Pandemic Influenza Preparedness

“Of the many health threats that we are preparing for, this is the one that we know will happen.”

Bruce G. Gellin, MD, MPH
Director, National Vaccine Program Office
Department of Health and Human Services

Influenza Epidemiology and Virology 101

- Influenza viruses change from year to year through either subtle changes to proteins on the surface of the virus (drift), more significant changes (shift) or major changes (influenza A), which can lead to pandemics.

- Previous exposure to one strain does not protect against a new one – you can catch it again.

- Influenza is very contagious, transmission occurs before symptom onset
Annual Influenza Impact

- One of the top 10 killers in the U.S.
- Annual average U.S. winter epidemics
  - 10% - 20% of US population infected
  - 200,000 hospitalizations
  - 36,000 deaths during 1990s
- >90% among the elderly
- P&I 6th or 7th leading cause of death

Influenza Vaccination – United States

Coverage Levels
Persons ≥65
Race / Ethnicity
1989-2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Doses Produced (million)</th>
<th>Doses Distributed (million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985-86</td>
<td>23.2</td>
<td>20.1</td>
</tr>
<tr>
<td>1990-91</td>
<td>32.3</td>
<td>28.3</td>
</tr>
<tr>
<td>1995-96</td>
<td>71.5</td>
<td>54.9</td>
</tr>
<tr>
<td>2000-01</td>
<td>77.9</td>
<td>70.4</td>
</tr>
<tr>
<td>2001-02</td>
<td>87.7</td>
<td>77.7</td>
</tr>
<tr>
<td>2002-03</td>
<td>95.0</td>
<td>83.0</td>
</tr>
<tr>
<td>2003-04</td>
<td>86.9</td>
<td>83.1</td>
</tr>
</tbody>
</table>
Influenza Vaccine Coverage Rates 2002-2003

TABLE 2. Influenza vaccination coverage rates among adult target* population groups — United States, National Health Interview Survey, 2002 (n = 34,044 [crude]) and 205,625,085 [weighted])

<table>
<thead>
<tr>
<th>Population group</th>
<th>Crude sample size</th>
<th>Weighted sample size</th>
<th>Influenza vaccination rate (%) (96% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All aged 50–64 years</td>
<td>6,424</td>
<td>42,945,096</td>
<td>34.0 (32.7–35.3)</td>
</tr>
<tr>
<td>Aged 50–64 years and not at high risk†</td>
<td>4,373</td>
<td>29,621,511</td>
<td>29.7 (29.2–31.1)</td>
</tr>
<tr>
<td>All aged 25+ years</td>
<td>5,757</td>
<td>32,524,874</td>
<td>65.6 (64.1–67.0)</td>
</tr>
<tr>
<td>Persons with high risk conditions‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aged 18–49 years</td>
<td>2,428</td>
<td>10,883,570</td>
<td>23.1 (21.1–25.2)</td>
</tr>
<tr>
<td>Aged 50–64 years</td>
<td>1,966</td>
<td>12,825,547</td>
<td>43.6 (41.2–46.0)</td>
</tr>
<tr>
<td>Pregnant women††</td>
<td>315</td>
<td>2,112,535</td>
<td>12.4 (9.5–15.3)</td>
</tr>
<tr>
<td>Health-care workers††</td>
<td>2,066</td>
<td>13,850,228</td>
<td>39.4 (35.9–40.9)</td>
</tr>
<tr>
<td>Household contacts of persons at high risk†‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aged 18–64 years</td>
<td>1,127</td>
<td>24,290,105</td>
<td>10.1 (10.0–10.2)</td>
</tr>
<tr>
<td>Aged 16–49 years</td>
<td>2,054</td>
<td>20,450,903</td>
<td>14.6 (14.1–15.0)</td>
</tr>
<tr>
<td>Aged 50–64 years</td>
<td>473</td>
<td>3,847,172</td>
<td>38.3 (37.7–39.9)</td>
</tr>
</tbody>
</table>

*Target groups are the populations for which influenza vaccine is specifically recommended by the Advisory Committee on Immunization Practices (ACIP).

†Persons with high risk conditions include those with chronic medical conditions, those on chronic medication, and those 6 months of age and older who are residents of nursing homes or chronic-care facilities.

‡Persons at high risk include persons who are household contacts of persons at high risk.

# Influenza Vaccine Manufacturing Timeline

- Order birds
- Receive candidate seed viruses
- Prepare high-growth reassortants
- Start 1st strain
- Start 2nd strain
- Start 3rd strain
- Monovalent concentrate production
- Vaccine formulation
- Vaccine filling
- License issued
- Vaccine distributed

CBER/CDC Manufacturing and Distribution
“...it’s conceivable, in fact, that in certain places microbial ‘perfect storms’ could occur – convergences of all the factors – and unlike meteorological perfect storms, the events would not be on the order of once-in-a-century, but frequent . . .”

Influenza Pandemics: Biological Perfect Storms

Institute of Medicine, March 2003
“Microbial Threats To Health: Emergence, Detection, and Response”
The Influenza Pandemic of 1918-1919

- 500 million people infected worldwide
- 20-40 million deaths worldwide
  - ~50% percent in people ages 20-40
- >500,000 deaths in United States
  - 196,000 in October, 1918 alone
Approximate beginning of the epidemic, 1918

Source: America's Forgotten Pandemic - The Influenza of 1918 - 1919
Virologic and Epidemiologic Criteria for a Pandemic

- Novel HA subtype
- Naïve populations
- Morbidity and mortality in humans
- Easily transmissible from person to person
Influenza Structure

8 RNA segments

Hemagglutinin

Neuraminidase

Timeline of Emergence of Influenza Viruses in Humans


H1

H2

H9 H7 H5 H5

Avian Influenza

Russian Influenza

Pandemic vaccines

Regular vaccines

Spanish Influenza

Hong Kong Influenza

**Documented Human Infection with Avian Influenza Viruses: A Timeline**

<table>
<thead>
<tr>
<th>Year</th>
<th>H5N1</th>
<th>H9N2</th>
<th>H7N7</th>
<th>H7N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Hong Kong</td>
<td>18 cases</td>
<td>Netherlands</td>
<td>84 cases</td>
</tr>
<tr>
<td></td>
<td>2 cases</td>
<td>1 death</td>
<td>Thailand and Vietnam</td>
<td>34 cases</td>
</tr>
<tr>
<td></td>
<td>6 deaths</td>
<td></td>
<td></td>
<td>2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Canada</td>
<td>2 cases</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Sporadic cases of mild human disease associated with avian influenza viruses were reported prior to 1997.

Source: WHO
Epizootic of Influenza A (H5N1) in Asia, 2003-04

- Largest epizootic of highly pathogenic avian influenza in poultry ever described
- Very complex epizootic due to back yard flocks and infection of wild birds—rapid eradication of virus impossible
- Eight countries reported poultry outbreaks
  - Over 100 million birds died or destroyed so far

Impact of Avian Influenza (1)

- Hundreds of millions of affected poultry
  - Disease and culling operations
  - >100 million birds died or destroyed
  - Inadequate compensation to farmers
    - Discourages reporting
    - Encourages hiding/smuggling of valuable birds
  - Poultry and poultry products have become a food staple, may provide 30% of total protein intake
Impact of Avian Influenza (2)

- Elimination of H5N1 in short terms unlikely
  - Large size of epizootic unprecedented in geographical scope, international spread, and economic consequences for the agricultural sector
  - Capacity to control varies significantly by country
  - Backyard flocks pose particular difficulties
    - China has 13 billion birds
    - ¾ of “farms” have < 100 birds
  - Infections in wild birds documented
  - Many factors underlying spread not understood

Avian Influenza: Implications for Human Health (1)

- 10’s to 100’s of thousands directly exposed people
- Human isolates from VN & Thailand and 1 group of VN avian isolates
  - Resistant to adamantanes
  - Sensitive to oseltamivir (Tamiflu)
Avian Influenza: Implications for Human Health (2)

- Human influenza surveillance poor or nonexistent in countries affected by poultry outbreaks
- Small number of human cases suggests virus not (currently) easily transmitted from birds to humans.
- No evidence to date of efficient human-to-human transmission
- Circulation of avian H5N1 and human H3N2 viruses increases possibility for reassortment or adaptation through mutation

Lessons from 2004-2005 influenza vaccine shortage
Lessons from 2004-2005 influenza vaccine shortage

Vendors overcharging for flu vaccine

Survey: Some distributors offer U.S. hospitals flu vaccine at up to 10 times the original price

October 13, 2004

NEW YORK (CNN/Money) - U.S. hospitals have been actively solicited by pharmaceutical distributors, who are offering the flu vaccine at vastly inflated prices, since the supply has been cut in half due to Chiron Corp.’s plant contamination problems, a survey said Wednesday.
Lessons from 2004-2005 influenza vaccine shortage

HHS Draft Pandemic Influenza Preparedness and Response Plan

News Release

FOR IMMEDIATE RELEASE
Thursday, August 26, 2004

Contact: Sarah Landry, OPHS/NVPO
(202) 580-5566

HHS Issues National Pandemic Influenza Preparedness Plan

HHS Secretary Tommy G. Thompson today unveiled the department’s draft Pandemic Influenza Response and Preparedness Plan, which outlines a coordinated national strategy to prepare for and respond to an influenza pandemic. The draft plan can be found online at [http://www.dhhs.gov/nvpo/pandemics](http://www.dhhs.gov/nvpo/pandemics) and is available for public comment for 60 days.

www.dhhs.gov/nvpo/pandemics
The U.S. Pandemic Influenza Preparedness and Response Plan

- **Core Plan**
  - Describes National coordination and decision-making
  - Provides an overview of key preparedness issues
  - Outlines response actions at national, state, & local levels

- **Annexes** (12)
  - Guidance for State/local Health Departments planning
  - Guidance for health care system planning
  - More detailed and technical information on key preparedness and response issues
    - (e.g., surveillance, vaccine development and production, vaccine and antiviral drug use strategies, strategies to decrease influenza transmission, communications, research, lessons learned from 1976 swine influenza program, comparisons between influenza and SARS)
Goals of Pandemic Influenza Response

• Decrease the burden of disease
• Minimize social disruption
• Reduce economic impacts

U.S. Impact Estimates for the Next Influenza Pandemic

Deaths: 89-207,000
Hospitalizations: 314-733,000
Outpatient care: 18-42 m
Total infected: 43-100 m

Absent vaccination, health related economic impacts = $71 to $166 billion

Meltzer, Emerg Infect Dis J 1999
Purposes of the Pandemic Influenza Preparedness and Response Plan

- Define and recommend preparedness activities
- Describe roles, responsibilities and actions of federal coordination of response
  - International
  - State and local levels
- Guide health departments and health care system in developing state and local preparedness and response plans
- Provide technical information on which preparedness and response are based
Public Health Preparedness and Pandemic Influenza Preparedness

• State and local health departments
  – Majority of States have or are developing plans
  – Tabletop exercises are being developed
  – CDC support
    • Synergy with BT/other preparedness planning
    • Support for surveillance and public health laboratories
• Health care system
  – Synergies with other response plans
  – Need for influenza-specific planning and education
  – HRSA hospital preparedness program
• FY’04: Encouragement of integrated planning

Critical Components of a Pandemic Response

• Detect the pandemic strain through surveillance
• Develop and license vaccine against the pandemic strain
• Produce sufficient vaccine for the US population
• Rapidly and equitably deliver vaccine to target groups
• Provide antiviral medications for therapy and prophylaxis
• Implement measures to decrease disease spread
• Effectively coordinate international, federal & state activities
• Assure quality medical care & provide community services
• Effectively communicate with community leaders, medical providers, the public and the media
Pandemic Phases
(WHO, 1999)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Inter-pandemic Phase</td>
<td>0</td>
<td>Epidemic influenza viruses circulate in human populations causing yearly outbreaks; no evidence that a novel influenza virus has infected humans</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Novel Virus Alert: Identification of a novel influenza virus in a person</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Confirmation that the novel influenza virus has infected two or more people, but the ability of the virus to spread rapidly person-to-person and cause multiple outbreaks of disease leading to epidemics remains questionable.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Pandemic Alert: Confirmation of person-to-person spread in the general population with at least one outbreak lasting for more than 2 weeks in one country</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Confirmation that the novel influenza virus is causing several outbreaks in one country and has spread to other countries, with consistent disease patterns indicating serious morbidity and mortality is likely in at least one segment of the population</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Outbreaks and epidemics are occurring in multiple countries and spreading across the world</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>End of the first wave of the pandemic</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Confirmation of a second or later wave caused by the same novel virus strain</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Confirmation that the pandemic has ended</td>
</tr>
</tbody>
</table>

Vaccine Purchase and Distribution: Potential for Changes Over Time

Vaccine available

- Current
- Increased public
- All public

Timeline and waves of pandemic disease

First wave

Second wave

**Note:** This is presented as an illustration and not to endorse as a preferred option
Vaccine and Vaccination Preparedness Goals

• Shorten timelines to availability
• Assure year-round production and surge capacity (egg supply and availability)
• Increase and diversify U.S. manufacturing capacity (cell culture methodology)
• Develop and test investigational lots of pandemic-like vaccine strains
• Clarify potential role of live attenuated influenza virus vaccine
• Ensure effective distribution & administration to achieve pandemic response goals

Priority Groups for Pandemic Vaccine

• Definition of priority groups based on pandemic response goals:
  – **Reduce health impacts** – Maintain quality healthcare system & protect those at highest risk
  – **Reduce social and economic impacts** – Maintain essential community services

• Defining priority groups:
  – National guidance vs. state-by-state decisions
  – Definition of target groups at State/local levels
    • (e.g., Who provides essential community services?)
Expanding Vaccine Supply from Existing Production Capacity

• Vaccine administration strategies
  – Syringes that decrease waste from multi-dose vials
  – Intradermal injection

• Immune enhancement strategies
  – Adjuvanted vaccines
  – Other immune stimulant approaches

• Manufacturing process improvements to increase yields

Estimated Pandemic Influenza Vaccine Supply and Need

Assumes monovalent vaccine, 15 ug/dose, 2-doses needed for protection, entire population susceptible, and production capacity 125% annual supply
U.S. Actions to Achieve Pandemic Influenza Vaccine Security -- 2004

- Assure year-round egg supply for U.S.-based production
- Provide industry incentives to expand and diversify U.S.-based influenza vaccine production
- Influenza vaccine industry study (PRTM)
- Produce annual lots of pandemic-like vaccine
- Produce H5N1 vaccine
  - Conduct clinical trials
  - Commercial scale production/stockpile 2 M doses

Interventions to Decrease Disease Spread in an Influenza Pandemic

- Health care system interventions
  - Infection control and isolation of patients in hospitals
  - Vaccination/antiviral prophylaxis of HCWs and in LCTF
- Community interventions
  - Travel advisories and precautions and protocols
  - Screening travelers from areas with disease
  - Quarantine of exposed persons

...based on the epidemiology & transmission of infection
Interventions to Decrease Influenza Spread

• Objectives
  – Contain clusters of human disease caused by strains not well transmitted between people
  – Slow spread of strains that are more effectively transmitted buying time for specific preventive measures (e.g., vaccine)

• Control strategies in avian influenza outbreaks
  – Cull infected flocks
  – Prevent reassortment with human strains by protecting exposed persons with vaccine and antiviral chemoprophylaxis

State & Local Preparedness

• State and local health departments
  – Synergy with BT/other preparedness planning
  – CDC support for surveillance and public health laboratories
  – Tabletop and field exercises

• Health care system
  – Need for planning and education and coordination with state/local health departments
  – HRSA grants to coordinate medical care and enhance capacity
Recent Developments Affecting Pandemic Influenza Planning

- Increased focus on influenza & other threats
  - Experience from 2003-04 influenza season
  - Global spread of SARS

- Improved infrastructures and technologies
  - Expanded influenza surveillance infrastructure
  - Improved vaccine development technologies
  - New antiviral medications
  - New communications systems
  - BT and other emergency preparedness activities

Public Health Preparedness and Pandemic Influenza Preparedness

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- Health care system
  - Synergies with other response plans
  - Need for influenza-specific planning and education
  - HRSA hospital preparedness program

- FY’04: Encouragement of integrated planning
Pandemic Influenza: Research Priorities

- Improve understanding of influenza molecular biology, emergence of new strains, and viral transmission characteristics
- Develop new antiviral drugs and vaccines
- Improve understanding of ecology and spread of influenza in animals; animal-human interface
- Improve antigen detection tests for patients and develop tests to rapidly detect new subtypes
- Improve timeliness, yield, and immunogenicity of influenza vaccines
- Communication/Risk communication

Public Health: More than a One-Shot Deal

A one-shot infusion of money or a single focus on stockpiling drugs and vaccines is not enough to protect Americans from biological and chemical threats, let alone diseases like asthma and cancer. Congress and the Administration must also make a long-term commitment to strengthen the fundamentals of our public health system:

- More and better-trained public health professionals
- A state-of-the-art early warning system and communications network
- Better-equipped laboratories
- And tracking of diseases and monitoring of environmental exposures.

Long neglected, America’s public health system is vital to our defense against biological and chemical attacks, as well as on-going serious health concerns such as asthma and cancer, and the unforeseen emergencies of tomorrow. We cannot afford to do less.