of the response, and development of guidance as the pandemic progresses.

b) Rationale

Persons in this sector have been critical for past influenza vaccine pandemics and influenza vaccine shortages and little surge capacity may be available during a public health emergency such as a pandemic.

5. Persons in skilled nursing facilities

a) Definition

Patients residing in skilled nursing facilities. Not included in this group are persons in other residential settings (e.g., assisted living) who are more likely to be mobile, in a setting that is less closed, and have decentralized healthcare.

b) Rationale

This group was not prioritized for vaccine because of the medical literature finding poor response to vaccination and occurrence of outbreaks even in the setting of high vaccination rates. Other studies have suggested that vaccination of healthcare workers may be a more effective strategy to prevent influenza in this group. Further, surveillance for influenza can be conducted in this group and antiviral medications used widely for prophylaxis and treatment. Ill visitors and staff should also be restricted from visiting nursing home facilities during outbreaks of pandemic influenza.

This strategy for pandemic influenza vaccine differs from the interpandemic vaccination strategy of aggressively vaccinating nursing home residents. The rationale considers several factors: 1) these populations are less likely to benefit from vaccine than other groups who are also at high risk; 2) other prevention strategies feasible for this group are not possible among other high-risk groups; 3) the overall morbidity and mortality from pandemic is likely to severely impact other groups of persons who would be expected to have a better response to the vaccine; and 4) a more severe shortage of vaccine is anticipated.

6. Severely immunocompromised persons

a) Definition

Persons who are undergoing or who have recently undergone bone marrow transplantation and others with severe immunodeficiency (e.g., AIDS patients with CD4 counts <50, children with SCID syndrome, recent bone marrow transplant patients). The numbers of persons in these categories is likely much smaller than the anticipated number assumed in tiering above, but sources for more specific estimates have not been identified.

b) Rationale

These groups have a lower likelihood of responding to influenza vaccination. Thus, strategies to prevent severe influenza illness in this group should include vaccination of healthcare workers and household contacts of severely immunocompromised persons and use of antiviral medications. Consideration should be given to prophylaxis of severely immunocompromised persons with influenza antivirals and early antiviral treatment should they become infected.

7. Children <6 months of age

a) Rationale

Influenza vaccine is poorly immunogenic in children <6 months and the vaccine is currently not recommended for this group. In addition, influenza antiviral medications are not FDA-approved for use in children <1 year old. Thus, vaccination of household contacts and out-of-home caregivers of children <6 months is recommended to protect this high-risk group.

C. Other discussion

There was substantial discussion on priority for children. Four potential reasons were raised for making vaccination of children a priority:

- At the public engagement session, many participants felt that children should have high priority for vaccination.
- Children play a major role in transmitting infection, and vaccinating this group could slow the spread of disease and indirectly protect others.
- Children have strong immune systems and will respond well to vaccine whereas vaccination of the elderly and those with illnesses may be less effective.
- Some ethical frameworks would support a pediatric priority.

ACIP and NVAC did not make children a priority (other than those included in tiers, because of their underlying diseases [Tiers 1B and 2A] or as contacts of high-risk persons [Tier 1C]) for several reasons:

- Healthy children have been at low risk for hospitalization and death in prior pandemics and during annual influenza seasons.
- It is uncertain whether vaccination of children will decrease transmission and indirectly protect others. Studies that show this impact or mathematical models that predict it rely on high vaccination coverage that may not be possible to achieve given limited supplies in a pandemic.
- The committees recognize that this is an area for further scientific work; that children may be a good target population for live-attenuated influenza vaccine (FluMist®) if it is available; and that education of the public will be needed to provide the rationale for the recommendations.



NVAC recognizes that recommendations [for antiviral drug use] will need to be reconsidered at the time of a pandemic when information on the available drug supply, epidemiology of disease, and impacts on society are known.

The committee considered the primary goal of a pandemic response to decrease health impacts including severe morbidity and death. Minimizing societal and economic impacts were considered secondary and tertiary goals.

NVAC RECOMMENDATIONS ON PANDEMIC ANTIVIRAL DRUG USE

On July 19, 2005, NVAC voted unanimously in favor of the antiviral drug use priority recommendations described here and summarized in Table D-2. These votes followed deliberations of a Working Group, which included as consultants representatives of public and private sector stakeholder organizations and academic experts. There was limited staff level participation from DoD, DHS, and VA. Several ethicists also served as consultants to the Working Group.

The recommendations were made considering pandemic response goals, assumptions on the impacts of a pandemic, and after thorough review of past pandemics, annual influenza disease, data on antiviral drug impacts, and recommendations for pandemic vaccine use.

Recommendations were made to guide planning needed for effective implementation at state and local levels. The committee recognizes that recommendations will need to be reconsidered at the time of a pandemic when information on the available drug supply, epidemiology of disease, and impacts on society are known.

The committee considered the primary goal of a pandemic response to decrease health impacts including severe morbidity and death. Minimizing societal and economic impacts were considered secondary and tertiary goals.

A. Critical assumptions

Assumptions regarding groups at highest risk during a pandemic and impacts on the healthcare system and other critical infrastructures are the same as those underlying the vaccine priority recommendations. Additional assumptions specific for antiviral drugs included:

- Treatment with a neuraminidase inhibitor (oseltamivir [Tamiflu®] or zanamivir [Relenza®]) will be effective in decreasing risk of pneumonia, will decrease hospitalization by about half (as shown for inter-pandemic influenza), and will also decrease mortality.
- Antiviral resistance to the adamantanes (amantadine and rimantadine) may limit their use during a pandemic.
- The primary source of antiviral drugs for a pandemic response will be the supply of antiviral drugs that have been stockpiled. Before annual influenza seasons about 2 million treatment courses of oseltamivir are available in the U.S. U.S.-based production of oseltamivir is being established; expected capacity is projected at about 1.25 million courses per month.
- Treating earlier after the onset of disease is most effective in decreasing the risk of complications and shortening illness duration. Generally, treatment should be given within the first 48 hours.
- Assumptions for the amount of antiviral drug needed for defined priority groups is based on the population in those groups and assumptions that 35% of persons in the priority groups will have influenza-like illness and 75% will present within the first 48 hours and be eligible for treatment. For persons admitted to the hospital, the committee assumed that 80% would be treated, as the 48-hour limit may sometimes be relaxed in more ill patients.
- Unlike vaccines, where each tier would be protected in turn as more vaccine is produced, for antiviral drugs, the number of priority groups that can be covered would be known at the start of the pandemic based on the amount of drug that is stockpiled. Additional supply that would become available during the pandemic could provide some flexibility.

Table D-2: Antiviral Drug Priority Group Recommendations*

	Group	Estimated population (millions)	Strategy**	# Courses (millions)		Rationale
				For target group	Cumulative	
1	Patients admitted to hospital***	10.0	T	7.5	7.5	Consistent with medical practice and ethics to treat those with serious illness and who are most likely to die
2	Health care workers (HCW) with direct patient contact and emergency medical service (EMS) providers ⁴	9.2	T	2.4	9.9	Healthcare workers are required for quality medical care. There is little surge capacity among healthcare sector personnel to meet increased demand.
3	Highest risk outpatients—immunocompromised persons and pregnant women	2.5	T	0.7	10.6	Groups at greatest risk of hospitalization and death; immunocompromised cannot be protected by vaccination.
4	Pandemic health responders (public health, vaccinators, vaccine and antiviral manufacturers), public safety (police, fire, corrections), and government decision-makers	3.3	T	0.9	11.5	Groups are critical for an effective public health response to a pandemic.
5	Increased risk outpatients—young children 12-23 months old, persons ≥ 65 yrs old, and persons with underlying medical conditions	85.5	T	22.4	33.9	Groups are at high risk for hospitalization and death.
6	Outbreak response in nursing homes and other residential settings	NA	PEP	2.0	35.9	Treatment of patients and prophylaxis of contacts is effective in stopping outbreaks; vaccination priorities do not include nursing home residents
7	HCWs in emergency departments, intensive care units, dialysis centers, and EMS providers	1.2	P	4.8	40.7	These groups are most critical to an effective healthcare response and have limited surge capacity. Prophylaxis will best prevent absenteeism.
8	Pandemic societal responders (e.g., critical infrastructure groups as defined in the vaccine priorities) and HCW without direct patient contact	10.2	T	2.7	43.4	Infrastructure groups that have impact on maintaining health, implementing a pandemic response, and maintaining societal functions
9	Other outpatients	180	T	47.3	90.7	Includes others who develop influenza and do not fall within the above groups
10	Highest risk outpatients	2.5	P	10.0	100.7	Prevents illness in the highest risk groups for hospitalization and death.
11	Other HCWs with direct patient contact	8.0	P	32.0	132.7	Prevention would best reduce absenteeism and preserve optimal function.

* This is inclusive of Federal healthcare providers to Indian Nations and Tribes.

B. Definitions and rationale for draft priority groups

1. Persons admitted to hospital with influenza infection

a) Definition

Persons admitted to acute care facilities (traditional or non-traditional with a clinical diagnosis of influenza; laboratory confirmation not required). Excludes persons admitted for a condition consistent with a bacterial superinfection (e.g., lobar pneumonia developing late after illness onset) or after viral replication and shedding has ceased (e.g., as documented by a negative sensitive antigen detection test)

b) Strategy

Treatment within 48 hours of system onset.

c) Rationale

This group is at greatest risk for severe morbidity and mortality. Although there are no data to document the impacts of antiviral drug treatment among persons who already suffer more severe influenza illness, benefit is biologically plausible in persons with evidence of ongoing virally-mediated pathology (e.g., diffuse pneumonia, ARDS). Providing treatment to those who are most ill is also consistent with standard medical practices, would be feasible to implement, and would be acceptable to the public.

d) Population size

The number of persons admitted to hospital in an influenza pandemic would vary substantially depending on the severity of the pandemic and on the ability to expand inpatient capacity, if needed.

e) Unresolved issues

More specific guidance should be provided to healthcare workers on implementing antiviral treatment, including when and when not to treat. In some persons with severe illness, the ability to take oral medication or its absorption may be important issues. For infants <1 year old admitted to hospital,

*The committee focused its deliberations on the domestic U.S. civilian population. NVAC recognizes that Department of Defense (DoD) needs should be highly prioritized. A separate DoD antiviral stockpile has been established to meet those needs. Other groups also were not explicitly considered in deliberations on prioritization. These include American citizens living overseas, non-citizens in the U.S., and other groups providing national security services such as the border patrol and customs service.

**Strategy: Treatment (T) requires a total of 10 capsules and is defined as 1 course. Post-exposure prophylaxis (PEP) also requires a single course. Prophylaxis (P) is assumed to require 40 capsules (4 courses) though more may be needed if community outbreaks last for a longer period.

***There are no data on the effectiveness of treatment at hospitalization. If stockpiled antiviral drug supplies are very limited, the priority of this group could be reconsidered based on the epidemiology of the pandemic and any additional data on effectiveness in this population.



decisions about whether to treat with antiviral drugs may depend on the child's age and potential risk versus benefit as the neuraminidase inhibitors are not licensed for use in infants. If possible, data on time from symptom onset to hospital admission, current use of antiviral drug treatment among inpatients, and its impacts should be collected during interpandemic influenza seasons.

2. Healthcare workers and emergency medical service providers who have direct patient contact

a) Definition

Persons providing direct medical services in inpatient and outpatient care settings. Includes doctors, nurses, technicians, therapists, EMS providers, laboratory workers, other care providers who come within 3 feet of patients with influenza, and persons performing technical support functions essential to quality medical care.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Maintaining high quality patient care is critical to reduce health impacts of pandemic disease and to prevent adverse outcomes from other health conditions that will present for care during the pandemic period. Treatment of healthcare providers will decrease absenteeism due to influenza illness and may decrease absenteeism from fear of becoming ill, given the knowledge that treatment can prevent serious complications of influenza. Good data exist documenting the impacts of early treatment on duration of illness and time off work, and on the occurrence of complications such as lower respiratory infections. Treating healthcare providers is feasible to implement, especially for inpatient care providers who can be provided drugs through the occupational health clinic. It also would be acceptable to the public, who would recognize the importance of maintaining quality healthcare and would understand that persons with direct patient contact are putting themselves at increased risk.

d) Population size

There are about 12.6 million persons designated as healthcare workers by the Bureau of Labor Statistics and about 820,000 EMS providers. Among HCWs, two-thirds are estimated to provide direct patient care services.

e) Unresolved issues

Further work is needed to hone definitions and estimate population sizes. Implementation issues include the approach to identifying healthcare providers who would be eligible for treatment and where the treatment would be provided, particularly for outpatient care providers.

3. Outpatients at highest risk for severe morbidity or mortality from influenza infection

a) Definition

The Advisory Committee on Immunization Practices defines groups at high risk (or increased risk) of complications from influenza infection during annual outbreaks based on age (6-23 months and >65 years) and underlying illnesses. Among this population of about 88 million persons, some can be identified who are at highest risk of severe disease and death. These include persons with hematopoietic stem cell transplants (HSCT) and solid organ transplants; those with severe immunosuppression due to cancer therapy or hematological malignancy; persons receiving immunosuppressive therapy for other illnesses (e.g., rheumatoid arthritis); persons with HIV infection and a CD4 count <200; persons on dialysis; and women who are in the second or third trimester of pregnancy.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Of the large group of persons who are at increased risk of severe disease or death from influenza, these groups represent the population at highest risk and who are least likely to be protected by vaccination. Studies show that neuraminidase inhibitor therapy decreases complications and hospitalizations from influenza in high-risk persons and one unpublished study shows a significant decrease in mortality among patients who have undergone a hematopoietic stem cell transplant.

d) Population size

About 150,000 persons have had an HSCT or solid organ transplant. Assuming that the period of severe immunosuppression after a cancer diagnosis lasts for 1 year, the population targeted with non-skin, non-prostate cancers would equal the incidence of about 1.35 million persons. Based on a birth cohort of 4.1 million, a 28-week risk period during the second and third trimesters, and an 8-week pandemic outbreak in a community, there would be about 400,000 pregnant women included in this risk group. Further work is needed to estimate the size of other immunosuppressed groups.

e) Unresolved issues

Specific definition of included groups and population sizes.

4. Pandemic health responders, public safety workers, and key government decision-makers

a) Definition

Public health responders include those who manufacture vaccine and antiviral drugs; persons working at health departments who are not included as healthcare workers; and those who would be involved in implementing pandemic vaccination or other response components. Public safety workers include police, fire, and corrections personnel. Key government decision-makers include chief executives at federal, state, and local levels.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Preventing adverse health outcomes and social and economic impacts in a pandemic depend on the ability to implement an effective pandemic response. Early treatment of pandemic responders will minimize absenteeism and ensure that vaccination and other critical response activities can be maintained. Implementing early treatment for public health workers and vaccine manufacturers is feasible at workplace settings. Public safety workers prevent intentional and unintentional injuries and death, are critical to maintaining social functioning, and will contribute to a pandemic response, for example by ensuring order at vaccination clinics. A small number of decision-makers at federal, state, and local levels are needed to for an effective pandemic response.

d) Population size

An estimated 40,000 workers who produce pandemic vaccine and antiviral drugs in the U.S.; ~300,000 public health workers who would not be included in the HCW category; 3 million public safety workers; and a small number of government decision-makers.

e) Unresolved issues

Need to define the exact composition and size of this group.

5. Outpatients at increased risk of severe morbidity or mortality from influenza

a) Definition

For planning purposes, this group would include those currently designated as high-risk groups, except for those who have been categorized as being at highest-risk and included in a separate category. This increased-risk group includes persons 6–23 months and >65 years old, or who have underlying illnesses defined by the ACIP as associated with increased risk. Definition of this group may change based on the epidemiology of the pandemic.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Early treatment has been shown to significantly decrease lower respiratory infections and to reduce the rate of hospitalization in elderly and high-risk populations. By extrapolation and based on the results of one small uncontrolled study, significant reductions of mortality can be expected as well. As these risk groups are familiar to the public given recommendations for annual vaccination, communication would be easy and acceptability high.

d) Population size

About 85.5 million persons are included in this group. Although all are at increased risk of annual influenza compared with the healthy under-65 year old population, there are different levels of increased risk for severe complications and death within this category. Further stratification may be possible based on several parameters including number of underlying conditions; recent hospitalization for a high-risk condition, pneumonia, or influenza; and age.

e) Unresolved issues

Stratifying this group into those at greater and lesser risk may be important if antiviral supplies are limited. Implementing treatment will be challenging given that it should be provided at the initial point of care to accrue the greatest benefit from early therapy.

6. Outbreak control

a) Definition

Use of antiviral drugs to support public health interventions in closed settings where an outbreak of pandemic influenza is occurring.

b) Strategy

Treatment of cases and post-exposure prophylaxis of contacts (once daily antiviral medication for 10 days).

c) Rationale

Influenza outbreaks in nursing homes are associated with substantial mortality and morbidity. Nursing home residents also are less likely to respond to vaccination. Post-exposure prophylaxis has been shown to be effective in stopping influenza outbreaks in closed settings.

d) Population size

The number of outbreaks that may occur during a pandemic is unclear. Measures should be implemented to prevent outbreaks including limiting visitors, vaccination of staff, furloughing non-critical staff, and screening and exclusion for illnesses consistent with influenza.

e) Unresolved issues

Should this policy also be implemented in prisons or other settings where explosive spread of illness may occur but the risk for severe complications is not high?

7. Healthcare workers in ER, ICU, EMS, and dialysis settings

a) Definition

Includes all staff in these settings who are required for effective functioning of these health care units.

b) Strategy

Prophylaxis

c) Rationale

Optimally effective functioning of these units is particularly critical to reducing the health impacts of a pandemic. Prophylaxis will minimize absenteeism in these critical settings.

d) Population size

Need to obtain population estimates.

e) Unresolved issues

Population sizes

8. Pandemic societal responders and healthcare workers who have no direct patient contact

a) Definition

This group includes persons who provide services that must be sustained at a sufficient level during a pandemic to maintain public well-being, health, and safety. Included are workers at healthcare facilities who have no direct patient contact but are important for the operation of those facilities; utility (electricity, gas, water), waste management, mortuary, and some transport workers.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Maintaining certain key functions is important to preserve life and decrease societal disruption. Heat, clean water, waste disposal, and corpse management all contribute to public health. Ensuring functional transportation systems also protects health by making it possible for people to access medical care and by transporting food and other essential goods to where they are needed.

d) Population size

Within these broad categories, there are about 2 million workers at healthcare facilities who have no direct patient contact; 730,000 utility workers; 320,000 waste management workers; 62,000 in mortuary services; and 2.3 million in transportation. Not all occupations within these categories would be classified as pandemic societal responders. Estimates are that 35% of this population will develop illness and present within 48 hours of onset regardless of pandemic severity.



e) Unresolved issues

Need to stratify within these groups to identify who fills specific pandemic societal response functions and to assess whether those functions could still operate if a substantial proportion of the workforce became ill during a 6-8 week pandemic outbreak within a community. Implementation issues need to be addressed, especially with respect to how persons would be identified as falling within this priority group when presenting for treatment and where that treatment would be provided.

9. Other outpatients

a) Definition

Includes persons not in one of the earlier priority groups.

b) Strategy

Treatment within 48 hours of illness onset.

c) Rationale

Treatment reduces the risk of complications and mortality, reduces duration of illness and shortens time off work, and decreases viral shedding and transmission. If sufficient antiviral supplies are available, providing treatment to all who are ill achieves equity and will be most acceptable to the public.

d) Population size

There are an estimated 180 million persons who are not included in previously targeted groups.

e) Unresolved issues

Consider whether there are any strata that can be defined within this population.

C. Additional NVAC recommendations on antiviral drugs for pandemic influenza

In addition to recommendations for priority groups, NVAC unanimously adopted the following recommendations:

- Sufficient drugs should be stockpiled to address top priorities. NVAC recommends that the minimum stockpile size be about 40 million courses, allowing coverage of the top 7 priority groups.
- Oseltamivir should be the primary drug stockpiled, but some zanamivir also should be obtained as it is effective against some oseltamivir-resistant strains, may be preferred for treatment of pregnant women, and supporting two manufacturers enhances security against supply disruptions. Approximately 10% of the stockpile should be zanamivir if feasible and cost effective. No additional adamantanes should be stockpiled.
- Antiviral drugs can also be used as part of an international effort to contain an initial outbreak and prevent a pandemic. Use to slow disease spread early in a pandemic may be useful but requires large amounts of drug.
- Critical research should be conducted to support development and implementation of recommendations for pandemic influenza antiviral drug use, including:
 - Impact of treatment at hospital admission on outcome
 - Optimal treatment dose for H5N1 and other potential pandemic strains
 - Sensitivity and use of rapid diagnostic tests for H5N1 and other influenza strains with pandemic potential
 - Safety and pharmacokinetics of oseltamivir among infants <1 year old
 - Investigation of the impact of other drugs (new antiviral agents and other classes such as statins) on influenza
- Additional work with public and private sector groups should be done to further hone definitions of target groups and their estimated population sizes, and to provide further guidance on antiviral drug distribution and dispensing.



appendix E: legal authorities

Legal authorities

Numerous Federal and state statutes authorize relevant public health actions to address pandemic influenza. Knowledge of these authorities is essential for planning and implementing an effective response to an influenza pandemic.

Section 319(a) of the Public Health Service (PHS) Act (42 U.S.C. 247d), authorizes the HHS Secretary to declare a public health emergency and "take such action as may be appropriate to respond" to that emergency consistent with existing authorities. Appropriate action may include, as otherwise authorized, making grants, providing awards for expenses, entering into contracts, and conducting and supporting investigation into the cause, treatment, or prevention of the disease or disorder that presents the emergency. The Secretary's declaration also can be the first step in authorizing emergency use of unapproved products or approved products for unapproved uses under section 564 of the Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb-3), or waiving certain regulatory requirements of the Department, such as select agents requirements, or—when the President also declares an emergency—waiving certain Medicare, Medicaid, and State Children's Health Insurance Program (SCHIP) provisions. Under the Robert T. Stafford Disaster Relief and Emergency Assistance Act (42 U.S.C. 5121 et seq.), the Federal Emergency Management Agency (FEMA), Department of Homeland Security, is authorized to coordinate the activities of Federal agencies in response to a Presidential declaration of a major disaster or emergency, with HHS having the lead for health and medical services. The President may also declare an emergency under the National Emergencies Act (50 U.S.C. 1601 et seq.)

The PHS Act provides additional authorities for core activities of HHS that will be needed to plan and implement an emergency response. For example, Sections 301, 319F-1, 402, and 405 of the PHS Act authorize the HHS Secretary to conduct and support research. Section 351 of the PHS Act and provisions of the Federal Food, Drug, and Cosmetics Act authorize the Secretary and the FDA to regulate vaccine development and production. Infrastructure support for preventive health services such as immunization activities, including vaccine purchase assistance, is provided under section 317 of the PHS Act. Section 319F-2 of the PHS Act authorizes the Secretary, in coordination with the Secretary of Homeland Security, to maintain the Strategic National Stockpile.



Section 361 authorizes the Secretary to make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the United States, or from one state or possession into any other State or possession. CDC administers these regulations as they relate to quarantine of humans. Diseases for which individuals may be quarantined are specified by Executive Order; the most recent change to the list of quarantinable diseases was the April 1, 2005 Executive Order 13375, which amended the Executive Order 13295 by adding "influenza caused by novel or reemergent influenza viruses that are causing, or have the potential to cause, a pandemic" to the list. Other provisions in Title III of the PHS Act permit HHS to establish quarantine stations, provide care and treatment for persons under quarantine, and provide for quarantine enforcement. Section 311 of the PHS Act provides for Federal-state cooperative activities to enforce quarantine and plan and carry out public health activities. Section 311 also authorizes the Secretary to make available the resources of the PHS to help control epidemics and deal with other public health emergencies. HHS may also engage in certain international activities under section 307 of the PHS Act. Statute 42 U.S.C. § 97, which provides that the Secretary of Health and Human Services may request that Customs, Coast Guard, and military officers aid in the execution of quarantines imposed by states. The Secretary also has the authority to implement disease control measures in Indian country, if necessary. (25 U.S.C. 198, 231; 42 U.S.C. 2001). Indian Tribes, like states, are sovereign entities with police power authority to enact their own disease control rules and regulations. Tribal law should be consulted as well.

Further, HHS has broad authority to coordinate vaccine development, distribution, and use activities under section 2102 of the PHS Act, describing the functions of the National Vaccine Program. The Secretary has authority for health information and promotion activities under Title XVII and other sections of the PHS Act. HHS can provide support to states and localities for emergency health planning under Title III of the PHS Act.

Both Federal and state statutes may apply to specific interventions that would be implemented to control a pandemic. Key issues and relevant Federal authority are shown in Table E-1. States should review their authorities to respond to a public health emergency and to take necessary actions for its control.

Table E-1. Key Pandemic Response Components and Legal Authorities.

Issue	Authority
<ul style="list-style-type: none"> ■ Public sector vaccine or antiviral drug purchase 	<ul style="list-style-type: none"> ■ Antivirals have been added to the Strategic National Stockpile. ■ At the time of a pandemic, the Federal Government could consider purchasing vaccine or antiviral drugs, if available.
<ul style="list-style-type: none"> ■ Indemnification of manufacturers 	<ul style="list-style-type: none"> ■ Executive Order 10789, as amended by Executive Order 13232, extends authorities under P.L. 85-804 to HHS to use indemnification provisions of the Federal Acquisition Regulations, 48 C.F.R. 50.403, if the contractor performs an activity that involves unusually hazardous risks and insurance is not available or sufficient to cover those risks. A contracting officer must review a request for indemnification, and the Secretary must personally approve the request and in some cases consult with Department of Homeland Security and the Office of Management and Budget. ■ Other relevant, but more limited, indemnification authorities such as section 301(a)(7) of the PHS Act may also be available.

Table E-1. Continued

Issue	Authority
<ul style="list-style-type: none"> ■ Distribution of vaccines or antiviral drugs and liability protections 	<ul style="list-style-type: none"> ■ The Federal Government may mobilize the PHS Commissioned Corps to distribute vaccines or medications to Federal agencies with direct patient care responsibilities, or to states, tribes, and other localities through the National Disaster Medical System and through agreements between the Federal government, states, and localities. Provision of the medication by particular health care providers is a matter of state law. ■ If a Federal employee administers an antiviral medication or vaccine in the course of his/her official duties, the employee is covered under section 224 of the PHS Act, which makes the Federal Tort Claims Act the exclusive remedy. ■ If the provider were a Federal contractor generally, the contractor would be expected to carry malpractice insurance; expenses of purchasing such insurance generally are an allowable cost of the contract. ■ State employees may be covered for malpractice or tort claims coverage under state law. States should consult their laws on this matter. ■ Private sector employees would generally carry private malpractice insurance. They may also be covered by the Volunteer Protection Act, State Good Samaritan Act, or State Emergency compact provisions.
<ul style="list-style-type: none"> ■ Compensation for persons injured by vaccine or antiviral medications 	<ul style="list-style-type: none"> ■ If a person is injured following administration of a vaccine or antiviral medication, in connection with his/her employment, compensation may be available under a state's worker's compensation program. For Federal employees, compensation may be available under the Federal Employees' Compensation Act.
<ul style="list-style-type: none"> ■ Measures to decrease the transmission of infection 	<ul style="list-style-type: none"> ■ Individuals may be denied admission to the U.S. if thought to have a communicable disease of public health significance, as defined in CDC regulations. Individuals also may be isolated or quarantined by the Federal Government, or restricted from moving within or between states, if thought to have been exposed to or to be a source of infections to others of a communicable disease listed in an executive order signed by the President. ■ State governors generally may restrict travel within their states and access to their states. Individual state law should be consulted to determine permissible exercise of this authority. ■ States also may impose quarantine. The Secretary may aid states and localities in enforcement of their quarantine actions and accept state and local assistance in enforcing Federal quarantine. ■ In settings such as long-term care facilities where there are public health risks associated with spread of a pandemic strain, states also may be able to compel an individual to take antiviral prophylaxis or be vaccinated, as circumstances warrant. State law should be consulted.



appendix F: current HHS activities

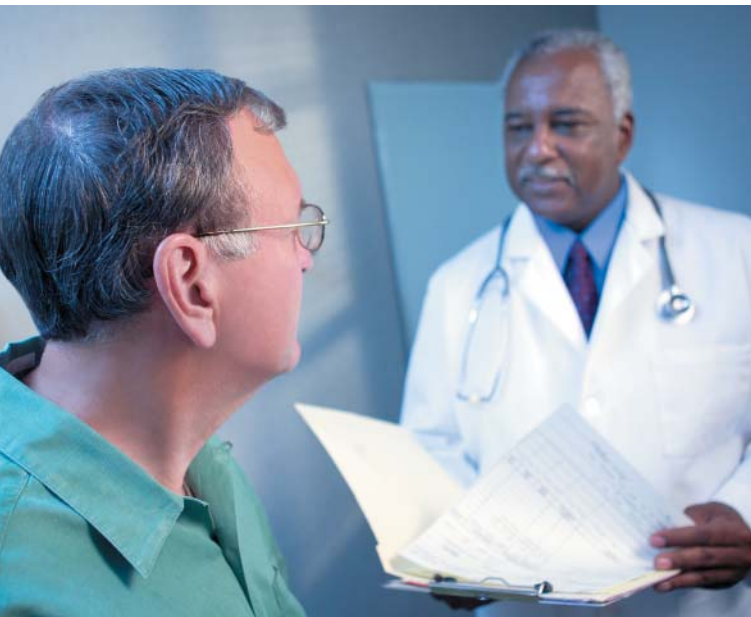
HHS is engaged in a broad array of activities to prepare for an influenza pandemic, although substantial work remains to be done to achieve the capabilities projected in this plan. Ongoing preparedness activities are summarized below.

Planning and Coordination

State and local planning. During the past several years, HHS has provided financial assistance to states to enhance their emergency preparedness activities, including pandemic influenza, through cooperative agreements. CDC provides preparedness funding annually to the public health departments of all the states, certain major metropolitan areas, and other eligible entities through cooperative agreements. HRSA, in conjunction with CDC, awards complementary cooperative agreements to provide preparedness funding annually to the same set of awardees for investment primarily in hospitals and other healthcare entities.

Part 2, Public Health Guidance for State and Local Partners, provides HHS' state partners with guidance, in the form of 11 supplements that provide information they can consider in refining and updating their plans concurrent with the release of the HHS Pandemic Influenza Strategic Plan. A major objective will be to achieve interoperability with the federal government plan and thus compliance with the principles and procedures of the National Response Plan. In particular, HHS will encourage states and municipalities to conduct drills and exercises with which to assess their readiness to respond to an influenza pandemic. HHS will assist federal, state, and local decision-makers in understanding the contents of the Plan. HHS will also work with national associations, such as the Association of State and Territorial Health Officials (ASTHO), to assist in determining their roles and responsibilities.

International collaborations. Sustained human-to-human transmission anywhere in the world will be the triggering event to initiate a pandemic response by the U.S. Because we live in a global community, a human outbreak anywhere means risk everywhere. The U.S. will pursue a containment strategy, where feasible, acting in concert with WHO and other nations as appropriate.



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HHS and the Department of State, Agency for International Development (USAID), the Department of Agriculture (USDA), and other agencies are developing a comprehensive international strategy on avian influenza and pandemic influenza. For example, HHS participates in ongoing global influenza surveillance through the CDC's WHO Collaborating Centers for Influenza. During the current pandemic alert, under the leadership of WHO, surveillance activities have been intensified and include strengthening national influenza center laboratories, training public health personnel, providing diagnostic reagents and other material support, and testing novel virus isolates from humans and animals. HHS has also contributed expertise to the WHO's influenza program and to WHO-led investigations of human cases of avian influenza in Asia. WHO has received additional funding by HHS to strengthen its Global Outbreak and Response Network (GOARN) to assist in surveillance and response worldwide and to establish a fund to ensure that laboratory specimens are shipped in a timely way to reference laboratories for further diagnostic work and confirmation.

As the pandemic threat continues, the U.S. will provide ongoing collaboration and assistance as part of the international response. During a pandemic, under the leadership of the HHS Office of Global Health Affairs (OGHA), the HHS Office of Public Health Emergency Preparedness (OPHEP), and the CDC, expertise and assistance will be provided for a coordinated international response. The U.S. is strengthening capacities in the currently affected region of East Asia and enhancing the ability of affected and high-risk countries to address the threat posed by H5N1 avian influenza. Currently, a number of bilateral and multilateral projects are underway in Asian countries to strengthen surveillance and laboratory capacity, develop rapid response capability, develop best practices for clinical case management of those infected, and develop vaccine production capability. In addition, the U.S. is working with the WHO to support international risk communication activities.

The newly formed International Partnership on Avian and Pandemic Influenza, announced by President Bush at the United Nations General Assembly on September 14, 2005, was created to improve international surveillance, transparency, timeliness, and response capabilities. Over 200 delegates from 88 countries and nine international organizations attended the first Senior Officials meeting on October 7, 2005. This initiative will strive for complete transparency, rapid response capabilities, and cooperative surveillance, and will facilitate the sharing of epidemiological data and samples among nations and with the World Health Organization (see Appendix H).



Surveillance, Investigation, and Protective Public Health Measures

Surveillance and epidemiological response. Global collaboration, facilitated by the WHO Secretariat, is a key feature of influenza surveillance. The WHO established an international laboratory-based surveillance network for influenza in 1948, which currently consists of 112 National Influenza Center (NIC) laboratories in 83 countries, and 4 WHO Collaborating Centers for Reference and Research of Influenza (one is located at CDC). The primary purpose of this surveillance network is to detect the emergence and spread of new antigenic variants of influenza, use this information to update the formulation of influenza vaccine, and provide as much warning as possible about the next pandemic. This system provides the foundation of worldwide influenza prevention and control.

The WHO Collaborating Center located at CDC annually produces and distributes worldwide the WHO influenza reagent kits needed to identify the influenza viruses that are expected to circulate. This center also conducts comparative serologic and molecular studies of representative and unusual influenza viruses sent from NIC laboratories around the world.

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The current HHS surveillance strategy expands the geographic coverage of sentinel disease reporting sites and seeks to improve the timeliness of reporting to public health officials. Clinical and epidemiological assessment tools and investigation strategies are being developed to help guide treatment and assess risk, respectively. Finally, HHS is working to ensure real-time outbreak identification for both domestic and international events. (More information is available at www.cdc.gov/mmwr/preview/mmwrhtml/su5301a13.htm).

Diagnostics and detection. Diagnostic testing for pandemic influenza virus may involve a range of laboratory assays, including rapid antigen tests, reverse-transcription polymerase chain reaction (RT-PCR), virus isolation, and immunofluorescence antibody (IFA) assays. Currently available rapid antigen detection tests are not sufficiently sensitive to reliably distinguish influenza subtypes. In addition, capacity for molecular detection of H5N1, and other strains with pandemic potential, is available at CDC and state reference labs, but is not widely distributed. Capability for production, validation, and distribution of reagents for inclusion in WHO reference typing kits is severely limited.

HHS has augmented state and local laboratory capacity to respond to anticipated surges in laboratory needs by establishing the Laboratory Response Network (LRN). The LRN has trained laboratory personnel in the detection and characterization of novel influenza strains and will work with health departments to provide surge capacity processing and test clinical specimens from patients who meet the case definition of pandemic influenza. Health departments and LRN laboratories will also provide guidelines to clinical laboratories for the safe handling, processing, and testing of specimens. Local public health departments with laboratories not part of LRN or clinical laboratories should contact their state health department for more information regarding laboratory guidelines.

Infection control. On its website, CDC provides guidance to healthcare and public health partners on infection control measures designed to limit the spread of pandemic influenza. Guidance is included on the selection and use of personal protective equipment, such as masks, gloves, and gowns; hand hygiene and safe work practices; cleaning and disinfection of environmental surfaces; handling of laboratory specimens; and post-mortem care. The guidance also covers infection control practices related to the management of infectious patients, the protection of persons at high risk for severe influenza or its complications, personal protection in homes and in communities, and issues concerning occupational health.

CDC recommendations also outline actions that may be taken during the earliest stage of a pandemic when the first potential cases or disease clusters are detected. In this setting, individual-level containment measures (e.g., patient isolation and identification, monitoring, quarantine of contacts) may be useful in slowing the spread of pandemic influenza.

The overall HHS strategy includes a comprehensive approach to protect travelers and decrease entry of pandemic influenza into the United States. This includes: 1) issuing travel advisories and providing education to travelers to decrease their risk of acquiring pandemic influenza infection; 2) identifying persons with influenza-like illness during transit and implementing protocols to limit potential transmission to other passengers; 3) implementing point-of-entry interventions to rapidly identify persons who may have pandemic influenza; 4) isolating persons and identifying and quarantining contacts using fixed quarantine stations and other sheltering models; and 5) attempting to prevent exportation of illness from the United States to other countries and encouraging affected countries to implement similar exit screening.

HHS public health research priorities include evaluating the extent to which infection control measures, such as social distancing, mask use, and hand hygiene, prevent or minimize the spread of pandemic influenza within healthcare settings. Related to these priorities, the study of the relative clinical importance of the various modes of transmission is necessary to better define scientific rationale for various types of personal protective equipment.

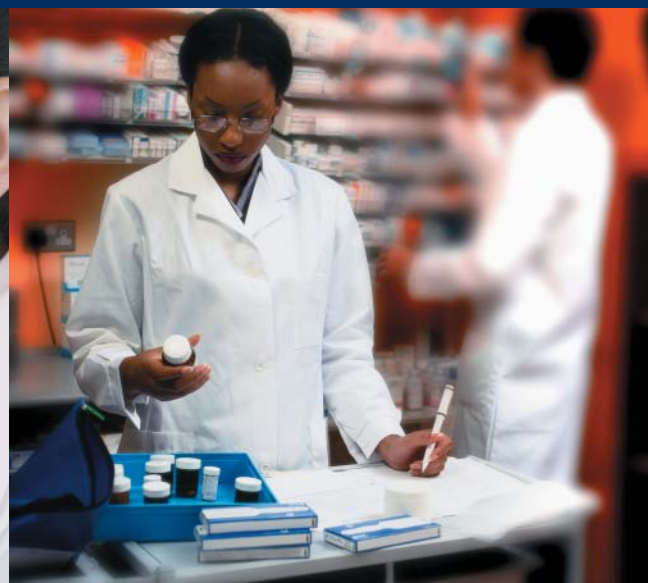
Vaccines and Antivirals

Influenza vaccine. Currently, influenza vaccine for the annual, seasonal influenza program comes from four manufacturers. However, only a single manufacturer produces the annual vaccine entirely within the U.S. Thus, if a pandemic occurred and existing U.S.-based influenza vaccine manufacturing capacity was completely diverted to producing a pandemic vaccine, supply would be severely limited. Moreover, because the annual influenza manufacturing process takes place during most of the year, the time and capacity to produce vaccine against potential pandemic viruses for a stockpile, while continuing annual influenza vaccine production, is limited. Since supply will be limited, it is critical for HHS to be able to direct vaccine distribution in accordance with predefined groups (see Appendix D); HHS will ensure the building of capacity and will engage states in a discussion about the purchase and distribution of pandemic influenza vaccine.

Vaccine production capacity: The protective immune response generated by current influenza vaccines is largely based on viral hemagglutinin (HA) and neuraminidase (NA) antigens in the vaccine. As a consequence, the basis of influenza vaccine manufacturing is growing massive quantities of virus in order to have sufficient amounts of these protein antigens to stimulate immune responses. Influenza vaccines used in the United States and



The overall HHS strategy includes a comprehensive approach to protect travelers and decrease entry of pandemic influenza into the United States.



HHS is currently supporting a number of vaccine manufacturers in the advanced development of cell-based influenza vaccines with the goal of developing U.S.-licensed cell-based influenza vaccines produced in the United States.

around world are manufactured by growing virus in fertilized hen's eggs, a commercial process that has been in place for decades. To achieve current vaccine production targets millions of 11-day old fertilized eggs must be available every day of production.

In the near term, further expansion of these systems will provide additional capacity for the U.S.-based production of both seasonal and pandemic vaccines, however, the surge capacity that will be needed for a pandemic response cannot be met by egg-based vaccine production alone, as it is impractical to develop a system that depends hundreds of millions of 11-day old specialized eggs on a standby basis. In addition, because a pandemic could result from an avian influenza strain that is lethal to chickens, it is impossible to ensure that eggs will be available to produce vaccine when needed.

In contrast, cell culture manufacturing technology can be applied to influenza vaccines as they are with most viral vaccines (e.g., polio vaccine, measles-mumps-rubella vaccine, chickenpox vaccine). In this system, viruses are grown in closed systems such as bioreactors containing large number of cells in growth media rather than eggs. The surge capacity afforded by cell-based technology is insensitive to seasons and can be adjusted to vaccine demand, as capacity can be increased or decreased by the number of bioreactors or the volume used within a bioreactor. In addition to supporting basic research on cell-based influenza vaccine development, HHS is currently supporting a number of vaccine manufacturers in the advanced development of cell-based influenza vaccines with the goal of developing U.S.-licensed cell-based influenza vaccines produced in the United States.

Dose-sparing technologies. Current U.S.-licensed vaccines stimulate an immune response based on the quantity of HA (hemagglutinin) antigen included in the dose. Methods to stimulate a strong immune response using less HA antigen are being studied in H5N1 and H9N2 vaccine trials. These include changing the mode of delivery from intramuscular to intradermal and the addition of immune-enhancing adjuvant to the vaccine formulation. Additionally, HHS is soliciting contract proposals from manufacturers of vaccines, adjuvants, and medical devices for the development and licensure of influenza vaccines that will provide dose-sparing alternative strategies.

Antiviral drugs. One of currently circulating H5N1 virus strains is resistant to one of two existing classes of antiviral drugs. Only the neuraminidase inhibitors, oseltamivir (Tamiflu®) and zanamivir (Relenza®) provide clinical benefit against all of the H5N1 virus strains currently circulating in Asia. As of October 2005, the Strategic National Stockpile includes 2.3 million treatment courses of oseltamivir (Tamiflu®) and 84,000 treatment courses of zanamivir (Relenza®). The Strategic National Stockpile is expecting delivery on an additional 2 million courses of Tamiflu by the end of 2005. HHS is committed to acquiring additional courses of these drugs, as stated earlier, and increasing U.S.-based antiviral production.

Further research and development. HHS plans to accelerate basic discovery in priority areas such as natural history of influenza progression, animal-to-human transmission of disease, and virus/host interaction. It plans to do this by supporting academic and private-sector research grants in priority areas that could contribute to the generation of new vaccines, drugs, and diagnostics and expanding support for multidisciplinary focus in priority areas.

HHS also plans to accelerate development of vaccines, drugs, and diagnostics by 1) supporting and accelerating the clinical testing of candidate products that are in advanced states of development (e.g. recombinant influenza vaccine and new and/or long-acting neuraminidase inhibitor antiviral drugs); 2) supporting evaluation and licensure efforts for injectable and pediatric formulations of currently licensed drugs, of new antiviral drugs, 3) supporting accelerated preclinical development including in vitro and animal model studies of promising countermeasures (e.g. siRNA and common-epitope vaccines, new immune-stimulating adjuvants, novel antiviral drugs, and genomic/proteomic microchip approaches to rapid diagnostics using surrogate markers of early infection). These will be accomplished using milestone-driven grants with private-sector partners and public/private sector collaborations; 4) supporting revised protocols and increased resources to reduce the time to prepare and qualify influenza virus reference strains used in vaccine manufacturing and to calibrate HA content in influenza vaccines for potency assays; and 5) developing accurate, rapid point-of-care diagnostic tests for clinical use during a pandemic, which will require additional investment in new technology leading both to better diagnosis of influenza and differentiation among the various respiratory infections.

Healthcare and Emergency Response

Clinical care. HHS is working with the medical community to establish clinical procedures for the initial screening, assessment, and management of patients with suspected novel influenza during a pandemic. Early recognition of illness caused by a novel influenza virus strain will rely on a combination of clinical and epidemiological features. Guidelines for the management of influenza-related complications, including community-acquired pneumonia, have also been developed.

Healthcare surge capacity. An influenza pandemic may increase the demand for hospital inpatient and intensive care unit (ICU) beds and assisted ventilation services by more than 25%. HHS is developing a deployable mass casualty capability that could be used to supplement hospitals. HHS recommends that hospitals develop their own response plans. **Supplement 3** provides guidance to hospitals on several components of a plan including hospital surveillance, hospital communication, staff education and training, triage and admission procedures, staffing and bed capacity, consumable and durable supplies, and planning for provision of care in non-hospital settings.

Psychosocial support services. HHS is focusing on the institutionalization of psychosocial support services that will help healthcare workers manage emotional stress during the response to an influenza pandemic and resolve related personal, professional, and family issues. HHS is also addressing the preparation of informational materials for employees and their families and the development of workforce resilience programs to assist families of deployed workers.

Mass fatalities and mortuary services. HHS understands that the timely, safe, and respectful disposition of the deceased is an essential component of an effective response. Pandemic influenza may quickly rise to the level of a catastrophic incident that results in mass fatalities, which will place extraordinary demands (including religious, cultural, and emotional burdens) on local jurisdictions and the families of the victims. A catastrophic incident involving mass fatalities will require federal assistance to transport, process, and store deceased victims and support final disposition and personal effects processing. Most local jurisdictions will be severely strained to handle mass fatalities or may experience profound difficulties.

If local and state fatality management capacities are exceeded, HHS, under ESF #8, will coordinate with the Department of Homeland Security (DHS) and the Department of Defense (DoD) to assist in providing mortuary services; establishing temporary morgue facilities; and processing, preparation, and disposition of human remains.

An influenza pandemic may increase the demand for hospital inpatient and intensive care unit (ICU) beds and assisted ventilation services by more than 25%. HHS is developing a deployable mass casualty capability that could be used to supplement hospitals.

Communications and Outreach

Risk communication. HHS is the federal government's lead agency in pandemic influenza communications. An HHS Communications and Public Outreach Strategy for Pandemic Influenza has been developed. This strategy is designed to prepare U.S. citizens and communities for a pandemic; communicate the need for local preparedness and an understanding of the implications of a pandemic; and develop consistent, clear, honest messages and materials that can be shared broadly in the U.S. and with global partners. Components of the strategy include 1) assessment of current public (or community) knowledge through ongoing surveillance of media and surveys of the public and providers; 2) development of materials such as message maps that have been developed and tested in focus groups; 3) formative audience research; 4) cross-government communication coordination; 5) facilitating community and business continuity planning by helping these sectors communicate with their constituents and prepare; 6) public engagement through forums and stakeholder meetings on such important policy issues as allocation of limited drugs and vaccines; 7) web communications development through a consolidated, centralized U.S. government website; 8) international outreach to support our global partners, in cooperation with the WHO Secretariat; and 9) continuing efforts to raise awareness about the importance of seasonal influenza vaccine and to promote increased yearly compliance of influenza and pneumococcal vaccination.

A Public Engagement Pilot Project on Pandemic Influenza was initiated in July 2005 to discuss goals for a pandemic influenza vaccination program and to pilot test a new model for engaging citizens on vaccine related policy decisions. The pilot project was sponsored by interested organizations including the Atlanta Journal Constitution, the Lounsbery Foundation, the Keystone Center, the Institute of Medicine, the University of Georgia, the CDC's National Immunization Program, the HHS National Vaccine Program Office, and the Study Circles Resource Center. To conduct this public consultation, the sponsors made use of an innovative model for engaging stakeholders from various organizations with an interest in pandemic influenza, and individual citizens-at-large from the 4 principal regions of the United States. The anticipated major benefits from this public consultation were the development of an improved plan to combat pandemic influenza and one more likely to gain public support, and a demonstration that citizens can be productively engaged in informing vaccine-related policy decisions. A complete assessment of the potential benefits from this pilot project is still underway and important potential outcomes such as improved relationships and increased trust among the participants have not been yet been measured.



HHS understands that the timely, safe, and respectful disposition of the deceased is an essential component of an effective response.



appendix G

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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.

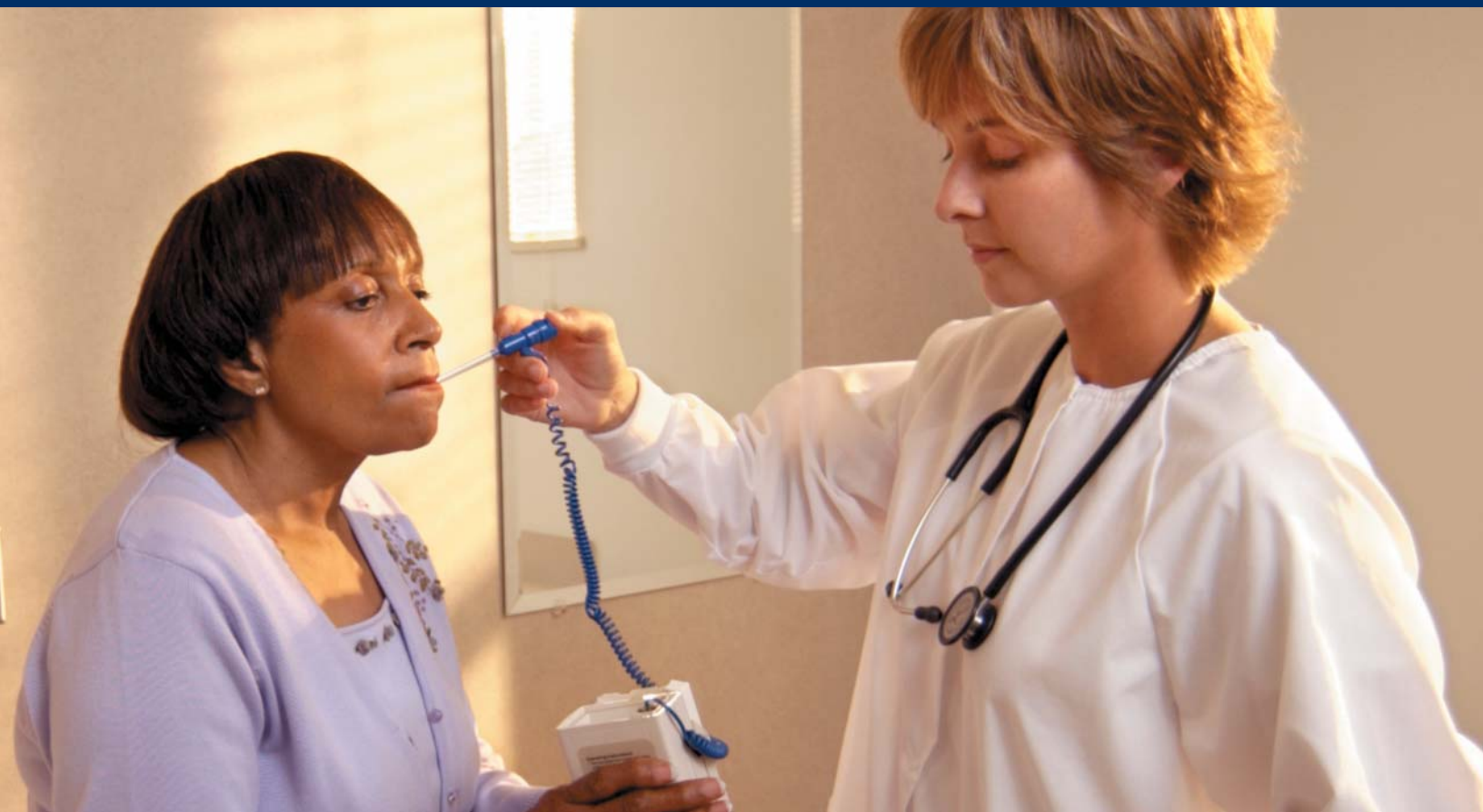
B. The transition to applied research

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
- Studying 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 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.



appendix H: international partnership on avian and pandemic influenza

The newly formed International Partnership on Avian and Pandemic Influenza (IPAPI), announced by President Bush at the United Nations General Assembly on September 14, 2005, brings together countries that share a set of core principles to generate and coordinate political momentum for addressing avian and pandemic influenza. With commitment from the highest political levels in countries around the world, IPAPI will strive to improve international surveillance, transparency, timeliness, and response capabilities and facilitate sharing of epidemiological information and samples critical for the response effort.

The Senior Officials Meeting of IPAPI, held in Washington, DC, on October 7, 2005, launched the Partnership and led to a jointly developed plan of action for coordinating national activities, evaluating national capabilities and filling gaps. This plan, based on the partnership's core principles (below), will supplement ongoing and planned international efforts and support the work of the relevant international organizations, including the World Health Organization (WHO), the World Animal Health Organization (OIE), the United Nations Food and Agriculture Organization (FAO), and other international and regional bodies and the private sector, NGOs, and others.

At the first meeting of IPAPI **over 80 countries and 8 international organizations came together, endorsing the core principles and agreeing to follow up on a number of major policy issues** that need further discussion at the highest political levels to resolve concerns or gain true consensus so that necessary movement can occur. A summary document that identifies the issues of greatest policy significance for dealing with the threats of avian and pandemic influenza was developed. Sub-groups of partners will deal with these, so that by the middle of 2006, progress made in raising the political attention on the problem and addressing the issues identified will be reported. Countries will convene the meetings of the sub-groups to focus on the issues identified. These sub-groups will coordinate with the relevant international organizations on technical matters. The sub-groups will identify any gaps needing further attention, and additional sub-groups may form to address issues as they arise.

The **Core Principles** that underpin the Partnership are:

1. International cooperation to protect the lives and health of our people;
2. Timely and sustained high-level global political leadership to combat avian and pandemic influenza;
3. Transparency in reporting of influenza cases in humans and in animals caused by strains that have pandemic potential, to increase understanding, preparedness, and especially to ensure rapid and timely response to potential outbreaks;
4. Immediate sharing of epidemiological data and samples with the World Health Organization (WHO) and the international community to detect and characterize the nature and evolution of any outbreaks as quickly as possible by utilizing, where appropriate, existing networks and mechanisms;

Since pandemics are diseases without borders, the influenza virus will not respect political or geographic boundaries—a threat against one nation is a threat against the entire world.

5. Rapid reaction to address the first signs of accelerated transmission of H5N1 and other highly pathogenic influenza strains so that appropriate international and national resources can be brought to bear;
6. Prevent and contain an incipient epidemic through capacity building and in-country collaboration with international partners;
7. Work in a manner complementary to and supportive of expanded cooperation with and appropriate support of key multilateral organizations (WHO, Food and Agriculture Organization, World Organization for Animal Health);
8. Timely coordination of bilateral and multilateral resource allocations, dedication of domestic resources (human and financial), improvements in public awareness, and development of economic and trade contingency plans;
9. Increased coordination and harmonization of preparedness, prevention, response, and containment activities among nations, complementing domestic and regional preparedness initiatives and encouraging where appropriate the development of strategic regional initiatives;
10. Actions based on the best available science.

This Partnership will help us improve international surveillance, transparency, timeliness, and response capabilities. Since pandemics are diseases without borders, the influenza virus will not respect political or geographic boundaries—a threat against one nation is a threat against the entire world. This initiative will strive for complete transparency, rapid response capabilities, cooperative surveillance, and will facilitate the sharing of epidemiological data and samples with each other and with the relevant international organizations. This will give us commitment from the highest political levels in countries around the world to adhere to these principles.

Future activities

In addition to participating in IPAPI, HHS will continue to work with other governments, international organizations such as GHSAG and WHO, the newly appointed UN Secretary-General's Special Representative on Pandemic Influenza, and other U.S. agencies individually as part of the overall USG international strategy. We will pursue a diplomatic strategy and provide technical assistance to affected countries and countries at risk. We will provide additional funding in FY 06 and thereafter, building on the work we are doing now in Southeast Asia. We expect to broaden our coverage to other parts of the globe. We will continue to look for increasing human-to-human transmission anywhere in the world as a triggering event for initiating a pandemic response by the U.S. HHS will pursue a prevention approach if possible, and a containment strategy where feasible—acting in concert with WHO and other nations as appropriate. At the core of this strategy, basic public health measures will be essential in reducing transmission in affected countries.



appendix I: acronym list

Abbreviations and Acronyms

ACF.....	Administration for Children and Families
ACIP.....	Advisory Committee on Immunization Practices
ASH.....	Assistant Secretary for Health
ASPA.....	Assistant Secretary for Public Affairs
ASPHEP.....	Assistant Secretary for Public Health Emergency Preparedness
ASTHO.....	Association of State and Territorial Health Officials
CDC.....	Centers for Disease Control and Prevention
CONOPS.....	Concept of Operations
DHS.....	Department of Homeland Security
DoD.....	Department of Defense
EOC.....	Emergency Operations Center
ESF.....	Emergency Support Function
FDA.....	Food and Drug Administration
FEMA.....	Federal Emergency Management Agency
FMCS.....	Federal Medical Contingency Stations
HA.....	hemagglutinin (a protein on the surface of the influenza virus)
HHS.....	Department of Health and Human Services
HRSA.....	Health Resources and Services Administration
HSPD.....	Homeland Security Presidential Directive
ICS.....	Incident Command System
IIMG.....	Interagency Incident Management Group
ILI.....	influenza-like-illness
IOM.....	Institute of Medicine
NA.....	neuraminidase (a protein on the surface of the influenza virus)
NI.....	neuraminidase inhibitors

NIC.....National Influenza Center
NIHNational Institutes of Health
NDMS.....National Disaster Medical System
NIMSNational Incident Management System
NRP.....National Response Plan
NVAC.....National Vaccine Advisory Committee
NVPO/HHS.....National Vaccine Program Office, Department of Health and Human Services
OPHEP/HHSOffice of Public Health Emergency Preparedness, Department of Health and Human Services
OGHA/HHSOffice of Global Health Affairs, Department of Health and Human Services
OIGA/HHSOffice of Intergovernmental Affairs, Department of Health and Human Services
PHS.....Public Health Service
PPE.....Personal Protective Equipment
R&DResearch and Development
SARS.....Severe Acute Respiratory Syndrome
USAID.....U.S. Agency for International Development
USDA.....U.S. Department of Agriculture
VRBPACVaccine and Related Biological Products Advisory Committee
WHO.....World Health Organization



appendix J: internet resources on pandemic influenza

The links listed below were active as of October 2005. However, because Web sites can change without notice, no site can be guaranteed active or accurate indefinitely.

U.S. Government

www.pandemicflu.gov

Nongovernmental Organizations

Association of State and Territorial Health Officials (ASTHO) – www.astho.org

Infectious Disease Society of America – www.idsociety.org

National Foundation for Infectious Diseases – www.nfid.org

Institute of Medicine (IOM) – www.iom.edu

World Health Organization (WHO) – www.who.org

Influenza background information

CDC – Presents information on the symptoms, treatment, and complications of the disease, prevention and control, the types of influenza viruses, questions and answers on symptoms, vaccination, and myths. www.cdc.gov/flu

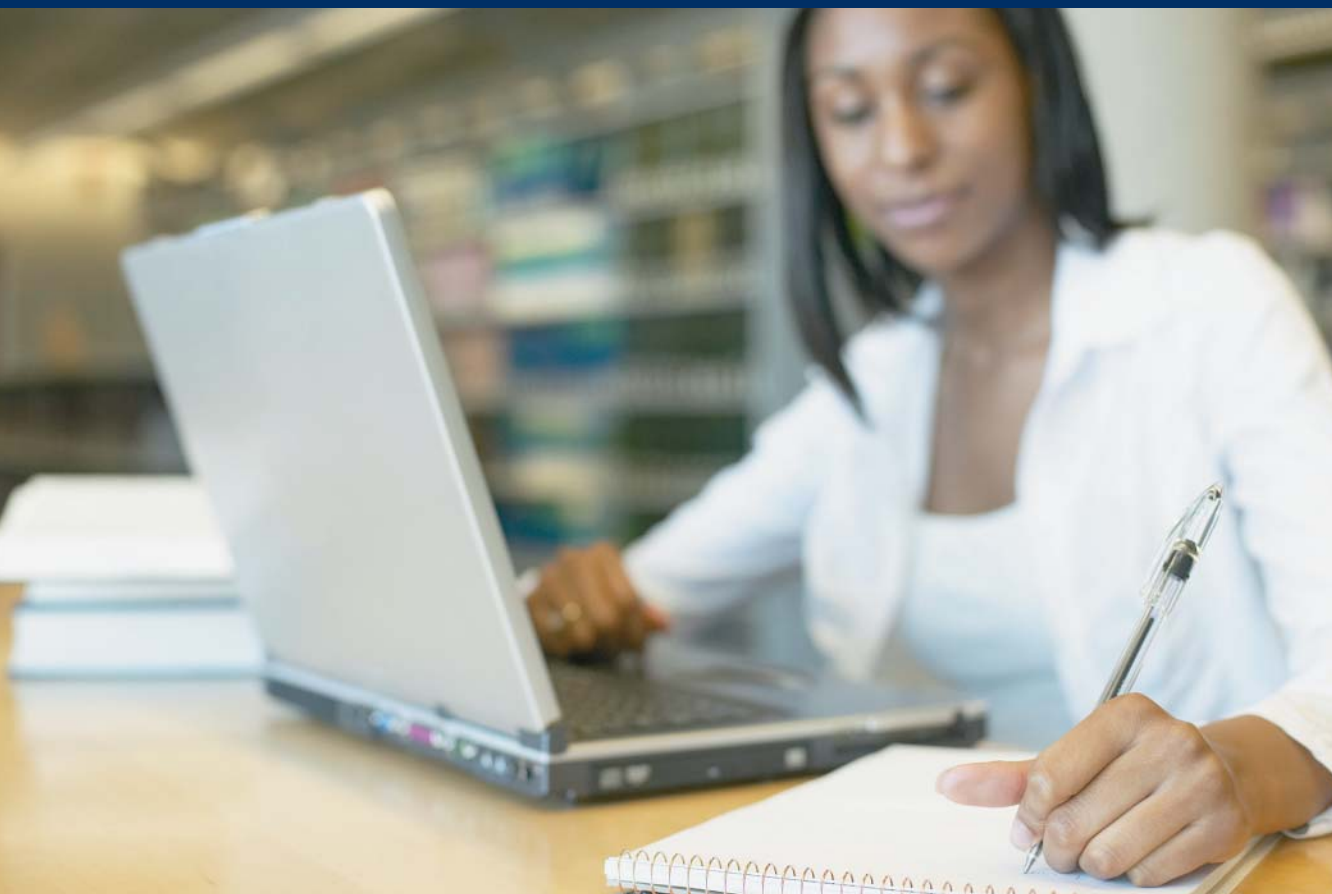
National Vaccine Program Office – Presents a historical overview of pandemics that occurred throughout the past century (Spanish Flu, Asian Flu, Hong Kong Flu), and three influenza scares (Swine Flu, Russian Flu, and Avian Flu). www.dhhs.gov/nvpo/pandemics

World Health Organization – Defines an influenza pandemic, explains how a new influenza virus can cause a pandemic, presents the consequences of an influenza pandemic, explains the global surveillance systems, and provides links to other pandemic plans from other nations. www.who.int/csr/disease/influenza/pandemic/en

Additional response resources

HRSA Bioterrorism and Emergency Preparedness Grants and Cooperative Agreements – Provides information about HRSA programs for bioterrorism and emergency preparedness activities available for state and local jurisdictions. www.hrsa.gov/bioterrorism

www.pandemicflu.gov



The Public Health Preparedness and Response Capacity Inventory – Provides a resource for state and local health departments undertaking comprehensive assessments of their preparedness to respond to bioterrorism, outbreaks of infectious disease, or other public health threats and emergencies. www.dhs.ca.gov/epo/PDF/NPSsmpvx1.pdf

CDC Cooperative Agreements on Public Health Preparedness – Provide funding to state and local public health jurisdictions for preparedness for and response to bioterrorism, other outbreaks of infectious diseases, and other public health threats and emergencies. www.bt.cdc.gov/planning/continuationguidance

Epidemic Information Exchange – Provides a secure, web-based communications network for information exchange among CDC, state and local health departments, and other public health professionals. www.cdc.gov/mmwr/epix/epix.html

Centers for Public Health Preparedness – A national system for competency-based training tools for the public health workforce. www.asph.org/acphp

Strategic National Stockpile – Provides information on the availability and rapid deployment of life-saving pharmaceuticals, antidotes, other medical supplies, and equipment necessary to counter the effects of nerve agents, biological pathogens, and chemical agents. www.bt.cdc.gov/stockpile

Smallpox Response Plan and Guidelines (Version 3.0) – Presents the most current criteria for implementation of CDC smallpox response plan, notification procedures for suspected smallpox cases, CDC and state/local responsibilities and action in the event of a smallpox outbreak, vaccine mobilization and deployment, and CDC personnel mobilization and deployment. www.bt.cdc.gov/agent/smallpox/response-plan

FDA, Center for Biologics Evaluation and Research – Discussion of influenza vaccines and related information. www.fda.gov/cber/flu/flu.htm

FDA, Center for Drug Evaluation and Research – Discussion of influenza antiviral drugs and related information. www.fda.gov/cder/drug/antivirals/influenza