“Are We Ready for the Influenza Pandemic?”

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Objectives

- Appreciate the history of pandemics
- How and when an influenza pandemic can take place?
- Recognize implications
- Clinical presentations and treatment
- Public health response?
- What can we do at hospital level?
History of Pandemics

- Plague of Athens, 430 BC, ¼ pop
- Antonine Plague, 165–180, 5 million
- Plague of Justinian, 541-750, ½ pop
- Black Death, 14th onward, 75 millions
- Third Plague Pandemic, mid 19th century in China, 10 millions
  - San Francisco plague of 1900–1904
History of Influenza

- **Hippocrates** first described influenza in 412 BC
- The first influenza pandemic was recorded in 1580
- Since then influenza pandemics occurred every 10 to 30 years
Recent Pandemic History

- The **1889–1890 flu pandemic**, also known as Russian Flu, 1 million
- The "**Spanish flu"**, 1918–1919, 500 millions infected
- The "**Asian Flu"", 1957–58, 2 millions
- The "**Hong Kong Flu"", 1968–69, 1 million
Origins of deadly pandemic debated

The “Spanish flu” outbreak of 1918-20 killed perhaps 50 million people worldwide. Here are three possible origins:

ALDERSHOT, U.K.
ÉTAPLES, FRANCE
World War I’s trenches were first seen as the source of the disease.

SHANXI PROVINCE,
CHINA
A respiratory disease outbreak in 1917 may have been the first stirrings of the flu.

KANSAS,
U.S.
At Camp Funston, 48 soldiers died in March 1918, just ahead of the outbreak.

JOHN TOMANIO, RYAN MORRIS, KELSEY NOWAKOWSKI, NG STAFF
SOURCES: WAR IN HISTORY; JOURNAL OF PUBLIC HEALTH POLICY
INFLUENZA PANDEMIC
MORTALITY IN AMERICA AND EUROPE DURING 1918 AND 1919

DEATHS FROM ALL CAUSES EACH WEEK
EXPRESSED AS AN ANNUAL RATE PER 1000

NEW YORK
LONDON
PARIS
BERLIN
BERLIN RATES MISSING FOR AUG. 7-31, OCT. 19, 1918.
Variable Case Mortality

- U.S. Army camps 5-10% or higher
- British Army in India, white troops was 9.6%, for Indian troops 21.9%.
Variable Case Mortality

- In isolated human populations, the virus killed at even higher rates.
  - In the Fiji islands, it killed 14% of the entire population in 16 days.
- In Labrador and Alaska, it killed at least one-third of the entire native population.
A letter from a physician wrote on the 1918 pandemic

- “It is only a matter of a few hours then until death comes [...]. It is horrible. We have been averaging about 100 deaths per day [...]. Pneumonia means in about all cases death [...]. We have lost an outrageous number of Nurses and doctors. It takes special trains to carry away the dead.”
Recent Pandemic History in US

- H1N1 2009 to 2010 over 12 months
- 60.8 million cases
- 274,304 hospitalizations
- 12,469 deaths
- Fatality rate at 0.02%
Unfolding pandemic of H1N1 in 2009

- Early cases started in Feb/March in Mexico
- As of June 9, 2009, a total of 73 countries had reported more than 26,000 laboratory-confirmed cases
- By August 2010, virtually all countries report lab-confirmed cases
Why early H1N1 cases so alarming?

- 899 hospitalized patients showed that 58 (6.5%) became critically ill, and of those, 41% died. (2.66% mortality rate)
- Mortality among children, young adults, and pregnant women was much higher than in a typical influenza season
Conclusion of WHO, International Committee Review

- “The world is ill prepared to respond to a severe influenza pandemic or to any similarly global, sustained and threatening public-health emergency.”
Why pandemics are so hard to manage and be prepared for?

- Limitations of scientific knowledge
- Difficulties in decision making under conditions of uncertainty
- Complexities in international cooperation
- Challenges in communication among experts, policymakers and the public
HPAI H5N1

- On May 21, 1997, a three-year-old boy died in Hong Kong from a viral infection that turned out to be influenza.
- It took an international team of virologists three months to identify it as H5N1—“bird flu”
HPAI H5N1

- Then re-emerged in 2003 with sporadic transmission to more than 600 humans from 15 countries
- Highest rates are in Indonesia, Vietnam and Egypt
- Endemic in many countries
When can a pandemic occur?

- A new influenza virus subtype must emerge for which there is little or no human immunity
- It must infect humans and causes illness
- It must spread easily and sustainably (continue without interruption) among humans
Good news on H5N1

- Has not changed since re-emergence in 2003
- The H5N1 virus in Asia and Middle East meets the first two conditions
- But misses the third
Limited, non-sustained human-to-human transmission?

- 2004 in Thailand from child to mother
- 2007
  - China, child to father
  - Indonesia, 8 cases in same family
  - Pakistan, 3 brothers
Study shows how easily pandemic H5N1 bird flu could evolve

Scientists discovered it took just five genetic mutations for a potentially pandemic strain of H5N1 bird flu virus to emerge

Alok Jha, science correspondent
theguardian.com, Thursday 21 June 2012 14.11 EDT
Jump to comments (35)
U.S. panel defends call not to publish research about hyper-contagious mutant bird flu
One of the Deadliest Viruses

-In late 2011, the Dutch researchers announced the creation of an H5N1 virus transmissible through the air between ferrets (the best animal model for studying the impact of disease on humans).
Basic Science News

- Allow mutated virus to serially infect ten ferrets
- End result is H5N1 became as easily transmissible as the seasonal flu
- Viable aerosol virus.
Ron Fouchier, of Erasmus Medical Center found that:

- Five mutations needed for it to gain ability to latch onto cells in the nasal and tracheal passageways.
- Very bad news
The Frightening Conclusion?

- “Re-assortment with mammalian viruses is not needed" for it to evolve to spread through the air
Other Less Welcoming News?

-A single-point mutation, for example, can render it resistant to commonly used antiviral medications, such as Tamiflu.
Other Basic Science Work

- Yoshihiro Kawaoka at the University of Wisconsin–Madison published in “Nature” May 2, 2012

  “Controversial study shows how dangerous forms of avian influenza could evolve in the wild.”
Yoshihiro Kawaoka’s team randomly mutated the H5N1 virus until a key protein could bind to a mammalian cell receptor. Infecting ferrets with the virus caused additional mutations that made it highly transmissible.

Two mutations in the HA protein allow the virus to stick to receptors on human upper airway cells.
The mutated HA gene was combined with seven genes from the 2009 H1N1 pandemic virus.

H5N1–H1N1 hybrid

Ferret infected with hybrid virus

One week later, the virus had acquired a third mutation.

During airborne passage between...
During airborne passage between ferrets, the virus acquired a fourth mutation.

The fourth mutation allowed the virus to spread more effectively, infecting ferrets.
H1N1
- Easily spread
- Rarely fatal

H5N1
- Spreads slowly
- Often fatal
'Appalling irresponsibility': Senior scientists attack Chinese researchers for creating new strains of influenza virus in veterinary laboratory
REPORT

H5N1 Hybrid Viruses Bearing 2009/H1N1 Virus Genes Transmit in Guinea Pigs by Respiratory Droplet

Ying Zhang, Qianyi Zhang, Huihui Kong, Yongping Jiang, Yuwei Gao, Guohua Deng, Jianzhong Shi, Guobin Tian, Liling Liu, Jinxiong Liu, Yuntao Guan, Zhigao Bu, Hualan Chen

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Influencing Influenza

Currently, there is anxiety that the avian H5N1 influenza virus will reassort with the highly transmissible and epidemic H1N1 subtype to trigger a virulent human pandemic. Y. Zhang et al. (p. 1459, published online 2 May) used reverse genetics to make all possible reassortants between a virulent bird H5N1 with genes from a human pandemic H1N1. Virulence was tested in mice and transmissibility was tested between guinea pigs, which have both avian- and human-like airway influenza virus receptors. To assess what is happening to the receptor-ligand interactions as a result of these mutations, W. Zhang et al. (p. 1463, published online 2 May) probed the structure of both wild-type and mutant hemagglutinin of H5 in complex with analogs of the avian and human receptor types. Certain mutations...
Biological Air Cleaning

Airborne Disease Transmission

Significantly reduced viruses, mold, bacteria

Large droplets

Graphic courtesy of Steven Welty, Green Clean Air
Why Influenza will always be a threat?

- Socioeconomic and political development
- Indigenous cultures and customs
- Dietary habits
- Continuing mutations in the wild
Protein Demand

China overtook the U.S. last year in total consumption of chicken meat, but Americans ate more per person.

Total broiler-meat consumption

- U.S.: 15 million metric tons
- China: 10 million metric tons

Consumption per capita, 2012

- U.S.: 94 lbs.
- China: 22 lbs.

Source: USDA
The Wall Street Journal
Symptoms of Swine influenzas

- Intestinal: Diarrhea
- Respiratory: Coughing, Sore throat
- Physiological: Lethargy, Lack of appetite
- Nasopharynx: Sneezing, Mucous: nose/eye
- Systemic: Fever, Weight loss, Poor growth
Influenza Case Study in Airplanes in 1970s

- The plane, carrying 54 persons, was delayed on the ground for three hours, during which time the ventilation system was not functional. Most of the travelers remained on board.

- Within 72 hours, nearly 75% of the passengers developed influenza. The source of the infection was a single person on the airplane with influenza.
747-400/-400ER
416 passengers

23 first
61-in pitch

80 business
39-in pitch

313 economy
32-in pitch
CDC explains mix-up with deadly H5N1 avian flu

By Jocelyn Kaiser | 15 August 2014 3:45 pm | Comments

A federal scientist may have accidentally contaminated a relatively benign avian influenza strain with the deadly H5N1 bird flu virus in part because he or she was overworked and rushing to make a lab meeting, according to an internal report released today by the Centers for Disease Control and Prevention (CDC).

In the March incident, CDC sent a sample of low-pathogenicity H9N2 bird flu virus that a lab had unknowingly contaminated with H5N1 to a U.S. Department of Agriculture (USDA) lab, which discovered the mistake when test chickens died. CDC Director Thomas Frieden first disclosed the incident in July at a press conference about other lab accidents. Frieden was especially troubled, he said, because the H5N1 incident was not reported to top CDC leaders for 6 weeks.
How H5N1 influenza is perpetuated?

- Per CDC HPAI H5N1 virus is considered endemic in poultry in six countries (Bangladesh, China, Egypt, India, Indonesia, and Vietnam)
- The disease can be carried without symptoms in wild birds.
Pooping on people
In 12 easy lessons.
H5N1 outbreaks in 2005 and major flyways of migratory birds
Situation on 30 August 2005

- Mississippi Americas flyway
- Atlantic Americas flyway
- East Atlantic flyway
- Central Asia flyway
- Black Sea/Mediterranean flyway
- East Africa West Asia flyway
- East Asia/Australian flyway

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Data sources: AI outbreaks: OIE, FAO and Government sources.
Flyways: Wetlands International
New Development (Jan 2015)

-An HPAI H5N1 virus was detected in a wild duck in the United States.
-This virus is a “reassortant” virus with genes from HPAI H5 Asian viruses and low pathogenic North American viruses.

(“Reassortment” occurs when the genes from two different viruses mix to create a new virus.)
Bird flu hits two more MN turkey farms

MPR News Staff · Apr 6, 2015
How many types of influenza viruses?

- Human influenza A and B viruses cause seasonal epidemics
- Influenza B viruses are not divided into subtypes
- Influenza type C infections cause a mild respiratory illness
Why Influenza tend to be more prevalent in colder climates?

- Transmission of infection was most efficient when the humidity was 20-35%;
- It was blocked at 80% humidity.
- The conclusion of both papers is the same: humidification of indoor air during the winter might be an effective means of decreasing influenza virus spread.
Influenza Basics

- The Influenza A virus subtypes are labeled according to an
  - H (hemagglutinin) (H1 to H16)
  - N (neuraminidase) (N1 to N9)
- Influenza A viruses are negative sense, single-stranded, segmented RNA viruses.
Serotypes pathogenic in Humans:

- H1N1, which caused Spanish Flu in 1918, and Swine Flu in 2009
- H2N2, which caused Asian Flu in 1957
- H3N2, which caused Hong Kong Flu in 1968
- H5N1, which caused Bird Flu in 2004
- H7N7, which has unusual zoonotic potential\(^{[39]}\)
- H1N2, endemic in humans, pigs and birds
- H9N2
- H7N2
- H7N3
- H10N7
- H7N9
What is striking about the H5N1 outbreak of 2003?

- Predominance of children and young adults
- High mortality rate
- Kills all afflicted poultry livestock
After influenza viruses enter the human body, they attach to cells within the nasal passages and throat (i.e., the respiratory tract). The hemagglutinin (HA) surface proteins of the influenza virus bind to the sialic acid receptors on the surface of a human cell like a key to a lock. The influenza virus is then able to enter and infect the cell. This marks the beginning of a flu infection.
Incubation Period

- Following exposure to infected poultry, 7 days or less, often between 2-5 days
- In clusters of human to human transmission, 3-5 days
Human Mortality from H5N1
As of April 11, 2007
Clinical Features of H5N1

- Most gave recent hx of recent exposure to dead or ill poultry
- Wide range of infection—mild symptoms to life-threatening disease
- Presentation may depend on duration of exposure to virus
Clinical Features of H5N1

- Conjunctivitis only
- Influenza-like illness
- Severe respiratory illness
- Nausea, abdominal pain, diarrhea, vomiting
- Neurologic changes (altered mental status, seizures).
Clinical Manifestations of Patients in Viet Nam

- Highest risk less than 16 years of age
- Two children from same family presented with only diarrhea and encephalopathy
- CSF, fecal, throat and serum specimens
Risk Factors associated with Severe Disease

- Delayed admission
- Presence of bilateral pneumonia
- In the 67 cases studied, neutropenia and increased ALTs at presentation are predictive of fatal outcome
Complications?

- Multi-organ failure with renal dysfunction and cardiac compromise
- Pulmonary hemorrhage
- Pneumothorax
- Pancytopenia
- Most deaths due to respiratory failure
Imaging Studies Findings

- Diffuse, multifocal, or patchy infiltrates
- Interstitial infiltrates
- Segmental or lobular consolidation
- Progression to respiratory failure is associated with diffuse bilateral ground glass infiltrates
Who Should Be Tested?

- Recent exposure to dead or ill poultry
- **HIGH RISK:**
  - Recent travel to H5N1 affected country within 10 days of symptom onset and
  - X-rays confirming pneumonia, ARDS or other severe respiratory illness
Samples

- Should be sent within 3 days of onset of symptoms
- Throat samples better than nasal
- Should be obtained with Dacron tip, not with cotton or calcium alginate tips.
Antigen Tests and PCR

- Commercial rapid tests are less sensitive in detecting influenza A than PCR assays
When to Contact CDC?

- Any + results of H5N1 virus testing should be confirmed immediately at the Influenza Division at CDC
Influenza Treatment

- Tamiflu(oseltamivir) and Relenza(zanamivir) are the only two options in our arsenal
- Rapivab(Peramivir) in IV only
- Supportive care
- Aggressive bacterial treatment as needed
CDC Guideline for antivirals

- As early as possible
- Hospitalized patients
- Has severe, complicated, or progressive illness
Antiviral Course of Treatment

- Ideally within window 72 hours
- Treat even if passed window period
- In severe cases, may treat for 10 days
Who are the likely on the frontline?

- ED physicians and PCPs
- Intensivists and ICUs across the country
Public health response?

- Early identification of sources (national and international surveillance)
- Maintain good contact with possible cases
- Systemic culling of infected poultry
- Isolation and treatment of suspected or confirmed cases.
National Influenza Surveillance


2. Outpatient Illness Surveillance

3. Mortality Surveillance

4. Hospitalization Surveillance

5. Summary of the Geographic Spread of Influenza
Influenza Surveillance

- Find out when and where influenza activity is occurring
- Track influenza-related illness
- Determine what influenza viruses are circulating
- Detect changes in influenza viruses
- Measure the impact influenza is having on hospitalizations and deaths in the United States
Worker collecting perished poultry
Source: CSL Limited
Bird flu and danger to humans

Bird flu, or avian flu, has a high mortality rate in humans, but as of yet, can not be transmitted from person to person.

Infection with type A virus H5N1

1. Most virulent bird flu virus; mutates rapidly, altering its genetic material
2. Humans infected by close contact with live infected poultry
3. Birds carry virus and excrete it in feces, which dries, becomes pulverized and then can be inhaled or taken in by touch
4. Humans have no immunity against this virus

Symptoms

- Fatigue
- Fever
- Conjunctivitis
- Sore throat
- Cough
- Muscle aches

When untreated

Rapid deterioration; viral pneumonia leading to respiratory distress, kidney failure, multi-organ failure, death

WHO, February 20th, 2006: “Human infections remain a rare event.”

Reason for concern

Humans infected with bird flu could serve as a host for a new genetic subtype that can be transmitted from person to person.

Might start influenza pandemic

Source: World Health Organization
Graphic: Jutta Scheibe, Morten Lychne
© 2004 KRT
What are impediments to culling?
A chicken breeder covers his face as he sits behind animals in China. He says his chickens are not infected with H7N9.
Bangladesh Case Study

- Annual per capita income is only $440
- There are more than 100,000 small poultry farms
- Producing $400 million worth of chickens and $300 million worth of eggs every year.
Problem with culling

- Loss of income
- Loss of source of protein
- Loss of employment for small farms
- Plummeting demand for chicken
Public health response goal

- Goal to contain outbreak as much and early possible
- Massive vaccination campaign to follow
Limitation to response

- Antivirals will be in short supply
- By the time it arrives in the US, vaccines may not be available
Vaccine Production Options

- Cell culture
- Recombinant DNA
- Egg based
Cell Culture Vaccine Production

- November 20, 2012, FDA approved the use of Flucelvax
- Uses animal cells (Madin-Darby Canine Kidney, or MDCK) in liquid culture as a host for the growing influenza virus.
- U.S.-licensed (trivalent inactivated) influenza.
Cell Culture Vaccine Production

- Faster start-up of the vaccine manufacturing process
- The cells used to manufacture Flucelvax are kept frozen and “banked
- Safe and effective for use in individuals 18 years of age and older
- Used to produce rotavirus, polio, smallpox, hepatitis, rubella and chickenpox vaccines
Recombinant DNA Vaccine Production

- On Jan 16, 2013, FDA has approved Flublok the first trivalent influenza vaccine made using an insect virus (baculovirus) expression system and recombinant DNA technology.

- Flublok is approved for the prevention of seasonal influenza in people 18 through 49 years of age.
Recombinant DNA Vaccine Production

- Flublok’s novel manufacturing technology allows for production of large quantities of the influenza virus protein, hemagglutinin (HA)
- Offers the potential for faster start-up of the vaccine manufacturing process in the event of a pandemic
Recombinant DNA Vaccine Production

- 44.6% effective against all circulating influenza strains, not just the strains that matched the strains included in the vaccine.
- Contains 3 full-length, recombinant HA proteins
- Shelf life of 16 weeks from the date of manufacture
Problem with egg based vaccine production?

- Need 100s millions of 11 day old fertilized egg at any given time
- Influenza virus can be lethal to embryonated eggs
- Lack of surge capacity
- Strain adaptation requires an additional 4-6 months before vaccine production can be initiated
Pandemic Response

- May need two doses-4 wks apart
- If require higher dose for protection, i.e. 180mcg, would pose barrier to rapid production of vaccine
- Consider include H5 component in annual vaccine-pre-priming, better immunological response after 16 months
Dose-sparing alternative strategies

- Immune response based on the quantity of HA (hemagglutinin) antigen
- Intradermal instead of IM
- Addition of immune-enhancing adjuvant to the vaccine formulation
Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults


BACKGROUND

As compared with a standard-dose vaccine, a high-dose, trivalent, inactivated influenza vaccine (IIV3-HD) improves antibody responses to influenza among adults 65 years of age or older. This study evaluated IIV3-HD in individuals 65 years of age or older.
Summary

- Influenza Pandemic will always be a threat
- Geopolitical, cultural, social, economic climate will ensure success or failure
- Global surveillance is the key to prevention
- Swift public health response along with timely vaccine production
Patient on a Ventilator

Endotracheal tube goes through patient’s mouth and into the windpipe.

Nasogastric tube goes through patient’s nose and into the stomach.

Mechanical ventilator blows air, or air with increased oxygen, through tubes into the patient’s airways.

Air flowing to the patient passes through a humidifier, which warms and moistens the air.

Exhaled air flowing away from the patient.

Nurse periodically checks the patient.