

## **B. Production Capacity**

As noted earlier, the current U.S. capacity for a pandemic vaccine is estimated to be approximately 300 monovalent doses. Steps to encourage expansion of capacity are currently underway and will continue to be driven by increasing vaccine demand during the inter-pandemic period. (*See Pandemic Influenza Preparedness and Response Plan: Core Document for discussion of influenza pandemic phases.*) Because the growth of vaccine strains may differ among manufacturers, as was observed during the 2000-2001 vaccine shortage, having more licensed manufacturers working in parallel increases the probability of successfully producing sufficient vaccine.

Increasing capacity through the use of incentives to encourage the diversification of vaccine manufacturing approaches and/or attract additional manufacturers into the U.S. market will take several years to accomplish. Discovery of methods to increase the yield of vaccine per unit of production, however, offers opportunities to expand the number of vaccine doses produced more quickly. Reference strains from which influenza vaccines are produced (reassortants) include the hemagglutinin (HA) and neuraminidase (NA) proteins of the wild type strain as well as other viral proteins from a strain known to grow well in eggs. Development of new molecular techniques, a better understanding of the genes that regulate growth of influenza virus, and methods to more rapidly identify and select high-growth reassortants all may increase the speed and the yield of vaccine per unit of production. Methods to increase virus yield also can be identified through systematic exploration of viral factors that affect growth in various culture system and through systematic assessment of various cell lines that are certified for production of vaccine.

**To advance pandemic vaccine preparedness specifically**, HHS recently announced two Requests For Proposals (RFPs) designed to encourage U.S.-based influenza vaccine manufacturers to have adequate surge capacity so that they can make large quantities of vaccine in the setting of a pandemic. In addition to ensuring that the manufacturers who make vaccines in eggs have the raw materials they need at any time of the year, these RFPs (\$50 million in fiscal year FY '04 and \$100 million in the President's FY '05 budget request) are also seeking to accelerate the development of domestically-produced U.S.-licensed cell-culture based vaccines. Not only will this potentially shorten the timelines to the production of large numbers of doses of vaccines, but also will decrease the potential vulnerability to egg-based production should an avian influenza epidemic threaten the egg supply.

## **C. Research (*see Annex 8: Pandemic Influenza Research*)**

The experience with current and past influenza vaccines suggests two doses may be required to induce adequate levels of immunity to a pandemic strain of influenza. Enhancing the immunogenicity of a new vaccine so that only one dose is needed to provide adequate levels of immunity could stretch available vaccine supply to protect more people. Enhancing the immunogenicity may require inclusion of an adjuvant – a substance included in vaccines to increase the strength of the immune response. Considerable work has been done to explore

adjuvants combined with influenza vaccines. Further investigation needs to be done to understand whether adjuvants will be useful in a pandemic situation.

#### **D. Vaccine Preparedness**

The ideal pandemic influenza vaccine is one that can be produced in the shortest amount of time, protect the largest number of individuals, and is efficient, safe, and easy to deliver. Actions to achieve this goal are listed below.

##### *Inter-pandemic phase preparedness actions*

- Expand global surveillance for the earliest possible detection of the emergence of a pandemic strain.
- Prepare a library of high growth reassortant viruses against influenza strains with greatest pandemic potential. This collection will have the greatest value if the pandemic strain is identical or similar to one of the strains included. Even if the strain is different, however, the experience gained by the development of high growth reassortant viruses to novel influenza strains will increase the speed with which a high growth vaccine seed virus can be developed to a pandemic strain.
- Prepare and clinically evaluate investigational lots of vaccine made against novel influenza subtypes. Going through the process of vaccine development and evaluation will help identify parts of the system that can be made more efficient and provide experience that can be applied when a pandemic occurs.
- Develop standardization reagents that will be required to assess the potency of investigational vaccines for potential pandemic viruses.
- Improve the yields of high-growth reassortant viruses to increase the number of available vaccine doses through systematic evaluation of growth in various tissue culture systems available for vaccine production. This effort will be complemented by ongoing fundamental research into the factors that affect growth characteristics of various influenza strains in a variety of tissue culture systems.
- Increase demand for yearly vaccine thereby increasing the size of the vaccine market and providing the financial incentive to expand capacity. Increasing demand and vaccine coverage has the additional benefit of preventing disease and death during the annual influenza epidemics.
- Provide incentives for new vaccine manufacturers to enter the U.S. market to increase production capacity and, through diversification, enhance the probability that vaccine will be produced rapidly and made available early.
- Prepare a clinical protocol that can be immediately implemented to rapidly evaluate the safety and the optimal dose and schedule of a pandemic vaccine in various populations. If vaccine containing less than 15 micrograms per dose is effective in inducing immunity, available production capacity could lead to a greater total number of doses. In addition, two doses may not be needed by all segments of the population, and will be dependent on whether a strain similar to the pandemic strain has ever circulated previously.
- Encourage development, evaluation, and licensure of an influenza vaccine that contains an adjuvant. An influenza vaccine that contains an adjuvant may produce a

## *Annex 5: Vaccination Development and Production - Draft*

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good immune response with a lower dose of antigen, allowing existing production capacity to be divided into more vaccine doses. Also, a vaccine that contains an adjuvant may produce protective immunity to a novel influenza strain after a single dose, reducing the total number of doses needed to protect the population.

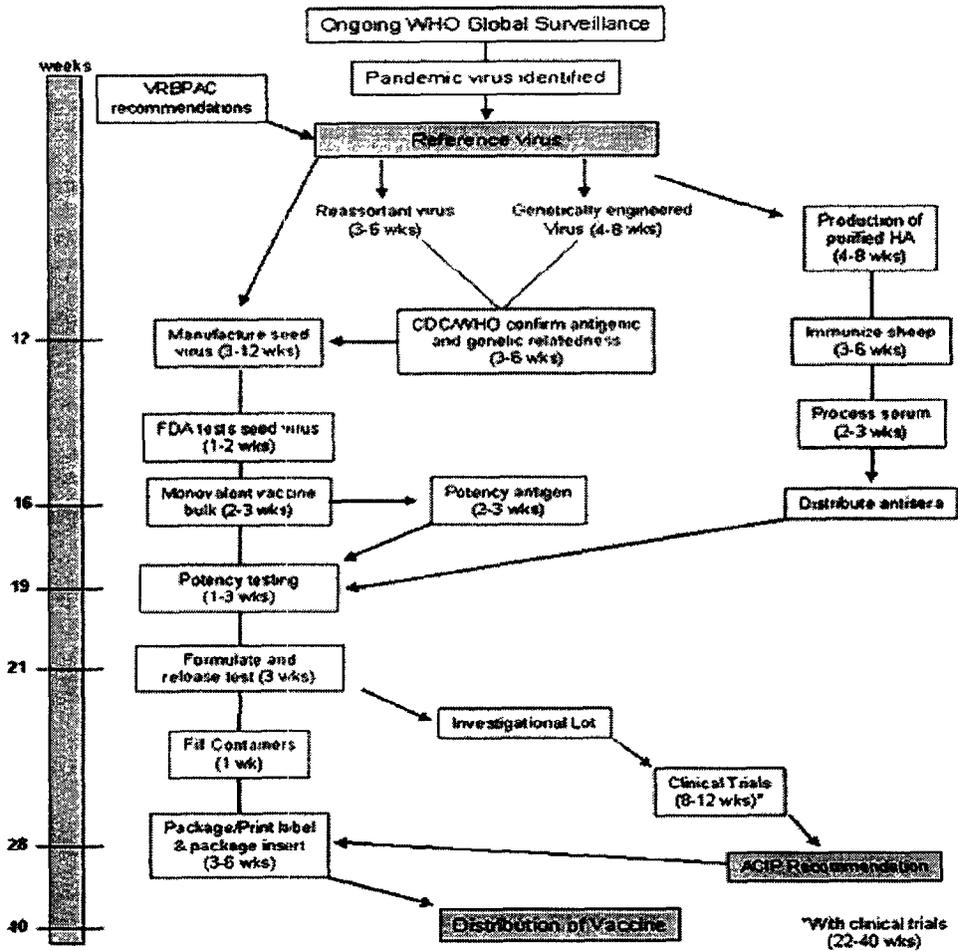
Development and licensure of any new influenza vaccine needs to be done in the inter-pandemic period because studies needed to demonstrate safety and efficacy cannot be done quickly enough at the time of a pandemic to be of value.

- Support the clinical development of promising alternate vaccine products. New technologies under study may decrease the time needed to produce influenza vaccine or to increase the yield or efficiency of production.

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**Annex 5: Vaccination Development and Production - Draft**

**Table: Approximate Timetable for Production of Inactivated Monovalent Vaccine**



**Table of Contents**

<b>I. Background .....</b>	<b>2</b>
A. Vaccine Supply .....	2
B. Population Susceptibility and Risk of Severe Illness.....	3
C. Mix of Public and Private Pandemic Vaccine Supply .....	4
<b>II. Pandemic Vaccine Supply Stages .....</b>	<b>5</b>
<b>III. Pandemic Vaccine Priorities .....</b>	<b>8</b>
A. Vaccination Goals.....	9
B. Vaccine Strategy Goals.....	9
<b>IV. Monitoring and Evaluation.....</b>	<b>9</b>
<b>V. Vaccine Safety .....</b>	<b>10</b>
A. Vaccine Contraindications and Adverse Events .....	10
B. Vaccine Safety Monitoring .....	10
<b>VI. Influenza Vaccine Research .....</b>	<b>12</b>
<b>VII. Pneumococcal Vaccination.....</b>	<b>12</b>

## **I. Background**

Vaccination is the primary intervention to decrease the health impacts of an influenza pandemic. The overall impact of vaccination during a pandemic depends on how rapidly vaccine becomes available; its supply; the ability to allocate, distribute, and administer it; and its effectiveness in preventing infection and disease. (*Vaccine development and production are described in Annex 3: Vaccine Development and Production*). There are several uncertainties that make planning vaccination strategies difficult at this time: vaccine supply, population susceptibility and risk of severe disease, and the mix of public and private pandemic influenza vaccine supply. As a result, national, state, and local planning needs to address possible contingencies so that appropriate strategies are in place for whichever situation accrues.

### **A. Vaccine Supply**

During the 2003-04 influenza season, three manufacturers supplied trivalent influenza vaccine to the U.S. market. Aventis Pasteur produced trivalent inactivated vaccine (TIV) manufactured at a U.S.-based facility while inactivated vaccine sold in the U.S. by Chiron was produced at facilities based in the U.K. In June 2003, the Food and Drug Administration (FDA) licensed a trivalent live attenuated influenza vaccine (LAIV) produced by MedImmune for use in persons 5 to 49 years old and who are not in high-risk groups. Steps in the LAIV production process occur both in the U.S. and Europe.

Overall, about 87 million doses of trivalent influenza vaccine were available for the 2003-04 U.S. influenza season: 83 million doses of TIV and 4 million doses of LAIV. Production capacity exceeds the actual amount of vaccine manufactured for the U.S. market as influenza vaccine production does not occur throughout the entire year and vaccine may be produced by some of these manufacturers for the Southern Hemisphere in the fall. In recent years, both Aventis Pasteur and Chiron have increased influenza vaccine production capacity to meet an increasing demand for influenza vaccine.

Several factors contribute to uncertainty about the amount of vaccine that would be available during a pandemic. To improve vaccine security for a pandemic in 2004, the President requested \$100 million (\$50 million was appropriated in FY'04) to assure the ability to produce influenza vaccine at full capacity throughout the year in U.S. facilities. In addition, these funds are designed to stimulate U.S. licensure and production of influenza vaccine produced using cell culture manufacturing technology as cell culture production systems are more amenable to rapid scale-up and surge capacity compared with current egg-based production technology. The President has requested \$100 million to support these initiatives in his 2005 budget submission.

Also contributing to uncertainty, are factors that affect the actual number of vaccine doses produced and the number of persons who could be protected with those vaccine doses. Because the production of vaccine depends on the growth of the virus in a biological system, the growth characteristics of different influenza strains in either egg-based or cell culture production technologies is variable and yield cannot be predicted, particularly in early production. Further, the amount of vaccine antigen that will be needed to achieve a good immune response for a

pandemic influenza strain also is not known. While vaccine used for annual influenza outbreaks contains 15 micrograms of hemagglutinin antigen (HA) for each of the three included virus strains, more antigen may be required to achieve a good immune response against a novel strain.

In addition, two vaccine doses may be needed for protection against a strain to which the population is immunologically naïve (lacking partial immunity) because of no prior illness or vaccination with that influenza subtype. In addition, two vaccine doses may be needed for enhanced protection against a pandemic strain. Since most, if not all of the population will have no prior exposure to the virus and will thus need a boosting dose. It is possible that a vaccine formulated with an adjuvant, a substance that enhances immune response, could reduce the amount of antigen needed for an adequate immune response, thereby allowing available production to be divided into more doses. Evaluation of the immune-stimulating potential of an adjuvanted influenza vaccine and the licensure of an such a vaccine during the inter-pandemic period might be needed for such a vaccine to be available during a pandemic.

Increasing vaccine demand and coverage before annual influenza epidemics will enhance pandemic preparedness by encouraging manufacturers to increase production capacity and vaccine supply to meet this demand; increasing vaccine acceptability as more people become familiar with the safety profile and benefits of vaccination; and strengthening the vaccine delivery system. Increasing coverage would also have the obvious additional impact of decreasing mortality and morbidity from annual influenza epidemics – a rationale that provides the basis of the HHS Healthy People 2010 objectives. These are 1) to annually vaccinate 90 percent of adults age 65 years and older as well as those in long-term care facilities and 2) to vaccinate 60 percent of non-institutionalized adults between 18 and 64 years old who have underlying medical conditions that increase their risk of severe influenza disease. By contrast, only about two-thirds of persons 65 years old and older currently are immunized against influenza each year, coverage rates have remained flat in recent years, and substantial disparities in coverage exist between racial and ethnic groups. In 2003, the Advisory Committee on Immunization Practices recommended influenza vaccination for all children 6 to 23 months old and influenza vaccine has been included under the Vaccines for Children (VFC) program that provides free vaccine for children under the age of 18 who are Medicaid eligible, uninsured, underinsured or Native American or Alaskan Natives.

#### **B. Population Susceptibility and Risk of Severe Illness**

Vaccination strategies that are designed to decrease the health impacts of an influenza pandemic must take into account susceptibility to infection and the risk that once infected, severe illness or death will occur. In recent years, influenza A outbreaks have been caused by strains that express hemagglutinin antigen subtypes H1 and H3. An influenza pandemic will be caused by a strain that possesses a hemagglutinin antigen subtype that has not circulated previously in the U.S., or has not circulated for many years. In the former case – a completely new strain -- the entire population will be susceptible, whereas in the latter —a strain that has not circulated in recent years -- some older persons who had prior exposure to disease or who were vaccinated with a vaccine that contained this subtype -- may have partial immunity. The avian influenza strains that have infected persons in Hong Kong, China, Vietnam, Thailand, and the Netherlands expressed hemagglutinin subtypes H5, H7, or H9 which are avian strains that have not previously

circulated in people. By contrast, if a strain expressing hemagglutinin subtype H2 that is antigenically similar to a previously circulating H2 emerged and caused a pandemic, some persons may be partially immune.

Although during annual influenza epidemics more than half of the hospitalizations and more than 90 percent of deaths occur in persons who are 65 years old or older, the age distribution of severe disease in a pandemic may be different. During each of the three 20<sup>th</sup> century pandemics, the proportion of severe disease in younger persons was higher compared with annual influenza disease. In 1918, the risk to young adults was particularly marked with the risk of death displaying a “W” shaped pattern, being highest among young children, young adults, and the elderly. Because of uncertainties regarding who will be most susceptible and most at risk for severe disease, strategies for pandemic vaccination will need to be flexible and possibly modified at the time of the pandemic based on the epidemiology of disease.

### **C. Mix of Public and Private Pandemic Vaccine Supply**

Vaccine purchase and distribution in the U.S. occurs through a mixed public and private sector system. For universally recommended childhood vaccines, about 55 percent to 60 percent of vaccine doses are purchased by the public sector, largely through the VFC program. By contrast, most influenza vaccine purchase and distribution occurs through the private sector with only about 15 percent of doses currently purchased directly by the public sector, though this proportion is likely to increase with the inclusion of influenza vaccine in the VFC program. In addition to this vaccine purchase, providers are reimbursed for the cost of influenza vaccine and its administration to persons aged 65 years and older through the Medicare program.

The current, primarily private sector system delivers influenza vaccine to over 80 million persons each year over about a three-month period. During the 2000-2001 influenza season, when slow growth of one of the viruses in the vaccine led to delayed vaccine availability early in the season, public health recommendations were adjusted in order to give priority to those at highest risk for the complications of influenza. However, despite these recommendations many persons who were vaccinated during the shortage period were not in these high-risk groups. Some providers were able to procure vaccine and immunize their high-risk patients while others had no vaccine. In some areas, a gray market occurred with inflated prices being charged for available vaccine doses.

Several factors may argue in support of a public sector role for vaccine purchase and distribution in an influenza pandemic:

- Public sector funding or guarantees may be required before vaccine manufacturers produce pandemic vaccine. This could result in public sector ownership of vaccine that is produced. This occurred in 1976 with the production of vaccine for the swine influenza strain.
- When pandemic vaccine first becomes available, the supply of vaccine will be far less than the amount needed to protect the susceptible population. Targeting available supply to defined priority groups will best assure that pandemic response goals can be met. Because such targeting may be accomplished more effectively by

the public sector, there may be a need for a greater public sector role early in a pandemic response. Thus, the relative proportion of vaccine in public and private sectors may change as the pandemic progresses and vaccine supply changes.

Although the public sector role in influenza vaccine purchase and distribution may be greater in a pandemic compared with annual influenza outbreaks, it is important to emphasize that public sector purchase of pandemic vaccine does not imply that all publicly purchased vaccine will be distributed to public sector vaccination sites and administered by public sector personnel. These functions could be implemented by private organizations under contract to or collaborating with state and local health departments. In addition, given that both public and private sectors will likely have an important role during the course of a pandemic response, planning, coordination, and education of all vaccine providers will be crucial in order to meet pandemic response goals.

## **II. Pandemic Vaccine Supply Stages**

Influenza vaccine availability will change during the course of a pandemic. Pandemic response strategies will vary with vaccine supply. Four vaccine supply levels can be defined.

### ***Stage 1: No Vaccine Available***

At the beginning of a pandemic, it is likely that no vaccine will be available. Interventions to decrease the burden of influenza illness will be limited to measures taken to decrease the spread of infection (such as quarantine, closing schools, canceling public events, infection control in hospitals and long-term care facilities) (*see Annex 6: Strategies to Limit Transmission*); to prevent infection by using antiviral chemoprophylaxis (*see Annex 5: Antiviral Drugs and Strategies*); and to effectively treat those who become ill. The duration of this period will depend on several factors:

- *The lag between when the pandemic strain is identified and when vaccine production begins relative to the occurrence of disease in the U.S.* In 1957 and 1968, pandemic strains were first detected between two and five months before their arrival in the U.S. The 1976 swine influenza strain was first identified in the U.S. in February 1976 and preparedness efforts focused on a possible outbreak beginning that fall. The origin of the 1918 pandemic strain is unknown and may have occurred in the U.S. Enhanced international surveillance may provide earlier warning of a pandemic and decrease the period during which U.S. disease occurs and no vaccine is available. Conversely, increased international travel may bring pandemic virus to the U.S. within days or weeks rather than months.
- *The time of year when the pandemic strain is identified.* This may be important because larger disease outbreaks are most likely to begin in the fall and end in the early spring. If a pandemic strain is first identified in the spring, preparedness activities may occur throughout the summer before a disease peak occurs in the fall. The time of year when a pandemic strain first is identified also may be important given the seasonal nature of annual influenza vaccine

production. Despite new initiatives to assure the year-round availability of embryonated eggs for vaccine production, the amount of pandemic vaccine that can be produced may vary depending on whether available capacity has been focused on production of trivalent vaccine for the annual influenza outbreak. Previous pandemic strains appeared in March 1918, April 1957, and July 1968 resulting in different amounts of time to prepare pandemic vaccine before disease outbreaks that began in the fall.

- *The time required for vaccine development and licensure.* Currently, the interval between identifying strains for the annual trivalent vaccine and vaccine availability is about six to eight months. This period may be shortened to about four months for a monovalent vaccine against a pandemic strain. Improving methods to develop high-growth reassortant reference strains could decrease time to development of a candidate vaccine. Establishing a library of novel influenza strains with pandemic potential and preparing reagents needed to evaluate candidate vaccines for those strains also could be useful (See Annex 8: Pandemic Influenza Research).

### ***Stage 2: Limited Vaccine Supply***

When first available, the pandemic influenza vaccine supply will be less than that required to protect the susceptible population. The duration of this shortage stage cannot be predicted but could include the entire first pandemic season. Several planning issues are of particular importance for this phase of vaccine shortage:

- *Priority groups for vaccination will need to be identified.* The ability to target available vaccine supply will be important to optimally reduce morbidity and mortality, and decrease social and economic disruption. Although broad guidance will be provided nationally based on the epidemiology of the outbreak, state and local health departments will need to more specifically define priority groups. Moreover, because available vaccine supply may initially be insufficient to vaccinate all persons in defined priority groups, specific sub-populations within these groups should be identified to further target vaccination.
- *Plans for rapid, efficient, and equitable distribution of vaccine will need to be formulated.* Under the current system, substantial disparities occur in availability of vaccine to health care providers and in vaccine coverage among racial and ethnic groups. State and local health department plans for vaccine distribution and administration should ensure equitable access by persons in defined priority groups.
- *Approaches to inform priority groups about the availability of vaccine and where to receive it; and to educate the public regarding vaccine priorities and their rationale will be needed.* Public education will be crucial to ensure that priority groups present for vaccination at times and places where vaccine is available. Persons not in groups identified for earliest vaccination also must be educated regarding the rationale for established priorities and must be assured that they will be vaccinated when additional vaccine becomes available (See

*Annex 10: Synergies and Differences in Preparedness and Response for Influenza and Other Infectious Disease Threats)*

- *Systems need to be developed to identify those who have been vaccinated.* If a two-dose schedule is needed, this system ideally should have the capability to identify those who are due for the second dose and to generate reminders. The system could be linked with or use the same technology as existing state and local immunization registries or could be similar to the pre-event vaccination system developed by the CDC to track smallpox vaccination.
- *Vaccine effectiveness and safety need to be monitored.* Whereas efficacy and safety are important at all phases of vaccine supply, evaluation is particularly important during the earliest stages of vaccine use. Results of efficacy studies may lead to modifying recommendations to optimize vaccine dosing or schedules. Epidemiological investigations of disease and mortality could lead to changes in priority groups for vaccination. Early and intensive vaccine safety monitoring can identify any unexpected and/or serious adverse events, help guide development of educational efforts and key communication messages and materials, and assure program acceptability.

***Stage 3: Adequate Vaccine Supply***

During this period, pandemic vaccine supply will match the need and ability to distribute and administer vaccine. This will allow a shift from targeted vaccination of priority groups to widespread vaccination, possibly of the entire population. Strategies for widespread vaccination could include public sector vaccination clinics and/or administration of vaccine by private sector providers. Despite increased vaccine supply, efforts to prevent unequal distribution and access remain important goals. Plans for widespread vaccination during a pandemic should identify potential barriers to vaccination of racial and ethnic minority populations and develop strategies to overcome them. These may include holding vaccination clinics in disadvantaged areas, vaccinating at community sites such as places of worship, involvement of local opinion leaders to promote vaccination, and development of focused educational messages and materials.

***Stage 4: Vaccine excess***

In this stage, vaccine supply will exceed that needed to protect the U.S. population, which may occur if pandemic influenza vaccine production levels remain high after much of the population already has been vaccinated. This stage is unlikely to occur before the second or third wave of pandemic disease.

**III. Pandemic Vaccine Priorities**

Identifying priority groups for vaccination is important because vaccine supply, when initially available, will be less than demand (*see Stage 2, above*). Priority groups can be defined based on national vaccination program goals. Because the attack rates of infection and the severity of disease caused by a pandemic strain cannot be predicted with certainty,

this goal-oriented approach will allow planners and health departments to modify priority groups, if needed, to achieve defined objectives.

#### **A. Vaccination Goals**

***Goal 1: Maintain the ability to provide quality health care, implement pandemic response activities and maintain vital community services.***

Protecting the health care workforce is essential to providing the quality of care that will decrease morbidity and mortality. This is particularly important at times of vaccine shortage when good clinical care will be the most important intervention to reduce influenza health impacts. Maintaining the capacity to implement pandemic response activities, for example, by protecting those in public health, vaccine production and administration; and preserving public safety (e.g., police and fire department services) also are high priorities.

***Goal 2: Protect persons at highest risk for influenza mortality***

Direct protection of high-risk persons is the strategy on which annual influenza vaccination is based. Despite changes in the age distribution of mortality that has occurred during recent pandemics, older adults and those who have underlying diseases still have been at highest risk of death.

***Goal 3: Decrease transmission of infection to those at highest risk for influenza mortality (provide indirect protection)***

Indirect protection is achieved by decreasing the spread of infection to those at high risk. Family members of older adults and persons with chronic illnesses are recommended for annual influenza vaccination in order to decrease disease in their high-risk contacts. Vaccinating health care providers and staff in institutional settings also can decrease transmission to persons at high risk. Some have advocated vaccination of school-aged children as a strategy to decrease transmission within a community. Data from Japan and mathematical modeling suggest that vaccinating children may decrease mortality among older adults. However, there are no data on the effectiveness of such an approach during a pandemic and the proportion of children who would need to be vaccinated to achieve significant indirect protection of others at higher risk within the community is not clear. Further consideration of such an approach should be assessed in the inter-pandemic period. However, this approach should not be considered until sufficient vaccine is available and other priority goals have been accomplished. Closing schools to decrease transmission among children and subsequent spread to other family members may have some impact.

***Goal 4: Maintain other important community services***

Achieving the pandemic influenza preparedness and response plan goals of decreasing social and economic impacts requires maintenance of important community services such as utilities and transportation. Such decisions can best be

made at state and local levels.

**Goal 5: Protect the susceptible population at large**

**B. Vaccination Strategy Goals**

State and local health departments should define priority groups for early vaccination in their pandemic influenza preparedness and response plans, consistent with pandemic response goals to decrease health, social, and economic impacts. Early vaccination of some persons across the highest priority groups, rather than sequentially vaccinating groups, may be an optimal strategy given the wide variety of roles that exist within a category such as “health care worker.” Increased specificity, particularly at the local level will be important to assure the greatest impacts when vaccine supplies are most limited. The Canadian Pandemic Preparedness and Response Plan provides one example of how such groups could be defined (<http://www.hc-sc.gc.ca/pphb-dgspsp/cpip-pclcpi/pdf-cpip-03/cpip-appendix-d.pdf>).

It also is important that vaccination strategies be flexible and responsive not only to vaccine supply but also to the epidemiology of the pandemic. Epidemiological investigations early during the pandemic will be important to help guide decision-making, for example, to determine the groups what are at highest risk for adverse health outcomes and the age-specific case-fatality rate.. In addition, programmatic feasibility must be considered in implementing priorities. For example, as vaccine supplies expand and after vaccination of those defined as being in the highest-priority target groups, it may be most feasible to vaccinate entire families or to provide vaccine by geographical area in mass clinics rather than further subdividing the population by priority.

**IV. Monitoring and Evaluation**

Monitoring vaccine coverage and effectiveness, and determining impacts on key health outcomes are integral components of any vaccination program. Assessing overall coverage is important to determine whether vaccine is being delivered efficiently and to provide information to public health authorities, policy-makers and the media regarding progress of the vaccination campaign. Also important is collecting data on who is being vaccinated. Are available vaccine doses being used in priority groups or is vaccine that is in limited supply being given to those at lower priority? Are vaccination rates comparable among racial and ethnic groups? And, if two doses are needed for protection, are persons who receive a first vaccine dose being given the second dose as well? Answering these questions requires collecting demographic and limited health data on vaccine recipients. State health departments will have the primary responsibility for monitoring and evaluation activities with support being provided by CDC.

Monitoring vaccine coverage can be done through a registry built into existing state and local immunization registries, or by using software provided by CDC, similar to that used for the pre-event smallpox vaccination program recently implemented among hospital and public health personnel. Developing such systems during the inter-pandemic period and testing them to identify and resolve any problems will assure their availability and readiness for use in a

pandemic.

Data on vaccine effectiveness should be collected rapidly to assess whether changes need to be made in formulation, dose, or schedule. Effectiveness data also could lead to changes in vaccination recommendations. Because randomized studies during a pandemic cannot be conducted, vaccine effectiveness will be determined in epidemiological studies. For example, case-control studies can be done comparing vaccination rates among persons hospitalized with influenza and controls matched for underlying disease and opportunity for vaccination. Because results from a small number of effectiveness studies can be applied generally, these studies should be coordinated nationally by the CDC and implemented in collaboration with State health departments or health care organizations. In addition, cross-sectional surveys would be useful to identify barriers to vaccination among those in priority groups and could lead to interventions to improve access to or acceptability of vaccination. Such studies also may be coordinated nationally.

## **V. Vaccine Safety**

### **A. Vaccine Contraindications and Adverse Events**

There are very few contraindications to vaccination against influenza. Vaccine should not be administered to persons with known anaphylactic hypersensitivity to eggs or other vaccine components, as described in the package inserts. In the setting of a pandemic, appropriate allergy evaluation and desensitization may be an option for those at particularly high risk of influenza or its complications. An alternative for prevention would be prophylaxis with an antiviral medication.

Contraindications are similar for the inactivated influenza vaccines and the recently licensed live attenuated vaccine. The live attenuated vaccine is currently licensed only for persons between 5 and 49 years of age who do not have high-risk conditions for influenza or its complications. Although it is possible that the live attenuated vaccine strain could be transmitted from an immunized person to their close contact, this should not restrict LAIV vaccine use during a pandemic, however, the use of such a vaccine in a pandemic needs to be evaluated.

Adverse reactions to inactivated influenza vaccine are uncommon. Fever, malaise, and myalgia occur infrequently following vaccination. Hypersensitivity is very rare. Guillian-Barre syndrome (GBS) was associated with swine influenza vaccine, but the increased risk associated with other influenza vaccines – if such risk exists – is small, perhaps one additional case per million persons vaccinated. Despite the common misconception that one can get influenza from the vaccine, the inactivated vaccine contains no viable virus and does not cause respiratory symptoms. The live attenuated vaccine may cause runny nose, nasal congestion, headache, and possibly sore throat, but not severe influenza-like symptoms.

### **B. Vaccine Safety Monitoring**

Carefully monitoring vaccine safety is important to assure that the benefits of any vaccination program far exceed the risks. The association of GBS with swine influenza vaccine was an

## Annex 6: Vaccination Strategies, Monitoring, and Safety - Draft

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unusual but highly prominent event that keeps some people from receiving an annual influenza vaccine and may make some persons reluctant to accept vaccine during a pandemic. Unusual adverse events recently associated with specific influenza vaccines available outside of the U.S. include Bells palsy in Europe linked with an intranasally administered inactivated influenza vaccine produced in Switzerland and conjunctivitis in some recipients of a Canadian inactivated influenza.

The ability to detect, in real-time, these or other adverse events is important to assure that the vaccine has an acceptable safety profile. It is also important to be able to assess events that are temporally linked with vaccination and to determine whether they are caused by vaccine or are coincidental. During the swine influenza vaccination program in 1976, three deaths occurred in Pennsylvania shortly after vaccination of elderly persons who had pre-existing cardiac disease. Concern that these deaths may have been caused by vaccine resulted in nine states temporarily halting their vaccination programs. Investigation and analysis showed that the deaths were not linked with vaccination and the program continued. Although primary responsibility for vaccine safety monitoring belongs to CDC and FDA, studies conducted at the state level may provide important information about potentially vaccine associated events. For example, initial concerns about GBS associated with swine influenza vaccination came from data collected by the health department in Minnesota.

In the U.S., national surveillance for adverse events following immunization is routinely conducted through the Vaccine Adverse Event Reporting System (*See Internet Resources*), which is managed jointly by CDC and FDA. Events that may be associated with vaccination can be reported on paper forms, by telephone, or electronically by health care providers, patients, or vaccine manufacturers. Reports of serious adverse events are followed up to collect additional information for analysis to determine whether such events are reported more frequently than expected. Signals of potential vaccine-associated events are analyzed for biological plausibility and may lead to specific epidemiological studies to further assess possible causation.

During a pandemic, it is likely that this system will be supplemented by additional surveillance and studies to rapidly evaluate the safety of vaccination program. Active surveillance for adverse events in a sample of vaccinees could be conducted by the use of self-report diary cards or by telephone interviews at specific intervals after vaccination. Existing databases can be analyzed to compare rates of medical visits and hospitalizations for persons who are vaccinated and those who are not. Databases also can be analyzed to compare rates of illness and medical care shortly after vaccination with other time periods. CDC's Vaccine Safety Datalink is a collaboration with ten managed care organizations that provides a source of data for such analyses. Clinical evaluation of adverse events – to better characterize the events and assess whether they are potentially caused by vaccine – can be done using an existing infrastructure, the Clinical Immunization Safety Assessment centers. Clinical and immunization experts at those centers implement protocols to evaluate events and assess the likelihood of a link with vaccination. Finally, existing expert committees such as the ACIP or *ad hoc* committees which could be established by the National Academy of Science's Institute of Medicine can provide independent expert review and recommendations to policy-makers.

## **VI. Influenza Vaccine Research**

The ability to achieve pandemic response goals and to vaccinate high priority persons early in the course of a pandemic is contingent on the amount of vaccine available and the speed with which it is produced. Research to improve the speed of pandemic vaccine production can be implemented during the inter-pandemic period. Developing investigational lots of vaccine against novel strains identified during the inter-pandemic period, testing the immunogenicity of different amounts of hemagglutinin antigen with and without adjuvants, and evaluating the need for one or more doses of vaccine in different populations are critical steps that should be undertaken in preparation for an influenza pandemic. *(Research activities to improve influenza vaccines are highlighted in Annex 8: Pandemic Influenza Research.)*

## **VII. Pneumococcal Vaccination**

Secondary bacterial complications of influenza infection contribute to death and illness in influenza outbreaks and pandemics. The bacterium, *Streptococcus pneumoniae*, is a leading cause of such complications, leading to pneumonia, bloodstream infections (bacteremia), and meningitis. Pneumococcal pneumonia with bacteremia has a case-fatality rate that may be as high as 30 percent in the elderly. Pneumococcal polysaccharide vaccine is recommended for persons 65 years old and older, those who have chronic underlying illnesses associated with increased risk, persons in long-term care facilities, and American Indian and Alaska Native populations. *(See Internet Resources for the ACIP recommendations for pneumococcal vaccine.)*

Epidemiological studies show vaccine effectiveness of about 50 percent to 80 percent in preventing invasive pneumococcal infections (such as bacteremia and meningitis) in the elderly. Neither controlled trials nor epidemiological investigations have shown a significant impact on pneumonia when not associated with bacteremia. Current pneumococcal vaccination coverage among recommended groups is less than 50 percent and significant racial and ethnic disparities in coverage exist. A pneumococcal conjugate vaccine was approved for use in 2000 and is recommended for young children. This vaccine has demonstrated an impact on the community as well as the individual vaccinee by decreasing transmission of infection from person-to-person. Pneumococcal and influenza vaccinations can be administered concurrently.

Continued activities to promote pneumococcal vaccination during the inter-pandemic period according to existing recommendations and consistent with Healthy People 2010 objectives will decrease the rate of influenza complications and death at the time of a pandemic. Protection following a single vaccine dose is estimated to last for 5 years or more. Given the range of response activities that will need to occur at the time of an influenza pandemic, increasing routine vaccine coverage before a pandemic occurs is a more feasible strategy than trying to implement pneumococcal vaccination as an additional intervention during a pandemic. Improving pneumococcal vaccination coverage during the inter-pandemic period also will decrease demand when a pandemic occurs and decrease the risk of a pneumococcal vaccine shortage.