



Slide 1

*“What do I need to know about this ‘bird flu’ that everyone is talking about?”*

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Last updated 03/12/07



People seem to have a lot of questions about the “bird flu.” So, I’ve developed this talk as a series of questions based on the issues that often arise during discussions on the topic. The speaker notes are extensive, and the speaker should not feel obligated to discuss content from the notes beyond what is referred to on the slides. However, the information is there to help the speaker field questions and to enrich the lecture if time allows.

Slide 2

What are the goals of the “talk?”

- Define “the flu.”
- Explain how influenza spreads
- Discuss epidemics vs pandemics
- Describe “bird flu”
- Share strategies to deal with influenza pandemics





Slide 3

What is ‘the flu’?

**Answer:** *An illness caused by influenza virus*

- A sudden onset respiratory illness accompanied by fever
- Flu causes yearly epidemics worldwide
- **NOT** the nausea/vomiting/diarrhea that people call “the stomach flu.”






Slide 4

Are there different types of flu?

**Answer: Yes!**




- Type A— moderate to severe illness
  - All age groups; many animals
- Type B— milder than A
  - Humans only; mainly children
- Type C— rarely reported in humans
  - No epidemics



Slide 5

Time out, coach! How are viruses different from other germs?

- Much smaller than animal cells or bacteria
- Viruses need to get a life!
  - Need to be inside our cells to live
- Our cells become virus factories
- Influenza virus kills cells in breathing passages



Typically, viruses are much smaller than most infectious agents. Viruses generally can't be visualized at all with ordinary light microscopes. How many times has your teenager told you to, "Get a Life!" Well now it's my time to say it about viruses...viruses need to get a life, literally! They are unable to carry out independent metabolism. Most living things including bacteria, reproduce by cell division but not viruses! They don't divide in order to reproduce. In fact they can only reproduce once they are inside living host cells. We have all heard about all the research on nanotechnology. One of the goals of nanotechnology is to create submicroscopic machines. Viruses are a model and testament to Nature's nanotechnology skills. They are essentially little "machines" that go about producing more little machines. Essentially, viruses turn host cells into virus factories. Once a virus is inside a cell it goes about creating lots and lots of viral parts. Once they are made the parts self-assemble into mature virus particles. These mature copies of the original virus are then released and are free to infect other cells. What are the potential outcomes? Productive viral infections can cause cell death. The body's immune response can eliminate the virus. Some viruses (e.g. herpes) can persist inside certain cells for life,

although this is not the case for influenza virus. In influenza, destruction of cells lining the respiratory tract and the related inflammation are responsible for the disease symptoms.

## Slide 6

What does an influenza virus look like?




Fig.1 Electron micrograph

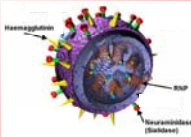


Fig.2 Schematic of influenza virus

- **Hemagglutinin protein**
  - Allows virus to stick to cells of some animals and not others
- **Neuraminidase protein**
  - Helps release new virus from cells
- **Genes (RNP) divided into 8 parts**
  - Allows 2 viruses to mix and match genes

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In the upper left is a picture from an electron microscope of an influenza virus. You'll notice the projections from the edge of the virus. These represent the neuraminidase and hemagglutinin proteins on the viral surface. There are three things I want you to remember from this slide. First, the hemagglutinin protein represented as yellow spikes in the schematic picture allows influenza virus to stick to cells by binding to a specific receptor. Second, the neuraminidase protein helps newly formed viral particles get released from the cell surface so that they have the potential to infect other cells. Third, the genetic material of the influenza virus (RNP= ribonucleoprotein; complex of protein and RNA) is divided amongst 8 separate segments as shown by the orange coils in the picture. Many infectious agents have their genetic material arranged in a single ribbon or circle. However, imagine what might happen if two different influenza viruses infected the same cell. The resultant self-assembling progeny viruses might contain some genetic material from each virus resulting in a hybrid virus. This has importance later when we talk about the occurrence of pandemics.

Slide 7

Why are the “H” and “N” numbered?

**Answer:** They stand for different hemagglutinins (“H”) and neuraminidases (“N”)

- Used to subtype influenza A strains
  - 16 different H’s
  - 9 different N’s
- Current human subtypes
  - A(H1N1) and A(H3N2) primarily
- Antibodies against H’s and N’s made by our immune system protect us
- H and N subtypes are basis for flu vaccines




The numbered H and N designations are used to describe various subtypes on influenza A but not B or C. There are 16 different hemagglutinins and 9 different neuraminidase subtypes. Thus there are very many possible combinations. Even within the same hemagglutinin or neuraminidase subtypes there are variations due to mutations. So, the H1N1 virus that circulated in a previous year might not be the same as H1N1 subtypes in subsequent years. It turns out that our immune systems make antibodies against H and N components (AKA antigens) of influenza virus when we become infected. Moreover, these antibodies protect us from getting reinfected by the same virus. So, various H and N viral components are included in flu vaccines. These components induce the immune system to make protective antibodies without the requirement of suffering through an actual bout of the flu. Unfortunately, there are slight changes in the H and N components of circulating influenza viruses in the the community each flu season. The antibodies from a previous infection or vaccination may not be able to recognize these changed viruses as well, and we may only have some partial protection. That is why we have to get a new flu vaccine each year. As you are probably well aware, H5N1 is the designation of the avian influenza strain that is circulating widely in birds and has caused many human deaths.

## Slide 8

What are the symptoms of influenza?

- Sudden fever, muscle aches, headache, lack of energy, dry cough, sore throat, runny nose
- Fever and body aches last 3 to 5 days
- Cough and lack of energy— 2 weeks
- Symptoms similar to other respiratory infections
- Supportive care (avoid aspirin)
  - Rest, fluids, anti-cough & anti-fever meds
  - Antivirals if symptoms for < 48 hours



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Influenza is characterized by the relatively sudden onset of fever, muscle aches, headache, lack of energy, dry cough, sore throat, and runny nose. The fever and body aches last 3 to 5 days. However, the cough and lack of energy may persist for 2 weeks. The symptoms of influenza are similar to other respiratory infections such as RSV (respiratory syncytial virus), rhinovirus, parainfluenza virus, and other infectious agents. You may recall that lung infection with anthrax or plague might start out similar to influenza. Treatment is mostly supportive with rest, fluids, cough medicine, and antipyretics such as Tylenol. Aspirin should be avoided as it is associated with a rare severe complication called Reye Syndrome.

**ANTIVIRALS:** When administered within 2 days of illness onset to otherwise healthy adults, amantadine and rimantadine can reduce the duration of uncomplicated influenza A illness, and zanamivir (Relenza) and oseltamivir (Tamiflu) can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day, compared with placebo. Benefit is greater if started sooner. For example, oseltamivir given less than 12 hours after the onset of illness resulted in a median decrease in the length of illness by 74.6 hours. Amantadine, rimantadine, are approved for prevention of influenza A (70-90% effective), and Oseltamivir approved for both A and B (82% effective). Amantadine and rimantadine are cheaper with the average wholesale price of \$5 to \$10 for a 5 day course compared to \$38 to \$57 for 5 day course of oseltamivir or zanamivir, respectively. Who should be considered for prophylaxis (excerpt from CDC website follows in bold)?

**Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun. Persons at high risk for complications of influenza still can be**

vaccinated after an outbreak of influenza has begun in a community. However, development of antibodies in adults after vaccination takes approximately 2 weeks). When influenza vaccine is administered while influenza viruses are circulating, chemoprophylaxis should be considered for persons at high risk during the time from vaccination until immunity has developed.

Children aged <9 years who receive influenza vaccine for the first time can require 6 weeks of prophylaxis (i.e., prophylaxis for 4 weeks after the first dose of vaccine and an additional 2 weeks of prophylaxis after the second dose).

**Persons Who Provide Care to Those at High Risk.** To reduce the spread of virus to persons at high risk during community or institutional outbreaks, chemoprophylaxis during peak influenza activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. Persons with frequent contact include employees of hospitals, clinics, and chronic-care facilities, household members, visiting nurses, and volunteer workers. If an outbreak is caused by a variant strain of influenza that might not be controlled by the vaccine, chemoprophylaxis should be considered for all such persons, regardless of their vaccination status.

**Persons Who Have Immune Deficiencies.** Chemoprophylaxis can be considered for persons at high risk who are expected to have an inadequate antibody response to influenza vaccine. This category includes persons infected with HIV, chiefly those with advanced HIV disease. No published data are available concerning possible efficacy of chemoprophylaxis among persons with HIV infection or interactions with other drugs used to manage HIV infection. Such patients should


**be monitored closely if chemoprophylaxis is administered. Other Persons. Chemoprophylaxis throughout the influenza season or during peak influenza activity might be appropriate for persons at high risk who should not be vaccinated. Chemoprophylaxis can also be offered to persons who wish to avoid influenza illness. Health-care providers and patients should make this decision on an individual basis.**

Slide 9

How is influenza spread?

**Answer:** *Very quickly due to short incubation!*

- 2 days after you catch the virus, you feel sick
- Infected people shed virus; make others sick
  - Shedding can begin 1 day BEFORE you feel sick
  - Peak shedding first 3 days of illness
  - Subsides by 5-7 days
    - Can be 10+ days in children




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The usual incubation period between the time someone is exposed and infected with influenza virus to the time that they experience symptoms of illness is about 2 days. Unfortunately, viral shedding can actually begin up to a day before the onset of symptoms. Peak shedding of virus generally occurs during the first 3 days of illness and correlates with the presence of fever. The amount of virus shed influences how infectious a sick individual is to those around him/her. In other words, it determines transmissibility. The viral shedding is influenced by the host immune system and the particular strain of virus. That is why I chose to show the multiplicative domino effect image. The transmissibility has a great deal to do with the occurrence of epidemics and pandemics.

Slide 10

Is flu only spread through the air?

**Answer:** *Mainly spread by large droplets in air.*



- **Large droplet mostly**
  - Generated by coughing, sneezing, talking
  - “spitting distance”
- **Contact with contaminated hands or surfaces, sometimes**
- **Microscopic droplets less common**

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There is not a lot of detailed experimental data to tease out the answer to this question. However, there is evidence that influenza can spread by contact with virus on surfaces as well as through the air. Droplet spread refers to large droplets expelled by coughing, sneezing or talking as shown in the picture. These particles generally settle out of the air within 3 to 6 feet from their origin...generally within “spitting distance.” This is felt to be the most common means by which influenza spreads. So most people who catch influenza get it from an infected person within “spitting distance.” Droplet nuclei are much smaller microscopic droplets that stay suspended in the air for a much longer time and can travel on air currents for longer distances infecting people beyond “spitting distance.” Tuberculosis commonly spreads this way, but this is a less important means by which influenza spreads compared to large droplet spread.

Slide 11

What is the difference between an epidemic and pandemic?

**Answer:** *They primarily differ in scope and the mechanisms by which they occur.*

- Epidemics occur every year due to **minor** changes in influenza A viruses that circulate
  - Same H and N as previous years
- Pandemics happen only occasionally when a completely new influenza A virus circulates
  - **DIFFERENT** H and/or N from previous years

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Influenza epidemics and pandemics differ primarily in scope and the mechanisms by which they occur. Epidemics occur every year due to minor changes (AKA mutations) in the influenza viruses that circulate. This results in an upswing of cases over about 6 weeks in a given community with an associated increase in hospitalizations and deaths. By contrast, pandemics happen only occasionally when a completely new influenza virus starts to circulate resulting in a really large worldwide epidemic often with multiple waves of illness. Pandemics result in more severe illnesses and more deaths than usual...especially if both the H and N components are novel. There were 3 pandemics in the last century.

Slide 12



How do yearly epidemics occur?

**Answer:** A process called *antigenic DRIFT*.

- Imperfect “manufacturing” of virus
  - Small changes in H and N
  - Partial immunity in population
    - Incomplete protection; still get sick
    - Need new flu vaccine every year

**Mutation**  
H3N2 → H3N2

Immune System:  
“Do I know you?  
You look vaguely familiar!”





Yearly epidemics occur because of a process called antigenic drift. The viral H and N components are sometimes called antigens by scientists. Because of imperfect manufacturing, in other words genetic mutations, of progeny viruses in the “cellular factory,” small changes occur in the hemagglutinin and/or neuraminidase of circulating strains. These changes can prevent the antibodies generated by the body’s immune system, either from past infection or vaccination, from efficiently neutralizing the virus. In that setting, reinfection with a mutant virus can occur. Antigenic drift is the reason that 1 or 2 of the three virus strains in the vaccine are updated every year based on what’s been circulating around the world. This necessitates the creation of a new flu vaccine every year.

Slide 13

What are the consequences of yearly epidemics in U.S.A?

- > 36,000 die and 200,000 are hospitalized
- 5 to 20% of general population infected
- Nursing home attack rates of up to 60%
- 85% of flu-related deaths in ages > 65
- Over \$10 billion lost



On average, in the United States, there are 36,000 deaths and 200,000 hospitalizations every year due to influenza and its related complications. Each flu season a range of 5 to 20% of the general population comes down with the flu. Nursing home attack rates can be quite a bit higher, e.g., up to 60%. Over 85% of influenza deaths occur in people over age 65. It is estimated that influenza costs more than \$10 billion in lost productivity and direct medical costs every year.

Slide 14

What drives the occurrence of a pandemic?

**Answer:**  
Instead of antigenic *DRIFT* occurring, an antigenic...

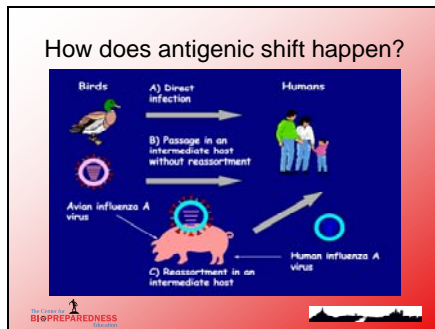
**SHIFT** **H5N1**

...happens.

Immune System:  
"Oh my gosh... I don't know you at all!"

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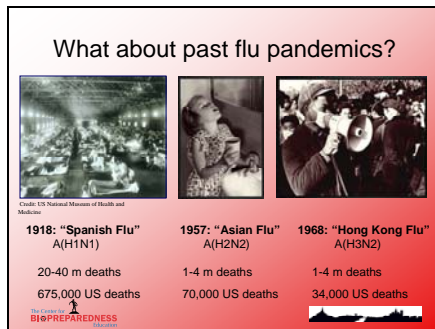
Slide 15



Antigenic shift refers to the emergence of a new H and/or N influenza subtype that circulates through a population. This can happen in three different ways. The most simple way is for an avian subtype to directly infect humans. If this subtype has the ability to spread person to person it may circulate widely in pandemic fashion. This type of event seemed to occur in the 1918 Spanish Flu pandemic. As it turns out, this may have been misnamed, as there is some evidence that this jump may have occurred in Kansas. A second way for antigenic shift to occur is for an avian influenza strain to pass through an intermediate host, such as a pig, on its way to infecting humans. As it replicates in the intermediate host, mutations may occur that facilitate spread to humans even though no reassortment of genetic material from human influenza strains has occurred. The third mechanism that results in antigenic shift involves the formation of a new hybrid virus in an intermediate host. The general scenario in this example is coinfection of a pig with avian and human influenza viruses. Due to the 8 segments of genetic material in each virus, resultant progeny viruses are hybrids of bird and human viruses containing some genetic material from each original strain. These hybrid viruses may be well-

adapted to growth in human cells yet have new H and N subtypes that lead to extensive pandemic spread due to the lack of population immunity to those new subtypes. This latter scenario appears to be the mechanism by which the Asian flu and Hong Kong flu pandemics emerged.

Slide 16

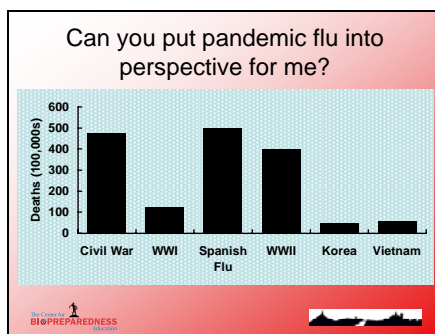


As you can see, the Spanish Flu in 1918 was the most severe of the three pandemics resulting in 20 to 40 million deaths worldwide and 675,000 U.S. deaths. The Asian Flu pandemic resulted in double the usual number of flu season deaths in the US. The Hong Kong Flu pandemic was relatively mild by comparison.

Slide images and figures from online slide set of Barbara Wallace, New York State Department of Health 2005.

Interestingly, the little girl in the picture is gargling, which was a commonly advocated defense against the flu during that period of time.

Slide 17



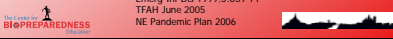
To put the Spanish Flu into perspective, one can see from this graph that it resulted in more deaths than many major military conflicts.

Slide 18

What consequences might result from a pandemic, now?

- Infected: 90 million US, >500,000 NE
  - Based on 30% attack rate
- Hospitalized: 865,000 to 9.9 million US
  - (NE Range 4,928 to 56,472)
- Deaths 209,000 to 1.9 million US
  - (NE Range 1,181 to 10,832)
- \$71-166 billion would be lost
- Serious social and economic disruption

Emerg. Inf. Dis. 1999;5:659-71  
TFAH June 2005  
NE Pandemic Plan 2006



Influenza pandemics are different from many of the threats for which public health and the health-care system are currently planning:

The pandemic will last much longer than most other emergency events and may include “waves” of influenza activity separated by months (in 20th century pandemics, a second wave of influenza activity occurred 3 to 12 months after the first wave).

The numbers of health-care workers and first responders available to work can be expected to be reduced; they will be at high risk of illness through exposure in the community and in health-care settings, and some may have to miss work to care for ill family members. It is reasonable to assume that absenteeism may exceed 25%. Resources in many locations could be limited because of how widespread an influenza pandemic would be.

Based on extrapolation from past pandemics in the United States, the U.S. Department of Health and Human Services (US DHHS) has estimated the number of people who may become ill and require various levels of health care. The estimates are based on a 30% attack rate (percentage of the population that becomes ill) and an assumption that 50% of people with illness will seek care. National data is reproduced from the PandemicFlu.gov website (<http://pandemicflu.gov/plan/pandplan.html>).

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. Planning should include the more severe scenario.

Risk groups for severe and fatal infection cannot be predicted with certainty but are likely to include infants, the elderly, pregnant women,

and persons with chronic medical conditions. 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.



The percentages used for the national estimates were applied directly to the Nebraska population to estimate the impact on Nebraska. This method is limited by the fact that the population profile of Nebraska is not exactly the same as for the entire country. However because of the many uncertainties and assumptions that factor into these estimates, they will provide a sense of what could possibly happen during a pandemic. These are not meant to attempt to predict what will happen. Rather, they are intended to be taken into consideration by pandemic influenza planners.

Slide 19

**What is “bird flu?”**

**Answer:** *Currently, the term refers primarily to avian influenza A strain H5N1.*

- Wild birds carry all known influenza A subtypes
- Recognized in Hong Kong '97
  - 1.5 million birds culled in 3 days
- Has spread throughout Asia & more recently to the Middle East, Africa, and some European countries.



Currently, the term bird flu refers primarily to avian influenza A strain H5N1. However, wild birds are actually reservoirs for all known influenza subtypes. So any influenza A strain has the capacity to be a “bird flu.” Birds tend to carry a large viral burden in their intestines and shed the virus in their saliva, nasal secretions, and feces for up to several weeks. The H5N1 strain was first recognized in Hong Kong in 1997. Over 1.5 million birds were purposely killed or culled in an effort to stop the outbreak.

Unfortunately, H5N1 has spread widely through migratory birds and into domestic poultry. As of 8/16/06, avian influenza (H5N1) has been found in domestic or wild birds in the following countries:

Afghanistan, albania, Austria, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Burkina Faso, Cambodia, Cameroon, China, Cote d’Ivoire,


Croatia, Czech Republic, Denmark, Djibouti, Egypt, France, Georgia, Germany, Greece, Hong Kong, Hungary, Kazakhstan, India, Indonesia, Iraq, Iran, Israel, Italy, Japan, Jordan, Kazakhstan, Korea, Laos, Malaysia, Mongolia, Myanmar, Niger, Nigeria, Palestinian Autonomous territories, Pakistan, Phillipines, Poland, Romania, Russia, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sudan, Sweden, Switzerland, Thailand, Turkey, Ukraine, United Kingdom, Vietnam, Zimbabwe.

Slide 20

How does "bird flu" affect birds?

**Answer:** Ranges from asymptomatic to fatal.

- Wild birds carry it, but usually don't get sick
- Domestic birds often suffer fatal infections
  - Current H5N1 outbreak most severe ever
  - Hundreds of millions of birds killed/culled
- Other animals can catch it (hosts expanding)
  - Pigs, horses, sea mammals
  - Recent spread to cats, leopards tigers



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Divided into high pathogenicity avian influenza (HPAI; >75% mortality) & low pathogenicity (LPAI)

For birds, the most virulent influenza strains are H5 or H7 subtypes. Aquatic birds (ducks, shorebirds, gulls) are considered to be the natural reservoirs of avian influenza. They generally don't develop significant illness from it. However, recent reports in 2005 of wild bird deaths suggests the virus may be developing increasing virulence. By contrast, when avian influenza enters domestic bird flocks, high numbers of fatal infections occur sometimes approaching 100%. The current H5N1 outbreak in Asia is the most severe ever detected. Hundreds of millions of birds have died or were culled as a result of the outbreak. Although avian influenza strains commonly also infect pigs, horses, sea mammals, and the weasel family, the current H5N1 strain has recently expanded its host range into cats, leopards, and tigers. A useful analogy is to think of the hemagglutinin binding to the neuraminic acid receptor like a key in a lock. Neuraminic acid receptors vary somewhat in different cells and different species of animal. If the hemagglutinin "key" mutates so that it fits in more neuraminic acid "locks" it starts to resemble a pass key with broader host ranges. This could eventually lead to enhanced

transmissibility in humans. There are some additional red flags of which to make note (**The following is excerpted directly from the avian influenza section of the IDSA website**):

**A report from the Food and Agricultural Organization of the United Nations (FAO) published in September 2004 indicates that H5 avian influenza viruses have become endemic in parts of Southeast Asia and that existing reservoirs in ducks, wild birds, and potentially pigs "pose a serious challenge to eradication". Other alarming features of H5N1 include the following.**

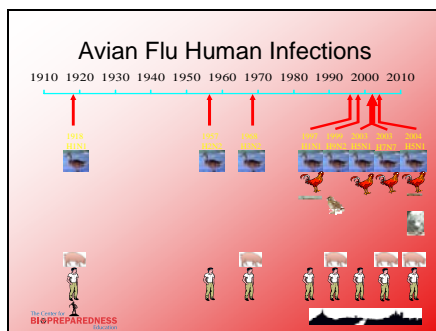
Studies comparing virus samples over time indicate that the virus has become progressively more pathogenic for poultry.

The current strain of the virus is now able to survive several days longer in the environment compared with when it first emerged.

The virus appears to be expanding its mammalian host range, as indicated above.

The virus has been found increasingly in dead migratory birds (which are usually not clinically affected by HPAI viruses); this supports the growing virulence of the current virus.

Slide 21



As this timeline illustrates, the incidence of avian strains infecting other animals and humans appears to be accelerating and the number of hosts affected seems to be increasing.

How does “bird flu” affect humans?

*Answer: There have been 278 human cases of H5N1 flu with 168 deaths as of 03/12/07.*

- Vietnam 93, Indonesia, Thailand, China, Turkey, Cambodia, Iraq, Azerbaijan, Egypt, Djibouti, Lao People’s Democratic Republic, Nigeria
- No sustained person-to-person transmission
- Most have severe viral pneumonia (lung infection)
- Unusual symptoms in patients from Vietnam (10 cases, 8 deaths)
  - Lacked sore throat, runny nose
  - 3 reported coughing up bloody phlegm
  - 7 with diarrhea

FOR UPDATES [http://www.who.int/csr/disease/avian\\_influenza/country/en/](http://www.who.int/csr/disease/avian_influenza/country/en/)

WHO  
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Infection of humans with “bird flu” has been limited to 278 cases as of 03/12/07. However, 168 of these individuals died of their infection. 93 of the cases were in Vietnam. Additional cases have been seen in Indonesia, Thailand, China, Turkey, Cambodia, Iraq, Azerbaijan, Egypt, Djibouti, Lao People’s Democratic Republic, and Nigeria. Updates for these statistics are available in table form at the WHO website:


[http://www.who.int/csr/disease/avian\\_influenza/country/en/](http://www.who.int/csr/disease/avian_influenza/country/en/)

So far there has been no sustained person-to-person transmission. However, in Thailand a child spread the infection to their mother and aunt via very close contact. This strain was not genetically different from the other bird flu isolates. Symptoms and signs of avian influenza infections were a little different than usual human influenza. The majority did not have a sore throat, nasal congestion, or eye inflammation which often is seen in influenza. 3 individuals reported coughing up bloody phlegm. This is unusual for influenza though it was described in the 1918 pandemic. 7 individuals reported diarrhea suggesting that the virus also replicates well in the intestinal tract of humans. Although gastrointestinal symptoms are sometimes reported with human influenza (more commonly in children), these complaints do not occur in a majority of cases. Lastly, these individuals tended to have low numbers of lymphocytes and platelets on complete blood count testing.

Slide 23

What is required for a pandemic to occur?

- **Answer:** A new virus with person-to-person spread.
- ✓ Novel virus to which population has little or no immunity
- ✓ Virus that causes severe illness in humans
- Virus must be capable of sustained person-to-person transmission




No one knows if H5N1 will be the subtype to emerge as a pandemic influenza virus, but it has several characteristics which suggest that it could. For a pandemic to occur, a new virus must emerge to which the population has little or no immunity. The virus must be pathogenic and virulent in humans. Lastly, the virus must be capable of sustained person-to-person transmission. H5N1 has met the first two criteria, but so far there has not been any sustained person-to-person transmission.

Slide 24

Can bird flu be treated?

- **Answer:** Possibly. We only have lab tests and animal experiments to rely on right now.
- Current strain resistant to older drugs
  - Amantadine and rimantadine
- Sensitive to "N" inhibitors
  - Oseltamivir (Tamiflu®)–
    - capsules and oral liquid
  - Zanamivir (Relenza®)–
    - Inhaled powder



It is possible that antiviral drugs can be used to treat avian influenza A H5N1. However, we only have laboratory tests and animal experiments on which to rely right now. The H5N1 strain infecting birds and a limited number of humans is resistant to some older influenza drugs, amantadine and rimantadine. Note that more than 90% of seasonal influenza A strains circulating in U.S. during the 2005-2006 flu season are also resistant to amantadine and rimantadine. CDC recommended in mid-January that these drugs not be used for the remainder of the 2005-06 flu season. However, bird flu strains (and also seasonal influenza strains) are sensitive to the newer neuraminidase inhibitors, oseltamivir (Tamiflu) and Zanamivir (Relenza). The former comes in capsules and suspensions, and the latter is inhaled. **Note: The following information on dosing is provided only in case an audience member asks. Time need not be spent on this for most audiences.**

Oseltamivir:

For oral dosage forms (capsules and oral suspension):

For treatment of the flu:

Adults: 75 milligrams (mg) two times a day for five days.

Children 1 year of age or older: Dose is based on body weight and must be

determined by your doctor. It is usually between 30 and 75 mg two times a day for five days.

Children up to 1 year of age: Use and dose is determined by weight; > 40Kg 75mg two times/day; 23-40 Kg 60mg two times/day; 15-23 Kg 45mg two times/day; <15 Kg 30mg two times/day

For prevention of the flu:

Children 1 yr to 13yrs: > 40Kg 75mg/day; 23-40 Kg 60mg/day; 15-23 Kg 45mg/day; <15 Kg 30mg/day  
Adults and teenagers 13 years of age or older: 75 mg once a day for at least seven days.

Zanamivir:

For treatment of flu (Influenza A and Influenza B)

Adults and children 7 years and older  
—Two puffs twice daily (one 5 mg powder capsule per puff, 1 dose = 2 puffs or 10mg; approximately 12 hours apart in the morning and evening) for 5 days. Two doses should be taken on the first day of treatment whenever possible provided there are at least 2 hours between doses. Zanamivir must be started within 48 hours after the onset of signs and symptoms of the flu.

For prevention of flu (influenza A and influenza B) in patients older than 5—  
Two puffs once per day (one 5 mg powder capsule per puff, 1 dose = 2 puffs or 10mg)

Canada:For treatment of flu (Influenza A and Influenza B)




Adults and children 12 years and older  
—Two puffs twice daily (one 5 mg powder capsule per puff, 1 dose = 2 puffs or 10mg; approximately 12 hours apart in the morning and evening) for 5 days. Two doses should be taken on the first day of treatment whenever possible provided there are at least 2 hours between doses. Zanamivir must be started within 48 hours after the onset of signs and symptoms of the flu.

Slide 25

Will a flu vaccine protect me?

**Answer:** No, current vaccines do not protect against bird flu.

- Protects against expected strains
  - A(H1N1), A(H3N2), and B
- H5N1 investigational vaccine
  - Able to induce antibodies in adults
  - May or may not protect against pandemic strain when it emerges



**Because of concerns about the pandemic potential of H5N1, WHO has been working with laboratories in the WHO influenza network to develop vaccines against this subtype.**

Candidate vaccines were developed during 2003 by network laboratories in London and in Memphis, Tennessee, for protection against the strain that was isolated from humans in Hong Kong in February of that year. However, the 2004 strain is different from that strain.

In April 2004, WHO made the prototype seed strain for an H5N1 vaccine available to manufacturers. The National Institute of Allergy and Infectious Diseases (NIAID) awarded two contracts to support the production and clinical testing of an investigational vaccine based on the prototype seed strain made available by WHO.

The contracts were awarded to Aventis Pasteur (now Sanofi Pasteur) of Swiftwater, Pennsylvania, and to Chiron Corporation of Emeryville, California. Each manufacturer is using established techniques in which the virus is grown in eggs and then inactivated and further purified before being formulated into vaccines.

Clinical trials of candidate H5N1 vaccines are currently under way. On August 6, 2005, NIAID announced that the Sanofi Pasteur vaccine was meeting

with positive results in the first wave of testing in healthy adults. However, the amount of antigen needed was 180 mcg versus the 15 mcg given in annual flu shots, which makes the problem of adequate production far more acute. Further testing is ongoing, including trials to determine effectiveness and safety in children and the elderly.

**At this point, it is not clear if prototype H5 vaccines will offer protection against an emergent pandemic strain. Research in this area is a high priority because stockpiling prototype vaccines may be worthwhile if protection against emergent strains can be demonstrated.**

One recent study demonstrated good cross-protection against H5N1 in mice following vaccination with an H5 influenza vaccine created through reverse genetics. Protection was achieved despite antigenic differences and incomplete matching between the vaccine strain and the challenge virus. Although these findings are promising, it is not clear if similar protection would occur for humans.

A second study suggested that use of adjuvanted prototype vaccines may induce antibody capable of neutralizing a pandemic strain until a well-matched vaccine can be made available. In the study, 14 human subjects vaccinated with an adjuvanted influenza A/duck/Singapore 97 (H5N3) vaccine demonstrated higher seroconversion rates to four strains of H5N1 compared with 11 subjects who were vaccinated with a nonadjuvanted vaccine. For those who received the MF59-adjuvanted vaccine, 100% seroconverted to A/HongKong/156/97 and A/HongKong/213/03, 71% to A/Thailand/16/04, and 43% to A/Vietnam/1203/04.

**One way of protecting against all types of influenza, including emerging pandemic strains, would be a universal flu vaccine that would not**

have to be reengineered each year. The British company Acambis announced in early August 2005 that it is developing such a vaccine and has had successful results in animal testing. The vaccine would focus on the M2 viral protein, which does not change, rather than the surface hemagglutinin and neuraminidase proteins targeted by traditional vaccines. The universal vaccine is made through bacterial fermentation technology, which would greatly speed up the rate of production over that possible with culture in chicken eggs, plus the vaccine could be produced continuously, since its formulation would not change. Still, such a vaccine is years away from full testing, approval, and use. Other researchers are also working on a universal agent.

The preceding was excerpted directly from the avian influenza section of the IDSA website.

Slide 26

What can public health do?

- **Enhanced surveillance**
- **Develop detailed response plans & practice**
  - Guidelines for vaccine and antiviral prioritization
- **Import and Travel limitations**
  - Limit travel to/from countries/continents affected by pandemic
  - Isolate ill and quarantine exposed
  - Trace contacts
  - Cancel public gatherings (school, meetings, sporting events)
- **Stockpile antivirals and vaccine**

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Slide 27

**Surveillance...am I being watched!?**

**Answer: Yes!**

- World Health Organization (WHO)
  - 6 regional offices
  - 112 National Influenza Centers in 89 countries
  - 4 WHO Collaborating Centers (WHOCCs)
    - Australia, Japan, UK, and USA
- WHO makes recommendations on vaccine composition based on surveillance data
- USDA has done avian flu surveillance in poultry for decades.






Above from Nebraska HHSS  
Careful surveillance may detect an emerging pandemic earlier facilitating earlier responses and perhaps slowing or stopping the spread.

Slide 28

**Who's watching in Nebraska?**

- Influenza Sentinel Provider Surveillance System
  - 11 providers (report to CDC)
  - LHDs have flu surveillance plans
- Lab test result reporting
  - 65 labs report
- School absenteeism survey
  - LHD enter data
- Influenza-Like-Illness admissions
  - 19 district/local health departments
  - 89 acute care hospitals





Here in Nebraska we keep track of the number of cases of influenza, the population being affected, its severity, its geographic distribution, etc. At least four surveillance systems are active during flu season: One uses reports from health care providers and local health departments (LHDs); A second uses test results reported by laboratories; A third monitors school absenteeism, and the fourth surveillance system keeps track of the number of patients admitted to acute care hospitals with a diagnosis of influenza-like-illness (ILI).  
Above is from Nebraska HHSS.

Slide 29

**Are stockpiles of antivirals and bird flu vaccine adequate?**

**Answer: No.**

- U.S. Oseltamivir stockpiles (hard to produce)
  - Current: 2.3 million courses; 4.3 by end of 2005
  - Ordered: 44 million courses (15%); states option 10%
  - IDSA need estimate: minimum 90 million (130 ideal)
- U.S. H5N1 vaccine stockpiles
  - Plan to purchase: 20 million doses
  - If not protective vs pandemic strain, will take 4-6 months to develop (egg production is a limiting factor)





The current stockpiles of antiviral meds, mainly oseltamivir, and avian influenza vaccine are judged by all to be inadequate. Currently the U.S. has 2.3 million courses of oseltamivir stockpiled and has ordered 20 million courses. 10 other countries have ordered enough oseltamivir to treat 20 to 40% of their population. However, the drug is difficult to produce and at maximal production rates it would take about 10 years to reach this level of stockpiling worldwide. The Infectious Diseases Society of America (IDSA) has estimated that the U.S. needs a minimum of 90 million courses stockpiled and that 130 million courses

would be ideal. These recommendations are in line with recent National Vaccine Advisory Committee recommendations. The committee felt that forty million courses would be the minimum needed to support critical pandemic responses, and 133 million would be enough to treat those infected as well as to use for prophylaxis for high-risk patients and health care workers. The US also plans to purchase 20 million doses of H5N1 vaccine for stockpiling. However, it is unknown if this will protect against the pandemic strain that emerges. If it does not match, it will require 4 to 6 months at a minimum to develop a new protective vaccine. The new vaccine will then need to be manufactured and will trickle out week by week. The President just announced the release of a new federal pandemic flu plan on November 1, 2005 and has asked for \$7.1 billion in emergency funds for pandemic planning. The synopsis of the plan can be found here: <http://www.whitehouse.gov/homeland/pandemic-influenza.html>  
The US government has ordered 44 million courses of oseltamivir (15% coverage) and has negotiated the option for states to purchase an additional 10% coverage of their population.

Slide 30

What has Nebraska done in planning?

- Pan Flu Plan– “Evergreen” document
- Engagement of stakeholders and citizens
  - Governor’s Pan Flu Committee–
    - April 11, 2005
    - November 14, 2005
  - Citizen’s review group– Sept. 24, 2005
  - Strong support of PH by both groups
- Widespread education of providers and guidance on antiviral use




Source: Nebraska HHSS  
Nebraska’s pandemic flu plan is a so-called “evergreen” document meaning that it is constantly being updated. Because prioritization of scarce health resources like vaccine and anti-viral medicines is an emotionally charged and ethical issue in addition to being a complicated medical one, the governor of Nebraska formed a pandemic flu committee composed of people who were businesspersons, clergy, ethicists, first responders, school officials, infectious diseases experts, individuals from the food industry, public health employees, veterinarians, etc. The

group was educated about the issues and provided input for recommendations to the governor. A citizen group in conjunction with public health officials from Nebraska and the CDC also was convened. Both groups voiced strong support for PH in developing strategic goals for prioritization of resources.

Slide 31

**What are Nebraska's pandemic flu vaccination goals?**


1. Maintain the ability to provide quality health care, implement pandemic response activities and maintain vital community services.
2. Protect persons at highest risk for influenza mortality.
3. Decrease transmission of infection to those at highest risk for influenza mortality.
4. Maintain other important community services.
5. Protect the population at large.



Slide 32

**Are there federal guidelines for vaccine priority groups?**

<b>Tier 1</b>	<ul style="list-style-type: none"> <li>A Vaccine Producers direct care medical workers</li> <li>B Persons &gt; 65 with compromising conditions</li> <li>C Pregnant women; Household contacts of compromised persons</li> <li>D Public health emergency responders and key public officials.</li> </ul>
<b>Tier 2</b>	<ul style="list-style-type: none"> <li>A Healthy 65 and older and children</li> <li>B Emergency response, essential services</li> </ul>
<b>Tier 3</b>	<ul style="list-style-type: none"> <li>Key government and society leaders</li> </ul>
<b>Tier 4</b>	<ul style="list-style-type: none"> <li>Healthy Persons</li> </ul>



**Above is a slide distilled from Table D-1 in the appendix of the Federal HHS Pandemic Influenza plan.**

**Below are some more details about the priority groups.**

<b>Tier</b>	<b>Subtier</b>	<b>Population</b>
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1	A	Vaccine and antiviral manufacturers and others essential to manufacturing and critical
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support [rationale: Need to assure maximum production of vaccine and antiviral drugs]; Medical workers and public health workers who are involved in direct patient contact, other support services essential for direct patient care, and vaccinators [rationale: 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 | 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; Persons 6 months or older with history of hospitalization for pneumonia or influenza or other influenza high-risk condition in the past year

[rationale: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 | Pregnant women [rationale:In past pandemics and for annual influenza, pregnant women have been at high risk; vaccination will also protect the infant who cannot receive vaccine.]; 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 [rationale: 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 | Public health emergency response workers critical to pandemic response; Key government leaders [rationale: 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]

2           A           ‡ Healthy 65 years and older; 6 months to 64 years with 1 high-risk condition; 6-23 months old, healthy [rationale: Groups that are also at increased risk but not as high risk as population in Tier 1B]

                  B           ‡ Other public health emergency responders; Public safety workers including police, fire, 911 dispatchers, and correctional facility staff; Utility workers essential for maintenance of power, water, and sewage system functioning; Transportation workers transporting fuel, water, food, and medical supplies as well as public ground public transportation; Telecommunications/IT for essential network operations and maintenance [rationale: 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                               ‡ Other key government health decision-makers; Funeral directors/embalmers; [rationale: Other important societal groups for a pandemic response but of lower priority]

4                               ‡ Healthy persons 2-64 years not included in above categories; [rationale: All persons not included in other groups based on objective to vaccinate all those who want protection

Slide 33

**How can businesses prepare?**  
**Answer:** *Make business continuity plan.*

- Identify staff for critical functions
- Suspend non-critical functions
- Build depth by cross-training workers
- Alternative work schedules
- Explore telecommuting possibilities
- Teach workers cough "etiquette" and hand hygiene
- Use government pandemic planning checklist  
– <http://www.pandemicflu.gov/plan/>



No data on benefits of masks, eye protection, gloves outside healthcare setting.

Cough etiquette:


Cover the nose/mouth when coughing or sneezing;

Use tissues to contain respiratory secretions and dispose of them in the nearest waste receptacle after use; Perform hand hygiene (e.g., hand washing with non-antimicrobial soap and water, alcohol-based hand rub, or antiseptic handwash) after having contact with respiratory secretions and contaminated objects/materials.

Slide 34

**How can I prepare?**

- Practice cough etiquette
- Wash hands or use alcohol-based hand gel
- Keep hands away from eyes and mouth unless hands were washed
- Annual flu vaccine to prevent seasonal flu
- Pneumonia shot if in high risk group
- Avoid others if you are sick
- Individual checklist:  
<http://www.pandemicflu.gov/plan/>
- **DO NOT STOCKPILE TAMIFLU OR RELENZA**



Individuals can prepare by developing good influenza risk reduction habits. These include practicing good cough etiquette until it is second nature. When respiratory infections circulate in the community, one should frequently practice good hand hygiene by washing hands frequently or using alcohol-based hand gels. Since influenza and other germs can be carried on hands, one should keep hands away from eyes and mouth unless hands were just cleansed, e.g., don't reach up and adjust one's contact without washing hands. An annual influenza vaccine can protect against seasonal non-pandemic strains of influenza. Besides saving lives, this will also reduce the chance that a bird flu strain and a human flu strain might mix and form a new novel hybrid virus that goes on to start a pandemic. If you are in a high risk group for complications of influenza, you should ask your doctor if you should also receive the pneumococcal pneumonia vaccine. Since bacterial pneumonias are more common after influenza, getting the pneumonia vaccine will reduce your risk of a life-threatening secondary complication of the flu. One should also avoid others when one is sick...no use making someone else miserable! Lastly, personal stockpiles of Tamiflu or Relenza are **STRONGLY**

discouraged. These potentially lifesaving medications are in short supply, and it would be a tragedy for many courses of treatment to sit in healthy private citizens' medicine cabinets, while severely ill individuals go untreated due to shortage of antivirals. It is reasonable for government to develop stockpiles of medication, because a plan for distributing the drug to those who need it is part of the stockpiling plan.

NOTE: The following website also has checklists and guidelines for families--  
<http://www.pandemicflu.gov/plan/>

Slide 35

What should I do if I want to travel to countries that have bird flu?



- No travel restrictions currently
- Avoid contact with live animal markets and poultry farms
- Ensure all food from poultry is thoroughly cooked (eggs, too!)
  - 165 degrees
- Careful hand hygiene
- Monitor health for 10d post return; if you get flu symptoms, tell provider about symptoms and travel **BEFORE** you get to office

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at home



Certainly one would want to avoid intimate contact with avian species during travel to countries with ongoing transmission of H5N1 influenza in wild and domestic bird populations. One should check with the CDC for travel advisories to these regions as circumstances change. Currently there are no travel restrictions. However, the following precautions should be taken: Avoid contact with live animal markets and poultry farms

Insure all food from poultry is thoroughly cooked (eggs, too!). Much like eggs can be contaminated with Salmonella, they could become contaminated with influenza virus. However, to date there is no evidence of human infection occurring from undercooked eggs.

Use careful hand hygiene with soap and water or alcohol-based hand gels  
Monitor health for 10d post return; if you get flu symptoms, tell your healthcare provider about your symptoms and recent travel to an H5N1 transmission region **BEFORE** you get to the healthcare facility so that appropriate infection control measures can be initiated upon your arrival.

Slide 36

A slide with a red-to-white gradient background. The text is centered and reads: "The only thing more difficult than planning would be explaining why you did not do it!" followed by "-- Marja Esveld" and "Healthcare Inspectorate, The Netherlands". At the bottom left is the "BIOPREPAREDNESS" logo, and at the bottom right is a silhouette of a city skyline.

*The only thing more difficult than planning would be explaining why you did not do it!*

-- Marja Esveld  
Healthcare Inspectorate, The Netherlands

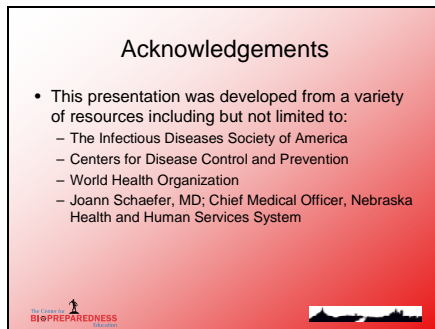
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Paraphrase content delivered by Marja Esveld

Excerpted directly from:  
Pandemic influenza  
preparedness planning

Report on a joint WHO/European  
Commission workshop  
Luxembourg, 2–3 March 2005

Slide 37

A slide with a red-to-white gradient background. The title "Acknowledgements" is centered. Below it is a bulleted list of resources. At the bottom left is the "BIOPREPAREDNESS" logo, and at the bottom right is a silhouette of a city skyline.

**Acknowledgements**

- This presentation was developed from a variety of resources including but not limited to:
  - The Infectious Diseases Society of America
  - Centers for Disease Control and Prevention
  - World Health Organization
  - Joann Schaefer, MD; Chief Medical Officer, Nebraska Health and Human Services System

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