Harvard Medical School Health Policy Education Initiative
The Tosteson Health Policy Lecture Series

ISSUE BRIEF – PANDEMIC FLU

The "flu" is an acute respiratory illness which presents with abrupt onset of systemic and respiratory symptoms. It is caused by infection with the influenza virus, a single-stranded RNA virus. Virus strains possess variable abilities to infect different animals, such that viruses infecting humans are referred to as "human flu", while those infecting birds are referred to as "avian flu".

The flu can become pandemic when novel strains of influenza arise that

A) express antigens which humans have not developed immunity against (either through vaccination or previous exposure), and
B) are capable of causing disease and being effectively transmitted to and among humans.

Why seasonal flu outbreaks occur	**Influenza A virus and pandemic flu**
Influenza virus antigens continually evolve into new variants through mutation, bypassing immune system recognition.	The most extensive and severe outbreaks of flu are caused by the influenza A virus and can affect even young, healthy adults.
▪ Each flu season leads to over 30,000 US deaths and over 200,000 hospitalizations ▪ Mostly among those over 85 or with serious comorbid conditions (COPD, heart failure) ▪ Vaccines are produced against the strains estimated as most likely to spread	▪ 1918 Spanish flu: 500,000 US deaths (40 million worldwide) ▪ 1957 Asian flu: 70,000 US deaths ▪ 1968 Hong Kong flu: 30,000 US deaths ▪ Death can occur due to necrotizing, hemorrhagic pneumonia

The Bush administration proposal: $7.1 billion in emergency funding

- $2.8 billion to develop cell-based techniques for vaccine manufacture – currently, flu vaccines are grown in eggs
- $1.5 billion to buy enough existing and new vaccines, such as an experimental H5N1 human vaccine being developed, for 20 million people by 2009
- $1 billion to stockpile existing antiviral therapies, like the neuraminidase inhibitors Tamiflu and Relenza, to treat 25% of the US population
- $644 million for national and state pandemic flu preparedness
- $251 million to help other countries detect and contain outbreaks

Source: *Pandemic or Not, Experts Welcome Bush Plan*, Science: 310, November 11 2005

Suggested benefits of the proposal:	Critiques:
▪ Provides significant support for national preparation against the possibility of pandemic flu ▪ Stimulates development of better vaccines and technology, which will also aid with seasonal flu ▪ Cell-based vaccine manufacturing will allow quicker vaccine development	▪ Vaccine developed for current H5N1 strain may not be effective for mutated pandemic strain ▪ Shields vaccine makers from lawsuits to further encourage vaccine development ▪ Does not provide enough support for state preparation plans ▪ Narrow focus on developing vaccines to H5N1, at risk of neglecting other strains

H5N1 avian flu and recent news

Influenza A viruses are classified into subtypes by their particular hemagluttanin (H) and neuraminidase (N) gene segments. H5N1 is a strain of avian influenza virus with the H5 hemagluttanin gene and N1 neuraminidase gene, which some fear may evolve and become capable of a pandemic.

As of June 2005, the World Health Organization reported 108 cases of human infection by the H5N1 avian influenza virus, with 54 deaths (50% mortality). This is lower than the 2% mortality of the 1918 pandemic, which killed millions. Most experts agree that H5N1 avian flu has not acquired the ability to be effectively transmitted from human to human, although these sporadic cases of animal-human transmission exist. China recently launched a plan to vaccinate over 14 billion poultry against the H5N1 strain of avian influenza.

How a pandemic influenza strain arises: two mechanisms

1) Exchange between avian and human flu viruses → novel human flu

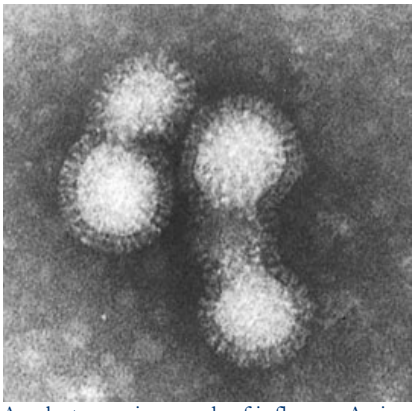
The influenza A virus has a segmented genome composed of 8 single RNA strands. These RNA strands encode different viral antigens and can be exchanged by different strains of virus, if multiple strains are present in the same host – this is known as reassortment. Billions of pigs and fowl in Asia carry influenza viruses and serve as host reservoirs where reassortment can take place.

In the 1957 and 1968 pandemics, human influenza strains infecting animals acquired genetic segments from avian viruses, resulting in antigen variations to which humans had not acquired immunity.

2) Avian flu → novel human flu

In the 1918 pandemic, an avian influenza virus strain acquired multiple mutations over time to become virulent and transmissible in humans.

This mechanism was suggested by the recent reconstruction of the 1918 virus by US scientists, in which all 8 RNA strands showed greater similarity to strains of avian influenza than human influenza.



An electron micrograph of influenza A virus (x140,000)
Source: Harrison's Online

What therapies exist for the flu?

Oseltamivir (Tamiflu) and ranamivir (Relenza) – inhibit viral neuraminidase, preventing spread of virus within the host
Amantadine and rimantadine – inhibit viral uncoating inside an infected cell, preventing replication of the viral genome

Amantadine and rimantadine are effective against some strains of influenza A virus, and there is some evidence that H5N1 has developed resistance. The neuroaminidase inhibitors are effective against all influenza strains.

For more information

1. National Institute of Allergy and Infectious Disease - www3.niaid.nih.gov/news/focuson/flu/default.htm
2. Centers for Disease Control and Prevention – www.cdc.gov/flu/pandemic/
3. The Official US Pandemic Flu website - www.pandemicflu.gov/
4. World Health Organization Avian Flu - www.who.int/csr/disease/avian_influenza/en/index.html
5. Belshe RB. The Origins of Pandemic Influenza – Lessons from the 1918 Virus. NEJM 2005. Vol 353; 21: 2209-11.
6. Pandemic or Not, Experts Welcome Bush Flu Plan. Science 2005. Vol 310: 952-3.
7. Moscona A. Neuroaminidase Inhibitors For Influenza. NEJM 2005. Vol 353; 13: 1363-73.
8. Avian flu special: Is this our best shot? Nature 2005. Vol 435: 404-6.

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