The views presented are those of the speaker and do not necessarily represent the views of the DoD, the Department of the Air Force, or the Department of the Army
Emergency hospital during 1918 influenza epidemic, Camp Funston, Kansas. Source: http://www.vaccineinformation.org/photos/flu_afp00
The influenza pandemic of 1918 killed more people than died in World War I.

- True. WWI casualties estimated at 16 million. 1918 influenza epidemic casualties estimated at 50 million (some estimate 100 million).
- Army: > 1 million hospitalized, >44,000 deaths
- Navy: ~5,000 deaths
- Death rate was 25% higher in Army population than civilian population of the US

What is influenza?

- Acute, usually self-limited illness caused by influenza type A or B, outbreaks every winter
- Attack rates 10-40% over peak 5-6 week period
- Fever, malaise, cough

- Unique among respiratory viral infections:
  - Epidemic nature
  - Associated mortality

Principles and Practices of Infectious Diseases. Mandell, Douglas, and Bennett’s, 8th ed.
History

- Outbreaks every 1-3 years for at least 400 years
- Greatest pandemic in history 1918-1919
  - >500,000 deaths in US
- Modern understanding: isolation of influenza A in 1933, influenza B in 1939
- Discovery of growth in chicken eggs facilitated research, vaccine development
- First inactivated vaccines developed in 1940s
- First live attenuated flu vaccine licensed 2003
Impact: Mortality

- Epidemics associated with increased morbidity and mortality, much due to complicating pneumonia
- **20-50,000 excess deaths/year in US**
  - Ebola: ~11,000 (largest known outbreak; 1 in US)
  - MERS-CoV: ~500 (last 3 years)
  - SARS: 775 deaths worldwide
  - AIDS: ~15,000 deaths in US/year
  - Suicide: 41,000
- Influenza and pneumonia together #1 infectious cause of death in US
- **114,000 hospitalizations/year in US**
Classification

- Orthomyxoviridae: A, B, C
- All share certain features: host-cell derived envelope, glycoproteins required for cell entry/exit, negative-sense RNA

- Standard nomenclature:
  - Type (A, B, C)
  - Place of initial isolation
  - Strain designation
  - Year of isolation

- Influenza A further subtyped on hemagglutinin, neuraminidase activity (e.g. H1N1, H3N2)
Impact: Morbidity

- **Estimated in US/year:**
  - 13.8-16.0 million excess respiratory illnesses in <20 yo
  - 4.1-4.5 million >20 yo
- **Typical case associated with:**
  - 5-6 days restricted activity
  - 3-4 days in bed
  - 3 days lost from work or school
- **Economic impact due to lost productivity:**
  - Per 100 schoolchildren, 37 lost days of school, 20 days missed work by parents
Influenza complications

- Pneumonia most common
  - Primary influenza pneumonia
  - Secondary bacterial pneumonia
- Myositis/rhabdomyolysis
- Central nervous system disease
  - Encephalopathy/encephalitis
  - Transverse myelitis
  - Aseptic meningitis
  - Guillain-Barré syndrome
- Cardiac complications
  - Acute myocardial infarction/unstable angina
  - Myocarditis/pericarditis
Figure 167-3. Typical epidemic curve in interpandemic era. Principles and Practices of Infectious Diseases. Mandell, Douglas, and Bennett’s, 8th ed.
Most at risk for morbidity, mortality

- Mortality highest in older adults >65
- High risk medical conditions
  - Cardiovascular, pulmonary, metabolic diseases, kidney disease, hemoglobinopathies, immune defects, neurologic disease
- Nursing home residents
- Immunosuppressed/HIV infected
- 2nd and 3rd trimester pregnancy, postpartum
- Morbidly obese
- Native Americans/Alaskan natives
- Children < 2 years old
Transmission

- Person-to-person via infected respiratory secretions
- Predominantly by large particles (droplet)
- Usual reproduction number (number of secondary cases generated by one case): 1-3
- Usually a single strain causes nearly all cases during an epidemic
- Antigenic variation of HA, NA determines “shift” vs “drift”
  - New variants, little to no preexisting immunity in population
Observations on Mortality during the 1918 Influenza Pandemic

Jeffrey Luk,1 Peter Gross,1,2 and William W. Thompson2

1Department of Internal Medicine, Hackensack University Medical Center, Hackensack, and 2New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; 3National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta
Figure 1. Age group-specific annual excess mortality due to pneumonia and influenza during the influenza pandemic in 1918. The average annual excess mortality for the period of 1913–1917 was used as the baseline.

Figure 2. Age group-specific annual excess mortality due to pneumonia and influenza during the influenza pandemic in 1968. The average annual excess mortality for the period of 1963–1967 was used as the baseline.
1918 Influenza Vulnerable Populations

- Men age 25-40 years
- South Africa:
  - Case fatality rate 5.9% nonwhites
  - 2.6% whites
  - Kimberly diamond miners 22.4%
  - Rand gold miners 1.9%
- Rhodesia 9.2% mining villages and 2.3% other villages
- New Zealand mortality rate 7x higher for indigenous Maori

Bacterial Pneumonia in 1918

- <5% of deaths occurred within 3 days of illness
- Median onset of illness to death 7-10 days

Figure 1. Percentage distributions of fatal cases of influenza–pneumonia during 1918–19 influenza pandemics, by estimated days of illness before death. A) Influenza–bronchopneumonia, Cook County Hospital, Chicago, Illinois, USA (n = 599)

Figure 2. Cumulative percentage deaths from influenza–pneumonia, by days (estimated) from illness onset, among fatal cases during various epidemics, 1918–19 (5,17–22). Vertical arrows indicate median no. days to death.

Predominant Pneumonia at Army Camps, Fall 1918

- Haemophilus influenza 6 camps
- Streptococcus pneumonia 12 camps
- S. pyogenes 3 camps
- Staphylococcus aureus 3 camps

“…These men start with what appears to be an ordinary attack of La Grippe or Influenza, and when brought to the Hospital they very rapidly develop the most viscous type of Pneumonia that has ever been seen. Two hours after admission they have the Mahogany spots over the cheek bones, and a few hours later you can begin to see the Cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the colored men from the white. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible. One can stand it to see one, two or twenty men die, but to see these poor devils dropping like flies sort of gets on your nerves. We have been averaging about 100 deaths per day, and still keeping it up…”

http://virus.stanford.edu/uda/
1918 Bacterial Pneumonia Theory

- Virus induced prolonged production of interferons and proinflammatory cytokines destroys respiratory epithelium, alters physical and immune defenses of lower respiratory tract
- Invasion of lungs by bacteria
- Some infected individuals, esp. in crowded spaces, become “cloud adults” or “super-spreaders”

Observations on Mortality during the 1918 Influenza Pandemic

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Figure 1. Age group–specific annual excess mortality due to pneumonia and influenza during the influenza pandemic in 1918. The average annual excess mortality for the period of 1913–1917 was used as the baseline.

Figure 2. Age group–specific annual excess mortality due to pneumonia and influenza during the influenza pandemic in 1968. The average annual excess mortality for the period of 1963–1967 was used as the baseline.
• Where did the 1918 virus originate?
  ○ Unknown; unlike H5N1, from an avian influenza lineage genetically distinct from those currently known

• What was the pathogenesis, and why did so many people die?
  ○ Different pathogenesis in 1918 not documented:
    ▪ Causes of death in 1918 similar to those during other pandemics
    ▪ Most fatalities had secondary pneumonias caused by common bacteria or, in a minority of cases, ARDS-like syndromes
    ▪ Higher proportion of severe cases at all ages
    ▪ 1918 virus-virulence determinants not yet mapped
“The 1918 Influenza Pandemic: Insights for the 21st Century”

- Why were there so many deaths among the young and healthy?
  - Unknown; unappreciated host or environmental variables possible, such as robust immunological response to the virus in younger individuals, resulting in enhanced tissue damage

- Why was mortality among the elderly lower than expected?
  - Unknown; evidence is consistent with prior exposure to a virus—conceivably the virus associated with the 1847 pandemic—eliciting protective immunity

- Why were there 3 pandemic waves during 1918–1919, and what are the implications for predicting future pandemic spread?
  - Unknown; at least 2 virus variants during second wave
  - Identity of viruses during first and third waves not known
  - Epidemiology of rapidly recurrent waves not understood

Age-specific influenza-associated mortality in Breslau, from July 1918 to April 1922.

Monthly influenza-associated mortality in Breslau, Silesia (now Wroclaw, Poland), from June 1918 through December 1922

“The 1918 Influenza Pandemic: Insights for the 21st Century”

- Do influenza pandemics occur in predictable cycles?
  - Insufficient evidence for pandemic cyclicity
  - Steps in pandemic emergence not fully understood

- Are we better able to prevent morbidity and mortality today?
  - Yes, in developed world with advanced medical care, antibiotics, antivirals, and effective public health
  - Preventive vaccines would be critical if available in time
  - However, developing world still at great risk

Lessons Learned from Reconstructing the 1918 Influenza Pandemic

Adolfo Garcia-Sastre¹ and Richard J. Whitley²

¹Department of Microbiology, Mount Sinai School of Medicine, New York, New York; ²Departments of Pediatrics, Microbiology, Medicine, and Neurosurgery and Center for Biodefense and Emerging Infections, University of Alabama at Birmingham, Birmingham
HA Gene

- Receptor binding glycoprotein, responsible for mediating fusion with host endosomal membrane
- Must be activated by host protease (tryps""
- Highly pathogenic avian viruses have multibasic cleavage site recognized by ubiquitous proteases
  - 1918 strain does not have this
- Yet 1918 HA essential for high virulence in mouse and egg pathogenicity models
HA of human flu binds to α2,6 sialic acids
Avian viruses bind α2,3 linked sialic acids
1918 HA differs only at aa 225
  ○ 225 glutamic acid: human binding
  ○ 225 glycine: dual specificity binding both human and avian receptors
Also, single aa change at 190 switches receptor binding from human to avian
Thus single point mutations can switch receptor specificity
Origin of 1918 Influenza

1917 Avian Influenza Virus Sequences Suggest that the 1918 Pandemic Virus Did Not Acquire Its Hemagglutinin Directly from Birds

Thomas G. Fanning, Richard D. Slemons, Ann H. Reid, Thomas A. Janczewski, James Dean, and Jeffery K. Taubenberger

Division of Molecular Pathology, Department of Cellular Pathology and Genetics, Armed Forces Institute of Pathology, Rockville, Maryland 20850-3125; Department of Veterinary Preventive Medicine, College of Veterinary Medicine, Ohio State University, Columbus, Ohio 43210; and Division of Birds, National Museum of Natural History, Washington, D.C. 20560

Received 29 January 2002/Accepted 25 April 2002
1957-58 Influenza Pandemic

- September opening of schools a major factor in initiating outbreak
- No school closings, but games canceled due to ill players

Henderson, DA et al, Biosecurity and Bioterrorism: Biodefense strategy, Practice and Science. 7:1-9, 2009
1957-58 Influenza Pandemic

- Large number of non flu excess deaths
- Vaccine arrived at the end of outbreak, 60% effective, sufficient for 17% population
- GDP decrease only 1%

Henderson, DA et al, Biosecurity and Bioterrorism: Biodefense strategy, Practice and Science. 7:1-9, 2009

Table 1. Mortality Characteristics of Type A Influenza Epidemics, United States, 1937-1963a

<table>
<thead>
<tr>
<th>Period of Excess Mortality</th>
<th>Number of Excess Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pneumonia and Influenza</td>
</tr>
<tr>
<td>Dec 1934-Jan 1935</td>
<td>5,800</td>
</tr>
<tr>
<td>Jan-Mar 1937</td>
<td>29,000</td>
</tr>
<tr>
<td>Mar 1939</td>
<td>3,100</td>
</tr>
<tr>
<td>Dec 1940-Feb 1941</td>
<td>7,200</td>
</tr>
<tr>
<td>Dec 1943-Jan 1944</td>
<td>21,000</td>
</tr>
<tr>
<td>Mar-Apr 1947</td>
<td>4,800</td>
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<tr>
<td>Mar-Apr 1950</td>
<td>3,200</td>
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<tr>
<td>Feb-Apr 1951</td>
<td>4,000</td>
</tr>
<tr>
<td>Jan-Mar 1953</td>
<td>10,000</td>
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<tr>
<td>Oct 1957-Mar 1958</td>
<td>19,000</td>
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<tr>
<td>Mar-Apr 1959</td>
<td>1,500</td>
</tr>
<tr>
<td>Jan-Mar 1960</td>
<td>12,000</td>
</tr>
<tr>
<td>Feb-Apr 1963</td>
<td>12,100</td>
</tr>
</tbody>
</table>
1977 H1N1 Reemergence in Humans


Genetic Relatedness between the New 1977 Epidemic Strains (H1N1) of Influenza and Human Influenza Strains Isolated between 1947 and 1957 (H1N1)

C. SCHOLTISSEK,¹ V. von HOYNINGEN, AND R. ROTT

Institut für Virologie, Justus-Liebig-Universität Giessen, Giessen, Germany
Accepted May 19, 1978

- May 1977 outbreaks in Tientsin, China
- November 1977 Soviet Union, Hong Kong
- Virus A/USSR/77 reestablished H1N1

ALAN P. KENDAL,* GARY R. NOBLE,* JOHN J. SKEHEL,† AND WALTER R. DOWDLE*

* WHO Collaborating Center for Influenza, Center for Disease Control, U.S. Public Health Service, Atlanta, Georgia 30333 and †WHO Collaborating Center for Influenza, National Institute for Medical Research, Mill Hill, London, England

Accepted May 19, 1978
H1N1 did not circulate from 1957-1977

Nov 1977 H1N1 strain appeared in former Soviet Union, Hong Kong and China

Affected primarily young people, mild presentation

Genetics of virus very close to 1950 strain, but different from 1947 and 1957, suggesting that the outbreak strain had been preserved from 1950

2 Palese, P. Nature medicine 12:S82-S87, 2004
H1N1 Reemergence in Humans

- “The reemergence was probably an accidental release from a laboratory source in the setting of waning population immunity to H1 and N1 antigens”\(^1\)
- “Although there is no hard evidence available, the introduction of this 1977 H1N1virus is now thought to be the result of vaccine trials in the Far East involving the challenge of several thousand military recruits with liveH1N1 virus”\(^2\)

\(^2\) Palese, P. Nature medicine 12:S82-S87, 2004
Virus of the Year
Science, 2009

Near miss. The H1N1 virus was less virulent than feared, but the next pandemic could be worse.

FOR YEARS, SCIENTISTS HAVE BEEN WARNING THAT an influenza pandemic could strike at any moment, triggering a global catastrophe on the order of the 1918 Spanish flu. They imagined the culprit would surface in Asia—and, since 2003, have worried that the avian influenza strain H5N1 might be it. Health officials worldwide drafted one preparedness plan after another.
Epidemic began in North America, not Asia

Originating swine virus already circulating in humans (and not H5N1)

Dangerous in young and pregnant, otherwise mild

Discovered early in humans
  - Mexico open with epidemiology, aggressive with intervention

New vaccines and drugs approved quickly

Good information flow over the internet
Poor flu surveillance in pigs, virus undetected for years, circulates for months in humans before detection (too late for quarantine)

Travel bans and human quarantines against the advice of WHO

Egypt kills all pigs despite no pig to human transmission found

Vaccines hit snags

Poor countries were last in line for vaccines
US did not use vaccine adjuvants to stretch vaccine supplies

European countries used adjuvants, but insisted on 2 dose regimen despite evidence that 1 dose was protective

Rumors and mistrust of vaccine high
- Denounced by celebrities
- “it hasn’t been tested on humans”
- “it’s a WHO-led plot to depopulate the world”

Enserink and Cohen, Science 326:1607, 2010
Initial Response of Health Care Institutions to Emergence of H1N1 Influenza: Experiences, Obstacles, and Perceived Future Needs

Ebbing Lautenbach,1,2,3,4 Sanjay Saint,5 David K. Henderson,6 and Anthony D. Harris7,8

1Division of Infectious Diseases, Department of Medicine, 2Department of Biostatistics and Epidemiology, 3Center for Clinical Epidemiology and Biostatistics, and 4Center for Education and Research on Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; 5Ann Arbor VA Medical Center and Department of Internal Medicine, University of Michigan, Ann Arbor; 6Hospital Epidemiology Service, and Office of the Director, Clinical Center, National Institutes of Health, Bethesda, 7Department of Epidemiology and Preventive Medicine, 8VA Maryland Healthcare System, University of Maryland, Baltimore, Maryland

(See the editorial commentary by Carlson and Perl, on pages 528–30.)
Survey of healthcare epidemiologists regarding the H1N1 outbreak

- 77.7% agreed with mandatory vaccination
- Problems to address:
  - Widespread hoarding of antiviral medicines
  - Neglect of other infection prevention programs as attention diverted to H1N1
  - Better availability of resources and personnel to prevent “burnout”

“The most difficult challenge would probably not be to increase medical knowledge about treatment and prevention but to increase medical capacity and resource availability (e.g., hospital beds, medical personnel, drugs, and supplies) and public-health and community-crisis responses to an event in which 25–50% of the population could fall ill during a few weeks’ time. Health-care systems could be rapidly overwhelmed by the sheer volume of cases; ensuring production and delivery of sufficient quantities of antivirals, vaccines, and antibiotics, as well as providing widespread access to medications and medical care, particularly in impoverished regions, would be a sobering challenge.”

Figure 2. Cumulative percentage deaths from influenza–pneumonia, by days (estimated) from illness onset, among fatal cases during various epidemics, 1918–19 (5,17–22). Vertical arrows indicate median no. days to death.

Predominant Pneumonia at Army Camps, Fall 1918

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“...These men start with what appears to be an ordinary attack of La Grippe or Influenza, and when brought to the Hospital they very rapidly develop the most viscous type of Pneumonia that has ever been seen. Two hours after admission they have the Mahogany spots over the cheek bones, and a few hours later you can begin to see the Cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the colored men from the white. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible. One can stand it to see one, two or twenty men die, but to see these poor devils dropping like flies sort of gets on your nerves. We have been averaging about 100 deaths per day, and still keeping it up...”

http://virus.stanford.edu/uda/
Fig. 1-20. Sleeping quarters for basic recruits in 1962. Notice the staggering of head and feet (by pillow placement) to help prevent the spread of airborne disease. Photograph: Courtesy of the 37th Training Wing Historian’s Office, Lackland Air Force Base, San Antonio, Texas.
Increased vulnerability

- Crowding
- Environmental exposures
- Constant introduction of immunologic naives
- Emotional stress
- Increased exertion
- Extremes of temperature
- Decreased hygiene
- Disincentives for seeking care

- Increased susceptibility as well as differences in presentation
Respiratory infection:

- **Definitions:**
- **Acute Respiratory Disease (ARD) =** Febrile Respiratory Illness (FRI)
  - Fever ($\geq 100.5^\circ F$) plus one or more of the following: sore throat, cough, stuffy nose, runny nose, or diagnosis of pneumonia
  - (Includes limitation from duty by the examining physician for at least 8 hours)
“During...WWII, from a mean strength of 6,076,135 there were 4,086,562 admissions for common respiratory disease recorded by the US Army. The average time lost from duty by a person admitted for treatment of common respiratory disease during this period was 6.2 days...The 4,086,562 cases admitted during the war period thus resulted in approximately 26.5 million man-days lost from duty, or approximately 18,000 each day of the war. An Army division is composed of 15,000 personnel. Thus, more than equivalent strength of one Army division were absent from duty every day of the war because of the common respiratory diseases.”

-Duff FL, Thesis, Johns Hopkins University, 1952
1942: recruits vs. non-recruits' FRI

Fig. 13-1. Comparison of respiratory illness rates among recruits as compared to non-recruit (“seasoned”) military populations.


**PRETRAINING**

**DURING 8-WEEKS TRAINING, OF EACH 10 MEN:**

- Two hospitalized with acute respiratory illness for average period of 10 days. Fifteen per cent develop pneumonitis.
- Two develop minor respiratory illnesses treated at dispensary.
- Four suffer very mild disease or inapparent infections.
- Two not infected.

**EIGHT BECOME INFECTED.**

**TWO ESCAPE INFECTION.**

*Figure 4.* The development of RI virus infections among recruits during winter training (February to March, 1954) at Fort Dix, N. J.
Combined Adenovirus Serotype Distribution and Febrile Respiratory Illness (FRI) Rates, US Military Basic Training Centers

Sanchez, Clin Micro Rev 2015 (NHRC data)
Influenza A

- Important cause of FRI and pneumonia
  - Distant 2nd to adenovirus for viral FRI pathogens; generally ~10% specimens + for influenza during flu season
  - 92% vaccine effectiveness

Influenza prevention issues

- LAIV vs TIV
  - Issues with antigen detection test
  - Inactivation of LAIV if antiviral prophylaxis required---25% of population unvaccinated at any given time assuming 14 d to immunity
- At JBSA-Lackland TIV preferred
- Directly observed therapy preferred for prophylaxis given 30-50% adherence
Other causes of FRI/ARD

- Rhinovirus
- *Bordetella pertussis*
- *Mycoplasma pneumoniae*
  - ~10% of CAP, year round, 6% seroconversion
- *Chlamydia pneumoniae*
  - Also causes conjunctivitis outbreaks
- RSV
- EBV

Sanchez, Clin Micro Rev 2015
Global influenza surveillance

- World Health Organization’s Global Influenza Programme
- 141 national centers in 111 countries conduct year-round surveillance
- Every spring WHO publishes recommendations for northern hemisphere
- In US, FDA then determines viruses to be used in US-licensed vaccines
US Military Surveillance

- **Surveillance for Basic Military Trainees**
  - Febrile Respiratory Illnesses monitored & reported weekly

- **Military wide**
  - Influenza and influenza like illnesses are monitored worldwide
  - Specimens of interest sent to one of three centralized military laboratories (Germany, Ohio, San Antonio)
  - Weekly reports generated on rates & subtypes
  - Influenza vaccination rate tracked

- **Limitation of data**
  - Lag in data
  - Samples must be of interest
  - Data obtained from diagnosis codes
After vaccine strains selected:

- Private sector manufacturers begin producing vaccine
- Takes ~6 months to produce large quantities
- Manufacturers may begin to grow one or more virus strains in January for October-November delivery
- Most vaccine doses produced in chicken eggs
February 24, 2010

ACIP panel voted to expand recommendation for annual influenza vaccination to all people >6 months

Took place against incremental increases in numbers/groups recommended

Lessons learned from pdm09(H1N1) influenza A pandemic
Antiviral medications: summary for clinicians

• Five now available in US:
  ○ Neuraminidase inhibitors (active against A and B): oseltamivir, zanamavir, peramivir
  ○ Amantidine and rimantidine (adamantanes; active against A only) not recommended

http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
Why peramivir?

- Oseltamivir only available in oral formulation
- Zanamavir only available as inhaled drug, not formulated for ventilator use
- Need for parenteral neuraminidase inhibitors underscored during pandemic
2009- Emergency Use Authorization

- Use limited to hospitalized patients with lab-confirmed influenza A who did not respond to other therapy

- Randomized trial terminated early due to futility---adding peramivir to standard of care oseltamivir

Clin Infect Dis 2014, advance access Aug 12, 2014
Doi: 10.1093/cid/ciu632
Now available

First-and-Only One-Dose IV Treatment for Influenza

Immediate drug delivery in your hands

Release

On December 19, the U.S. Food and Drug Administration approved Rapivab (peramivir) to treat influenza infection in adults.
• Licensed for treatment of “acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days.”

• Efficacy not established for patients with serious influenza requiring hospitalization
Peramivir---the bottom line

- Another (single dose) option for uncomplicated flu treatment
- Price is ~$950/dose vs ~$60-100 for oseltamivir
- We will know more after the next influenza pandemic
Questions?

http://www.archives.gov/exhibits/influenza-epidemic/records-list.html