

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

Prepared by:
Gary L. Gorby MD
Co-director, The Center for Biopreparedness Education
Interim Chief, Adult Infectious Diseases
Creighton University School of Medicine

Last updated 04/03/08



Slide 1

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.

What are the goals of the “talk?”

- Define “the flu.”
- Describe the unique features of viruses in general and influenza viruses specifically
- Describe the illness caused by influenza
- Explain how influenza spreads
- Discuss epidemics vs pandemics and the mechanisms by which they occur
- Discuss strategies to deal with influenza pandemics including prevention, treatment, and maintenance of societal and business functions



Slide 2

What is ‘the flu’?

- **Answer:** *An illness caused by influenza virus*
- A sudden onset respiratory illness with fever
 - Affects nose, throat, air passages, and lung
 - Yearly epidemics
 - Occurs worldwide causing significant illness and death every year
- NOT the nausea/vomiting/diarrhea that people call “the stomach flu.”



Slide 3

This may seem like a wasted slide for healthcare providers who know the difference between influenza and “the stomach flu”, however, it is interesting that a significant number of individuals infected with avian influenza had prominent gastrointestinal symptoms more frequently than with regular influenza. GI symptoms sometimes preceded respiratory symptoms by more than a week!

Are there different types of flu?

Answer: Yes!

- Type A— moderate to severe illness
 - All age groups
 - Humans and other animals
- Type B— milder epidemics
 - Humans only
 - Primarily affects children
- Type C— rarely reported in humans
 - No epidemics

ABC's

By Center for
BIOPREPAREDNESS
at UNMC

Slide 4

What does an influenza virus look like?



Fig.1 Electron micrograph

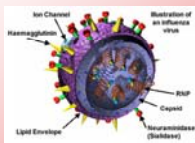


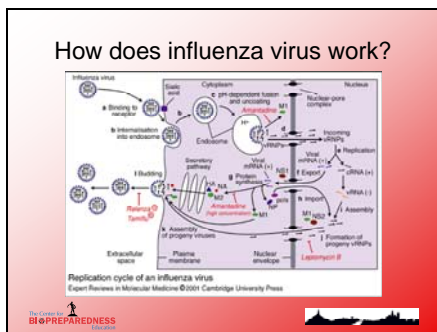
Fig.2 Schematic of influenza virus

- **Hemagglutinin protein**
 - Allows virus to stick to cells
 - Determines cell and species specificity
- **Neuraminidase protein**
 - Releases new virus particles from cells
- **Genetic material (RNP)** divided into 8 separate segments

By Center for
BIOPREPAREDNESS
at UNMC

Slide 5

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 6

This is a very complex slide that shows how the influenza virus goes about inducing host cells to manufacture more virus, and we are going to go through it step by agonizing step until you all know it well enough to pass a really hard test about influenza virus replication...JUST KIDDING! Actually, I only want you to remember a couple of things from this slide. First, at the top you can see the virus binding to sialic acid. Another name for this is neuraminic acid. The viral component that binds to this is the hemagglutinin. Thus, sialic AKA neuraminic acid is the receptor that allows influenza virus to stick to the cell before it enters. Second, once all the viral parts are made inside the cell, neuraminidase facilitates the release of new progeny viruses by acting as an enzyme that breaks the “teathering” of hemagglutinin to neuraminic acid. You’ll notice that two newer influenza drugs Relenza and Tamiflu inhibit neuraminidase and prevent the release of new progeny viruses from the cell. This in turn halts infection of additional host cells.

Why are the numbered “H” and “N” designations important?

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

- Used to subtype influenza A strains
 - 16 different hemagglutinins
 - 9 different neuraminidases
- Current human subtypes
 - A(H1N1) and A(H3N2) primarily
- Antibodies to H and N components made by our immune systems are protective against influenza
- H & N subtypes are the basis for current vaccines

BIOPREPAREDNESS

Slide 7

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 develop 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 more than 60 human deaths.

What are the symptoms of influenza?

- Sudden onset fever, muscle aches, headache, lack of energy, dry cough, sore throat, possibly runny nose
- Fever and body aches last 3 to 5 days
- Cough and lack of energy— 2 weeks
- Symptoms similar to other respiratory infections
 - RSV, rhinovirus, parainfluenza virus, etc.



Slide 8

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.

What should I know about complications of flu?

Answer: They are divided into respiratory and non-respiratory complications

- Very young, >65, chronic medical conditions
 - Sinusitis, bronchitis, COPD exac., bronchiolitis, croup are common examples
- Primary viral pneumonia 3-5 days
 - Most severe but least common pneumonic complication
- Secondary bacterial pneumonia 5-10 days
 - Accounts for >25% of flu-associated deaths
 - *Streptococcus pneumoniae* (48%), *Staph. aureus* (19%)



Slide 9

Influenza complications are divided into respiratory and non-respiratory categories. Overall, complications are most likely in the very young, people over age 65, people with chronic medical conditions such as patient with chronic cardiac or pulmonary diseases (COPD, asthma), patients with diabetes mellitus, renal disease, hemoglobinopathy, pregnancy or other immunosuppressing conditions. Primary viral pneumonia, which normally appears 3 to 5 days into the course of illness, is the most severe but least common pneumonic complication of influenza infection. Secondary bacterial pneumonia, which appears 5 to 10 days into the course of illness, is more common and accounts for about one fourth of influenza-related deaths. Pneumococcus accounts for about half of these cases and Staphylococcus aureus one fifth of them. In an animal model, the level of neuraminidase activity of the virus correlated with increased adherence and invasiveness of *S. pneumoniae*.

What are the non-respiratory complications of flu?

- Myositis and rhabdomyolysis
 - Can develop renal failure
- Reye syndrome— linked to ASA use & more with B
 - N/V, CNS, liver (↑ammonia, transaminase), low glucose
- CNS involvement: encephalitis, transverse myelitis, aseptic meningitis, and Guillain-Barre
 - Etiologic relationship not firmly established
- Myocarditis and pericarditis
- Toxic Shock Syndrome associated with *S. aureus* and acute influenza infections



Slide 10

True myositis is uncommon. It can result in myoglobinuria and renal failure if severe. The pathogenesis is not completely understood, but the presence of virus in affected muscles has been noted.

Reye syndrome is an extrapulmonary complication of influenza that has been reported with influenza B and, to a lesser extent, influenza A virus infections. It primarily affects children between the age of 2 and 16.

Reye syndrome is marked by nausea and vomiting for one to two days. This is followed by changes in mental status which can range from lethargy to coma, delirium, and seizures.

Hepatomegaly, marked elevations in serum aminotransferase LDH concentrations and ammonia levels with only moderate elevations of serum bilirubin are seen. Control of cerebral edema and hypoglycemia is important for management. The

prognosis is closely related to the level of consciousness at the time of admission; mortality rates have fallen to 10 percent or less with modern medical care. The syndrome is associated epidemiologically with aspirin use.

Myocarditis and pericarditis were seen in the 1918 pandemic but infrequently since then.

How does one diagnose flu?

Answer: It depends on the status of the outbreak.

- Viral culture (gold standard; 48-72 h)
 - Sputum & nasal washes superior to throat swab
- Rapid tests (IF, EIA, PCR)
 - Quick Vue A+B and ZstatFlu have CLIA waivers to be done in any office. Quick Vue only waived test A vs B
 - Sensitivity 72-95% and specificity 76-84% in 4 products; ZstatFlu had significantly lower sensitivity
 - In Thailand, only 36% sensitive for H5N1
 - Cost effective prior to treatment with neuraminidase inhibitor? Yes until probability reaches >42%
 - PCR (generally more sensitive than culture; costly)

By Center
BIOPREPAREDNESS



Slide 11

Viral culture is the traditional gold standard for diagnosing influenza infections. One study suggested that sputum and nasal washes are superior to throat swabs for viral recovery. Unlike human influenza A infection, avian influenza A (H5N1) may be associated with a higher frequency of virus detection and higher viral RNA levels in pharyngeal than in nasal samples. In Vietnam, viral loads in the pharynx of patients with H5N1 influenza 4 – 8 days after onset were at least 10 times as high as those from patients with H3N2 or H1N1.

Directigen Flu A, FLU OIA, Quick-Vue Influenza Test, and ZstatFlu Test were compared to viral culture in children with influenza-like illness. Influenza A was demonstrated in 49 percent. Sensitivity of the four tests ranged from 72 to 95 percent and specificity from 76 to 84 percent. The ZstatFlu test had a significantly lower sensitivity than the other tests. In Thailand, the results of rapid antigen testing were positive in only 4 of 11 patients with culture-positive influenza A (H5N1) 4 to 18 days after the onset of illness.

PCR-based testing can detect low quantities of viral RNA in specimens (e.g., nasopharyngeal aspirates, BAL, or nasal and throat swabs). These tests are generally more sensitive than culture and specific for both influenza A and B. This type of testing is costly. Creighton University Medical Center is working on implementing PCR diagnostics for the 2005 flu season. A decision analysis performed (prior to PCR) assessed the value of rapid diagnostic testing prior to the use of neuraminidase inhibitors versus empiric use. This analysis concluded that rapid diagnostic testing was appropriate first except during influenza epidemics. When the probability of a case being due to influenza reached 42 percent, the two strategies were equivalent. Conservative estimates for sensitive and specificity of the available tests at the time of the analysis were used. So, during the phase when influenza is

building in the community, rapid testing can be cost-effective. However, very early on in flu season, positive results are likely to be false positives, so viral culture is preferred. And, once influenza is circulating widely in the community, rapid tests do not add cost effectiveness to the treatment of influenza.

How is seasonal flu treated?

Answer: Treat symptoms and consider anti-virals if symptoms present <48 hours.

- Rest, fluids, anti-tussives, antipyretics (NOT aspirin)
- Antivirals (option if symptoms for < 48h)
 - Amantadine or rimantadine (influenza A only)
 - NOT recommended for remainder 2005-06 season (R>90%)
 - Neuraminidase inhibitors (influenza A & B)
 - Oseltamivir (Tamiflu®) 75mg p.o. bid for 5 days
 - Zanamivir (Relenza®) 2 inhalations bid for 5 days

Be Ready
Be Prepared
Be Safe



Slide 12

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 and oseltamivir 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 prophylaxis 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. Note that more than 90% of seasonal influenza A strains circulating in U.S. during the 2005-2006 flu season have been found to be 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. 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.

Dosing of antivirals (NOTE: the following does not constitute full prescribing information):

Amantadine and rimantadine (Although rimantadine is approved only for chemoprophylaxis of influenza A infection among children, certain specialists in the management of influenza consider it appropriate for treatment of influenza A among children):

Age 1-9yrs 5mg/kg/day up to a maximum dose of 75mg p.o. bid for 3-5 days or for 1-2 days after symptoms resolve

Age 10 to 65 yrs: 100 mg p.o. bid for 3-5 days or for 1-2 days after symptoms resolve.

Age >65 yrs: 100 mg p.o. QD (adjust for decreased renal function) for 3-5 days or for 1-2 days after symptoms resolve

Prophylaxis dosages are the same as for treatment (70-90% effective for influenza A prevention)

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 –12 years: Dose is 2mg/kg orally bid. 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 must be determined by a physician.

For prevention of the flu:

Adults and teenagers 13 years of age or older: 75 mg once a day for at least seven days.

Children up to 13 years of age: Use and dose must be determined by a physician.

Zanamivir:


For treatment of flu (Influenza A and Influenza B)
Adults and children 7 years and older —Two puffs twice daily (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.

Canada:For treatment of flu (Influenza A and Influenza B)
Adults and children 12 years and older —Two puffs twice daily (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.

How is influenza spread?

Answer: Quickly...due to short incubation!

- Incubation— Typically 2 days
 - Range 1 to 4 days
- Viral shedding
 - Can begin 1 day BEFORE the onset of symptoms
 - Peak shedding first 3 days of illness
 - Correlates with fever
 - Subsides usually by 5-7 days
 - Can be 10+ days in children



THE NATIONAL
BIOPREPAREDNESS
INSTITUTE

Slide 13

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.

Is flu only spread via droplets?



- Limited studies
- Contact, droplet, & droplet nuclei (airborne) may all occur
 - Relative contribution of each is unclear
 - Droplet most important
 - Generated by coughing, sneezing, talking
 - “spitting distance”



Slide 14

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.

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
- Pandemics happen only occasionally when a completely new influenza A virus circulates
 - A really large worldwide epidemic
 - Results in more severe illnesses and more deaths especially if both H and N components are novel



Slide 15

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.

How do yearly epidemics occur?

Answer: A process called *antigenic DRIFT*.

- Imperfect “manufacturing” of virus
 - Small changes in H and N components due to random genetic mutations
 - Can prevent the body’s immune system from fully protecting against the virus, and reinfection can occur (worse for weak immune systems)
 - Reason that 1 or 2 of the three virus strains in the vaccine are updated every year
 - Reason for yearly flu vaccination



Slide 16

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.

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

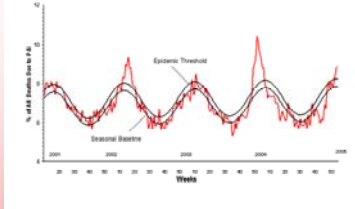
- > 36,000 deaths and 200,000 hospitalizations
- 5 to 20% attack rate in general population
- Nursing home attack rates of 60%
- Over 85% of influenza-related deaths occur in people over age 65
- Over \$10 billion lost in productivity and direct medical costs



Slide 17

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., 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.

Pneumonia and Influenza Mortality
for 122 U.S. Cities
Weeks Ending 3/5/2009



Slide 18

The figure above shows the cyclical yearly spikes in mortality due to pneumonia and influenza. The CDC sets the epidemic threshold, which varies according to the time of year. From the graph it appears about 0.4% higher than the seasonal baseline. The large red spikes in mortality in the winter weeks correspond to the yearly influenza epidemics.

What drives the occurrence of a pandemic?

Answer:

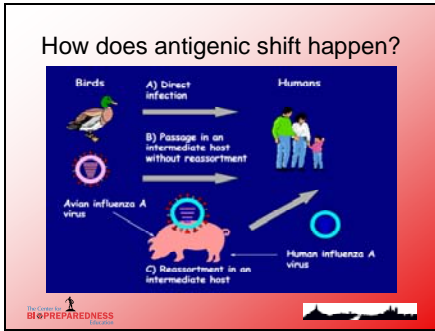
Instead of antigenic *DRIFT* occurring,
an antigenic...

SHIFT

...happens.



Slide 19



Slide 20

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 simplest 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.

What about past flu pandemics?

Credit: US National Museum of Health and Medicine

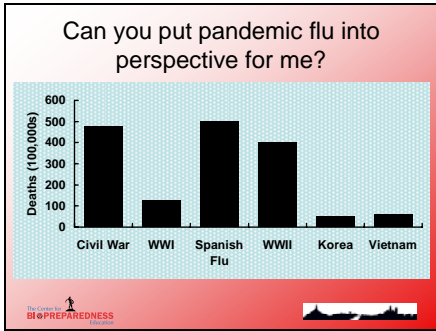
1918: "Spanish Flu" A(H1N1)	1957: "Asian Flu" A(H2N2)	1968: "Hong Kong Flu" A(H3N2)
20-40 m deaths 675,000 US deaths	1-4 m deaths 70,000 US deaths	1-4 m deaths 34,000 US deaths

© 2010 U.S. National Museum of Health and Medicine

Slide 21

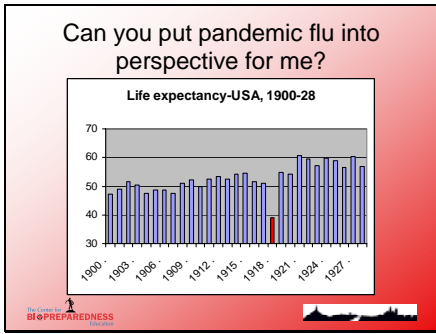
As you can see, the Spanish Flu in 1918 was the most severe of the three pandemics resulting in 20 to 40 million deaths worldwide and 675,000 U.S. deaths. The Asian Flu pandemic resulted in double the usual number of flu season deaths in the US. The Hong Kong Flu pandemic was relatively mild by comparison.

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



Slide 22

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 23

In actuality, the 1918 influenza pandemic temporarily lowered the life expectancy in the US by more than 10 years!

What consequences might result in the USA from a pandemic, now?

- \$71-166 billion would be lost (TFAH 6/2005)
- Serious social and economic disruption

Characteristic	Moderate (1959/68-like)	% of illness	Severe (1918-like)	% of illness
Total population (U.S.)	300,000,000	...	300,000,000	...
Illness (30% attack rate)	90,000,000	...	90,000,000	...
Outpatient medical care	45,000,000	50.0%	45,000,000	50.0%
Hospitalization	865,000	0.96%	9,000,000	11.00%
ICU care	128,750	0.14%	1,485,000	1.65%
Mechanical ventilation	64,875	0.07%	745,500	0.83%
Deaths	209,000	0.23%	1,903,000	2.11%

The Center for BIOPREPAREDNESS

Slide 24

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. An estimated economic cost of \$71-166 billion was published by Trust for America’s health in a report from June 2005 based on

projections from the relatively mild 1968 pandemic.

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. Table 1 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.

What consequences might result in Nebraska from a pandemic, now?

Characteristic	Moderate (1958/68-like)	% of illness	Severe (1918-like)	% of illness
Total population (NE)	1,711,263	...	1,711,263	...
Illness (30% attack rate)	513,379	...	513,379	...
Outpatient medical care	256,689	50.00%	256,689	50.00%
Hospitalization	4,928	0.96%	56,472	11.00%
ICU care	719	0.14%	8,471	1.65%
Mechanical ventilation	359	0.07%	4,261	0.83%
Deaths	1,181	0.23%	10,832	2.11%

The Center for BIOPREPAREDNESS

Slide 25

*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.

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.



Preparedness
BIO@PREPAREDNESS

Slide 26

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. Since December 2003 and as of 3/29/06, avian influenza (H5N1) has been found in domestic or wild birds in the following countries:

Africa: Cameroon Niger Nigeria;

East Asia & the Pacific: Cambodia China Hong Kong (SARPRC) Indonesia Japan Laos Malaysia Mongolia Myanmar (Burma) Thailand Vietnam

South Asia: Afghanistan India Kazakhstan Pakistan (H5)

Near East: Egypt Iraq (H5) Iran Israel Jordan Europe &

Eurasia: Albania Austria Azerbaijan Bosnia & Herzegovina Bulgaria Croatia Denmark France Georgia Germany Greece Hungary Italy Poland Romania Russia Serbia & Montenegro Slovak Republic Slovenia Sweden Switzerland Turkey Ukraine

How does "bird flu" affect birds?

Answer: Ranges from asymptomatic to fatal illness.

- Aquatic birds (ducks, shorebirds, gulls) are considered to be the natural reservoirs
 - Generally don't develop illness from it
 - Recent reports of wild bird deaths suggests increasing virulence
- Domestic birds often fatal infections
 - Current H5N1 outbreak in Asia most severe ever
 - Hundreds of millions of birds have died or were culled
- Host range expanding to cats, leopards, tigers
 - Commonly infects pigs, horses, sea mammals, mustelids



Preparedness
BIO@PREPAREDNESS

Slide 27

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. In fact the inability of researchers to find H5N1 virus in healthy aquatic birds suggests that it may be spreading in the wild through as yet unidentified nonconventional bird species. After all, dead ducks don't fly! 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.

How does “bird flu” affect humans?

Answer: There have been 207 human cases of H5N1 flu with 115 deaths as of 05/08/06.

- Vietnam 93, Indonesia, Thailand, China, Turkey, Cambodia, Iraq, Azerbaijan, Egypt
- 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/



Slide 28

Infection of humans with “bird flu” has been limited to 207 cases as of 05/08/06. However, 115 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, and Egypt. Updates for these statistics are available in table form at the WHO website:

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.

What infection control measures should be used for bird flu?

Answer: CDC recommends enhanced precautions in a non-pandemic setting for suspected bird flu.

- Seasonal influenza:
 - Standard precautions & respiratory droplet precautions
- Enhanced precautions for suspected bird flu cases
 - STRICT contact precautions: Gowns, gloves, dedicated equipment
 - Eye protection (within 3 feet of the patient)
 - Airborne precautions: Negative pressure (6-12 exchanges /hr); Fit-tested N95 mask

<http://www.cdc.gov/flu/avian/professional/infect-control.htm>



Slide 29

Excerpted from CDC website (see link below): Human influenza is generally thought to spread by large respiratory droplet. Standard precautions plus respiratory droplet precautions are normally recommended for care of people with **SEASONAL** human influenza, but additional precautions are recommended for suspected cases of avian influenza in a non-pandemic setting (the current situation in November 2005).

Standard precautions for **SEASONAL** influenza include:

Wear gloves if hand contact with respiratory secretions or potentially contaminated surfaces is anticipated.

Wear a gown if soiling of clothes with a patient's respiratory secretions is anticipated.

Change gloves and gowns after each patient encounter and perform hand hygiene.

Decontaminate hands before and after touching the patient, after touching the patient's environment, or after touching the patient's respiratory secretions, whether or not gloves are worn.

When hands are visibly soiled or contaminated with respiratory secretions, wash hands with soap (either plain or antimicrobial) and water.

If hands are not visibly soiled, use an alcohol-based hand rub for routinely decontaminating hands in clinical situations.

Alternatively, wash hands with soap (either plain or antimicrobial) and water.

In addition to Standard Precautions, health-care workers should adhere to Droplet Precautions during the care of a patient with suspected or confirmed **SEASONAL** influenza: Place patient into a private room. If a private room is not available, place (cohort) suspected influenza patients with other patients suspected of having influenza; cohort confirmed influenza patients with other patients confirmed to have

influenza.

Wear a surgical or procedure mask upon entering the patient's room or when working within 3 feet of the patient. Remove the mask when leaving the patient's room and dispose of the mask in a waste container.

If patient movement or transport is necessary, have the patient wear a surgical or procedure mask, if possible.

Enhanced precautions for cases of suspected avian influenza in a non-pandemic setting:

However, given the uncertainty about the exact modes by which avian influenza may first transmit between humans additional precautions (Contact precautions, eye protection, airborne precautions as per slide) for health-care workers involved in the care of patients with documented or suspected avian influenza may be prudent. For example, gowns and gloves are recommended in the case of seasonal influenza if contact with respiratory secretions or surfaces contaminated with respiratory secretions is likely. However, in suspected cases of bird flu gowns, gloves, and dedicated equipment should ALWAYS be used. In addition, airborne precautions have been substituted for respiratory droplet precautions. The rationale for the use of additional precautions for avian influenza as compared with human influenza include the following:

The risk of serious disease and increased mortality from highly pathogenic avian influenza may be significantly higher than from infection by human influenza viruses.

Each human infection represents an important opportunity for avian influenza to further adapt to humans and gain the ability to transmit more easily among people.

Although rare, human-to-human transmission of avian influenza may be associated with the possible emergence of a pandemic strain.

Patients with a history of travel within 10 days to a country with avian influenza activity and are hospitalized with a severe febrile respiratory illness, or are otherwise under evaluation for avian influenza, should be managed using isolation precautions identical to those recommended for patients with known Severe Acute Respiratory Syndrome (SARS) as shown in the slide above.

<http://www.cdc.gov/flu/avian/professional/infect-control.htm>

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 is pathogenic and virulent in humans
- Virus must be capable of sustained person-to-person transmission



Slide 30

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.

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 (only work on A)
- Sensitive to neuraminidase inhibitors (A&B)
 - Oseltamivir (Tamiflu®)–
 - capsules and oral liquid
 - Zanamivir (Relenza®)–
 - Inhaled powder
- ↑ dose longer course?



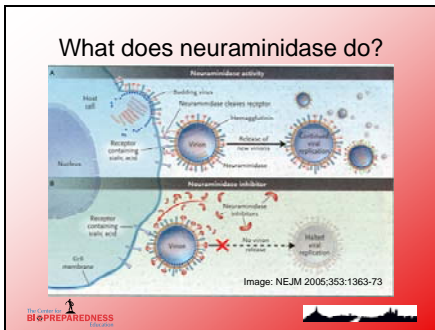
Slide 31

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. Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa. Drug-resistant viruses can appear in approximately one third of patients when either amantadine or rimantadine is used for therapy. During the course of amantadine or rimantadine therapy, resistant influenza strains can replace susceptible strains within 2--3 days of starting therapy. Resistant viruses have been isolated from persons who live at home or in an institution where other residents are taking or have recently taken amantadine or rimantadine as therapy; however, the frequency with which resistant viruses are transmitted and their effect on efforts to control influenza are unknown. Amantadine- and rimantadine-resistant viruses are not more virulent or transmissible than susceptible viruses (bolded text from CDC). These drugs normally only work on strains of influenza A. Although the H5N1 strain is resistant to amantadine and rimantadine, H5N1 is sensitive to the newer neuraminidase inhibitors, oseltamivir (Tamiflu) and Zanamivir (Relenza). The former comes in capsules and suspensions, and the latter is inhaled. Human influenza strains that become resistant to oseltamivir due to a single amino acid mutation (His274Tyr) in the neuraminidase usually are less infectious in cell culture and in animals than their parental strains. However, oseltamivir-resistant H1N1 variants are transmissible in ferrets. These variants retain full susceptibility to zanamivir in vitro. A study performed in mice suggests that more recent H5N1 isolates require higher doses and 8 day vs 5 day courses to have the same efficacy as for an older, less virulent isolate.

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 must be determined by your doctor.
 For prevention of the flu:
 Adults and teenagers 13 years of age or older: 75 mg once a day for at least seven days.
 Children up to 13 years of age: Use and dose must be determined by your doctor.

Zanamivir:
 Follow your doctor's orders or the directions on the label.
 For treatment of flu (Influenza A and Influenza B)
 Adults and children 7 years and older —Two puffs twice daily (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.
 Canada:For treatment of flu (Influenza A and Influenza B)
 Adults and children 12 years and older —Two puffs twice daily (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 32
 Legend from NEJM article: Panel A shows the action of neuraminidase in the continued replication of virions in influenza infection. The replication is blocked by neuraminidase inhibitors (Panel B), which prevent virions from being released from the surface of infected cells.

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
 - Both inactivated (shot; 6 mo or older) and live-attenuated (nasal spray; ages 5-49) available
- H5N1 investigational vaccine
 - Able to induce antibodies in adult tests
 - Unknown if it will protect against pandemic strain when it emerges
- Acambis universal vaccine (invariant M2 protein)



Preparedness



Slide 33

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.

Can a pandemic be prevented or delayed?

Answer: *It is being debated.*

- Computer models suggest possibility with aggressive antiviral use where strain starts
 - Non-urban area
 - Rapid detection
 - Rapid intervention (1 to 3 weeks)
 - Secondary cases < 1.8
 - Prophylaxis 80-90% in region (1-3 million courses)
 - Movement restriction and social distancing

The Center for
BIOPREPAREDNESS
America



Slide 34

One potential strategy to halt or abort a pandemic is to rapidly detect the event when it occurs, then use aggressive chemoprophylaxis in the region where the transmission is occurring. Computer models show that this could be feasible provided that the intervention occurs within 1 to 3 weeks of the onset. It would be necessary to give prophylactic antivirals to 80 or 90% of people in the region along with movement restrictions and social distancing. If the outbreak occurred in a very large urban area the number of people that would need to be treated prophylactically might be too large. The models also show that if the transmissibility of the virus exceeded an R_0 of 1.8, the strategy wouldn't work. R_0 reflects the number of secondary cases that occur from a single source case. It has been estimated that the R_0 of the 1918 Spanish Flu strain was between 2 and 4.

What response strategies can public health authorities use?

- 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



Slide 35

Surveillance...am I being watched!?

Answer: Yes!

- World Health Organization (WHO)
 - 6 regional offices
 - 112 National Influenza Centers in 89 countries (NICs)
 - 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.



Slide 36

Above from Nebraska HHSS

Who's watching in Nebraska?

- Influenza Sentinel Provider Surveillance System
 - 11 providers (report to CDC)
 - LHDs have flu surveillance plans
- Lab test result reporting and strain typing
 - 65 labs report total and (+) test results
- School absenteeism survey
 - LHD enter data and do monitoring
- ILI admissions survey
 - 19 district / local health departments
 - 89 acute care hospitals



Slide 37

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; 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.

Are stockpiles of antivirals and bird flu vaccine adequate?

Answer: No.

- U.S. Oseltamivir stockpiles
 - Current: 2.3 million courses; 4.3 by end of 2005
 - Ordered: 20 million courses;
 - IDSA need estimate: minimum 90 million (130 ideal)
 - 10 countries have ordered enough to treat 20-40% of their population; With limited production it will take 10yrs to meet this level worldwide
- U.S. H5N1 vaccine stockpiles
 - Plan to purchase: 20 million doses
 - If not protective vs pandemic strain, will take 4-6 months

THE NATIONAL
BIOPREPAREDNESS
COUNCIL



Slide 40

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. The Infectious Diseases Society of America 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>

What has Nebraska done in planning?

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

THE NATIONAL
BIOPREPAREDNESS
COUNCIL



Slide 41

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.

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 42

Are there federal guidelines for vaccine priority groups?

Tier 1	A	Vaccine Producers direct care medical workers
	B	Persons > 65 with compromising conditions
	C	Pregnant women; Household contacts of compromised persons
	D	Public health emergency responders and key public officials.
Tier 2	A	Healthy 65 and older and children
	B	Emergency response, essential services
Tier 3		Key government and society leaders
Tier 4		Healthy Persons



Slide 43

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.

Tier	Subtier	Population
------	---------	------------

1	A	Vaccine and antiviral manufacturers and others essential to manufacturing and critical support [rationale: Need to assure maximum production of vaccine and antiviral drugs]; Medical workers and public health workers who are involved in direct patient care, 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 44

What can businesses do to prepare?

Answer: Create business continuity plan.

- Identify staff to carry out critical functions
- Identify functions that could be suspended
- Build depth by cross-training workers
- Plan for alternative work schedules
- Explore telecommuting possibilities
- Teach workers cough "etiquette" and hand hygiene (soap & water or alcohol-based hand gel)
 - No data on benefits of masks, eye protection, gloves outside healthcare setting
- Use government pandemic planning checklist
 - <http://www.pandemicflu.gov/plan/>



What advice can I give patients?

- 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

The Center for
BIOPREPAREDNESS
Prevention



Slide 45

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.

The following website has checklists for individuals and families: Individual checklist:
<http://www.pandemicflu.gov/plan/>

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
- Insure 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

The Center for
BIOPREPAREDNESS
Prevention



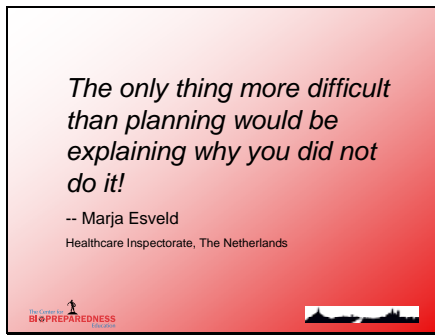
Slide 46

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

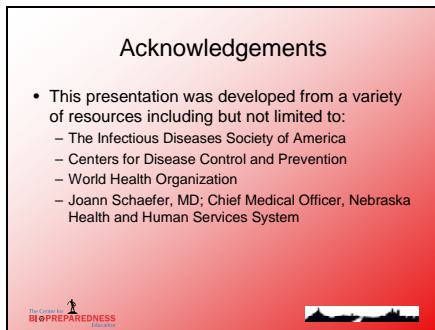
Monitor health for 10d post return; if you get flu symptoms, tell your healthcare provider about your symptoms and recent travel to an H5N1 transmission region **BEFORE** you get to the healthcare facility so that appropriate infection control measures can be initiated upon your arrival.



Slide 47

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 48