

## Influenza: The most worrisome infection of our time?

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## Influenza virus

- Roots come from the Latin term for "poison"
- First seen as poisons, then life forms, then biological chemicals
- Now known to be an RNA virus
- Like many other viruses now thought of as a grey area between the living and the non-living.

## Orthomyxoviruses

- Influenza A and B
- Enveloped and Pleomorphic
- 8 gene segments code for 10 proteins
- Single-stranded RNA viruses (13.6 kB)
- RNA exhibits high mutation rates

## Influenza

1. A historical perspective
2. The virus and the disease it causes
3. The benefits of using vaccine
4. The economics of flu
5. Background for the current vaccine shortage
6. Treatment for flu
7. Avian flu, antigenic drift and shift
8. The best strategy to combat flu

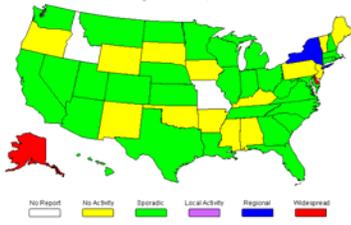
## Influenza A Epidemics vs. Pandemics

- In "**epidemic**" years, 10% - 20% of world's population gets influenza.
- Associated with 500,000 to 1,000,000 deaths worldwide.
- Caused by genetic "drifts"
- Point mutations in gene segments: H1 → H1
- In "**pandemic**" years, over 25% of world's population gets influenza.
- Associated with a disproportionate number of deaths worldwide.
- Caused by genetic "shifts"
- Complete substitutions of gene segments: H1 → H5

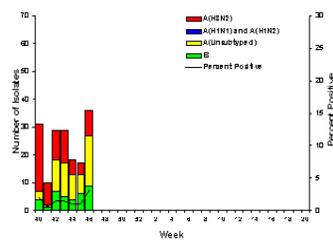
## US Influenza Morbidity & Mortality

- 50–60 million infections and illnesses
- 25 million physician visits
  - most by school-aged children and young adults
- 114,000–142,000 hospitalizations
  - rates highest in very young and elderly
- 20,000–40,000 deaths
  - influenza-pneumonia mortality highest in elderly
  - up to 51,000 when flu-related complications, like heart attacks and strokes, are included
- \$3–\$5 billion in direct medical costs
- Mimics other infections
- Role in complications often overlooked

Weekly Influenza Activity Estimates Reported by State & Territorial Epidemiologists  
Week ending November 20, 2004 - Week 46



U.S. WHO/NREVSS Collaborating Laboratories  
Summary, 2004-05



## History

### The Biggest Infectious Disease Events of the 20th Century

- Eradication of Smallpox
- Discovery of Penicillin
- Emergence of HIV/AIDS
- Childhood immunization
- The anthrax letters and the emergence of the bioterrorism threat
- Pandemic flu of 1918 - 1919

### The Early History of Influenza

- 2500 BC - domestication of ducks, bringing influenza close to human beings
- 412 BC - Hippocrates describes a disease that is probably influenza
- 1580 - 1st recorded pandemic: an outbreak in Europe & parts of Africa & Asia
- 1889 - Unknown influenza subtype (probably Russian flu) begins in Central Asia & spreads to Russia and other parts of the world.

### Medical care in the 19th Century

- No good knowledge of chemistry
- No autopsy
- Doubted germ theory
- Muttered about miasmas\*

\*A disease-causing noxious or poisonous or thick vaporous or emanation in the atmosphere formerly thought to rise from swamps and putrid matter

### Influenza in the 20th Century

- 1918 - Spanish flu **H1N1** (swine flu) killed 20-40 million people worldwide, more than on the battlefields of WWI
- 1930 - **H1N1** first isolated
- 1957 - Asian flu **H2N2** pandemic started in China and killed 70,000 in the US
- 1968 - Hong Kong **H3N2** pandemic killed 34,000 in the US
- 1976 - Swine flu scare (only 1 death)

**There is a flu pandemic about once every generation; the last being 1968. So we are overdue!**

### The Spanish Flu

- Duration: summer 1918 - spring 1919 (10 months)
- >500,000 deaths in the US (equivalent to 1.7 million today)
- >50 million killed worldwide (equivalent to 175-350 million today)

*Why Spanish and not Chinese or American?*

### Spanish Flu Caused

- Quarantines
- School closures
- Factory shutdowns
- Cancellation of Liberty Bond marches
- Disruption of the war effort?
- US response = Chinese SARS

**President Wilson, fixated on events on the Western Front, didn't delay the voyages of troop ships to France, even though jamming thousands of soldiers into fetid quarters guaranteed the spread of disease and the deaths of thousands.**



Normally flu kills the very young and the very old.

Spanish flu killed people in their 20s and 30s - in the prime of life!

We still don't know exactly why!

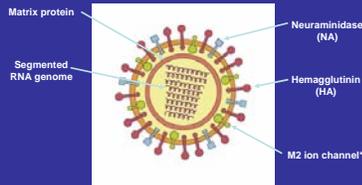
Would things be different now?

- We have antibiotics for secondary infections
- A distribution system
- Worldwide warning stations
- Vaccine and anti-viral medications

Maybe

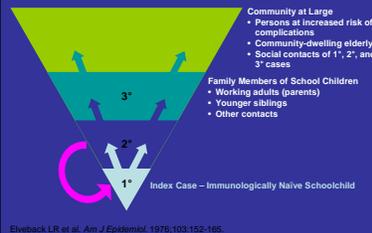
The virus,  
the disease  
and the vaccine

### The Influenza A Virus

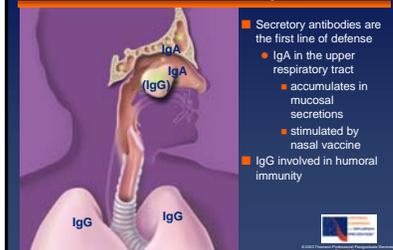


\*Influenza type B virus has a different ion channel protein

### Transmissibility of Influenza



### Mucosal and Humoral Immunity to Influenza



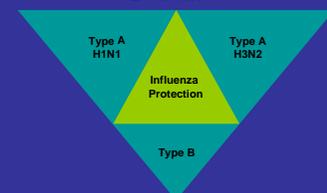
### Human Pathogenesis

- Invades respiratory epithelium with highly toxic viral particles
- Impairs mechanical and cellular host responses
- Elicits acute inflammatory response
  - Leads to ciliary abnormalities
  - Desquamation of ciliated and mucus-producing cells.
- Loss of mechanical clearance of respiratory tract (no escalator)
- Normal respiratory epithelium restored 2 - 10 weeks after infection
- Damage renders host susceptible to invasive bacterial superinfections
- Virus in blood is detected rarely

### EPIDEMIOLOGY: Influenza A circulates in three major pools of animals.

- In **humans**, infection spread by respiratory-droplet route.
- In **wild birds**, infection spread by fecal-oral route.
- In **farm animals**, infection spread by both routes
  - Swine (respiratory-droplet)
  - Chickens and ducks (fecal-oral)

### Influenza Vaccine: A Trivalent Defense



CDC. *MMWR* (Morbidity and Mortality Weekly Report). 2001;50(RR-4):1-44.

## World Health Organization Influenza Nomenclature



Influenza type B does not occur as subtypes.

## The 2004-2005 vaccine

Inactivated and live, attenuated vaccines

- A/Fujian/411/02 (H3N2)-like
- A/New Caledonia/20/99 (H1N1)-like
- B/Shanghai/361/2002-like

Antigenically equivalent

- A/Wyoming/3/2003 (H3N2)
- B/Jilin/20/2003 virus or B/Jiangsu/10/2003

## What's important here

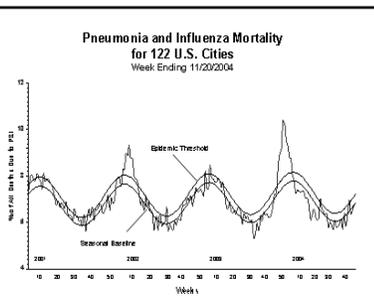
- Vaccine
  - Supply and current shortage
  - Vaccination rate & appropriateness
  - How well the vaccine strain matches with the circulating strain(s)
- Disease
  - Prevalence
  - Virulence
- Personal hygiene

## The benefits of using vaccine

## Preventing Flu deaths

- Estimated at ~36,000 per year in the US
- Calculated by looking at the average number of pneumonia deaths during a given period, and comparing that with what is known about flu activity during that period. When flu is present, they check for marked increases in the number of pneumonia cases. All the cases above the average are attributed to the flu.
- That mortality figure rises to 51,000 when flu-related complications, like heart attacks and strokes, are included

## Influenza is nationally tracked by CDC's Pneumonia & Influenza (P&I) Mortality System in selected US Hospitals



## Flu & Emergency Rooms

- From 1992 to 2002, the annual number of patient visits to our nation's emergency departments has increased 23%.
- The number of our emergency departments has decreased 15% during that same period.
- The nation's emergency departments report that 62% of them are "at" or "over" operating capacity.
- In LA, 6 ER's have closed down this past year
- In California, more than 65 ERs have closed in the past decade, and more close each month

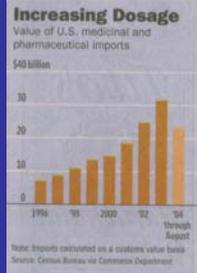
## The Economics of Flu

- The average worker misses about 1 to 1.5 days a year because of the flu
- \$20 billion in lost productivity — depending on the severity of the outbreak
- Employers typically purchase 10 million to 20 million flu shots to sponsor flu clinics at work
- Vaccinating healthy Americans against the flu is cost-effective, saving at least \$13.66 per person



## Vaccine makers have plummeted

- Three years ago, Wyeth was making more than 20 million doses of flu vaccines annually. The company decided in 2002 to end its flu vaccine program.
- Two years earlier, King Pharmaceuticals ended its program.



## Foreign not Domestic

- Chiron (an American company) was producing vaccine in a recently acquired British plant that had a known history of problems
- The other major manufacturer, with a plant in Swiftwater, Pa, was owned by a French company, Sanofi-Aventis SA

**80 percent of the world's measles vaccines come from one company in India!**

## Today's Problems

- Inadequate surge capacity
- Too few alternative treatment centers
- Dealing with the dual threat of biological terrorism and emerging infectious diseases
- Who should get vaccine?

## Vaccine Questions

- Is it a bit risky for a society to rely purely on free market economics to guarantee a stable and reliable supply of vaccines?
- If you have enough vaccine for hands-on health care employees or high-risk patients, but not both who should receive the vaccine?

## Vaccination Risk and rates\*

- Health care workers
  - All at risk
  - 38.4% vaccinated
- The American population
  - 90 million at risk
  - 65.6% of those >65 vaccinated
  - 34% of those 50-64 vaccinated

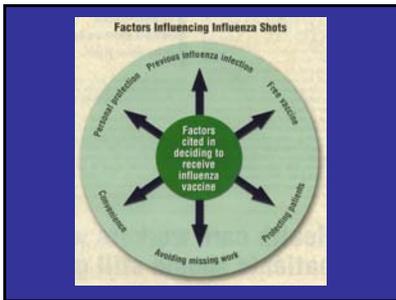
Santoli JM et al. JAMA 2003;290(23):3122-3128

## The Effectiveness of Influenza Vaccine

Age (years)	Status	Effectiveness*
<65	Healthy	70%-90% against infection
<65	Community-dwelling	30%-70% against hospitalization
>65	Nursing home or long-term care resident	30%-40% against infection, 50%-60% against hospitalization, 80% against death

## But effectiveness varies

- Age
- Immune status
- Vaccine match with circulating strain
- How much flu is out there
- Herd effect



### Absenteeism

- Only **7%** of employees vaccinated for the flu missed work due to that illness compared with **40%** who missed work for flu when they weren't vaccinated\*
- Parents of children vaccinated with FluMist missed **72%** fewer days of school\*\*

\*ComPsych study  
\*\*University of Maryland School of Medicine study

### Not to worry....yet

- The dominant virus strain, so far, is contained in this year's vaccine
- The strains are similar to last year's
- 30% of Americans got the flu last year providing some carry-over immunity

### Bioshield II

- Builds on "The Project Bioshield Act," (Bioshield I), which was signed into law in July 2004.
- Bioshield I is intended to stimulate the development of treatments, preventatives, and diagnostics related to bioterrorism preparedness and response
- IDSA has consistently urged Congress to extend the scope of both Bioshield I and II beyond bioterrorism to include research and development of vaccines and antibiotics to prevent and treat naturally occurring infections

### We know about supply... but what about demand\*?

- 49% said they did not intend to be vaccinated
- 54% did not feel at risk
- 45% said the vaccine was not effective
- 42% were worried about adverse events

\*Harvard survey of 1,048 people in 2003

### Why did we lose half of our vaccine supply in one swift blow?

### The Problem

- The excuses
  - Flu vaccine has to be reformulated every year
  - The FDA has a difficult task
  - Companies suffer huge losses if they overestimate the amount that will be needed because they end up having to destroy millions of doses
- The reality
  - We were incredibly stupid

### Why the flu vaccine crisis?

- Fear of lawsuits
- Excessive regulation
- Poor planning
- Relying on just 2 manufacturers
- Using a single plant in another country
- FDA and British regulators not communicating or acting early and decisively

### The Poor FDA

- Inspections are required at least every other year
- Rising number of factories to police all over the world
- Regulators around the world aren't required to share information about factories they oversee
- In 1999 there were 17,000 inspections of foreign and domestic food and drug plants. There were 22,543 in 2003

**In 2001-2002 only 2/3 of flu vaccine was available by October**

### **Influenza 2003-2004**

- Early childhood deaths in Colorado
- Early start and sudden early finish
- Scramble for limited vaccine
- The predominant circulating flu strain was not in the vaccine
- Thus the vaccine was only partially effective. A Colorado study for the CDC concluded last year's flu shots were 52% effective in protecting healthy adults against flu and 38% effective in preventing flu among those with health conditions putting them at higher risk.

**Last influenza season 87 million doses of flu vaccine were made, but only 83 million doses were used.**

### **Influenza 2004-2005**

- New antigenic drift strain from New Zealand to Norway: A/Wellington/1/2004(H3N2)-like virus
- A/Fujian is predominant vaccine strain
- Influenza was unusually mild throughout the Southern Hemisphere from May through October 2004

**But we have a vaccine shortage.....so**

### **Prioritizing Redistribution**

- CDC - Where's Waldo?
- National - State - Local conflicts
- Can't nationalize a therapeutic if not under federal control
- Bioethics of distributing 56 million doses
- VA got full shipment, San Antonio got 50 doses
- Social disruption
- Transmission to severely ill patients & long term care center patients; those with worst immune response
- Morbidity & mortality considerations

### **Continuity of Government & Physician Services**

- Should Bush and Cheney be vaccinated?
- Should Congressional staff? They shake many hands
- Is there bioethics in government?
- Physicians and their staff?
- Legal state issues to physicians

### **More Consequences**

- Price gouging
- Shame
- Crowds lining up
- Some who normally don't take the vaccine now want it

### **Our Friend Canada\***

- Many Americans have gone to Canada to find flu vaccines
- Health officials in Vancouver had a clinic specifically for American citizens on Oct. 30
- Any American with an appointment will be given a flu shot, provided he pays the \$40 charge\*
- We're trying to get 2 million doses from them

\*Viviana Zanocco, a spokeswoman for the Vancouver Coastal Health Authority



Link ahead of avian virus is still unclear, health officials say

## Avian Influenza

### Avian Flu in the later 20th Century

- 1983 - Avian flu **H5N2** in Pennsylvania chicken farms - 17 million birds slaughtered
- 1997 - Avian flu **H5N1** infects 18 in HK, 6 deaths, 1.4 million birds killed - **FIRST KNOWN AVIAN TRANSMISSION TO HUMANS**
- 2001 - **H5N1** resurfaces in Hong Kong's live poultry markets - more slaughter
- 2002 - **H5N1** again resurfaces in HK live poultry markets
- 2003 - Netherlands **N7N7** in poultry - vet death and 80 eye cases
- 2003 - Hong Kong **H5N1** case after visiting China, 1 death
- 2004 - Current avian flu **H5N1** outbreak in SE Asia

Why do we worry so much about flu in general and avian flu in particular?

Influenza is more contagious than smallpox (which is very stable)

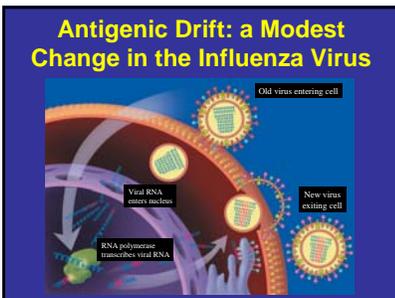
and

there is antigenic drift and antigenic shift

### Antigenic Drift

- Influenza types A and B<sup>1,2</sup>
- Modest variations (point mutations) in hemagglutinin and neuraminidase genes<sup>1,2</sup>
  - antigenic profile changes may compromise vaccine and immune system efficacy<sup>2</sup>
  - annual evaluation of circulating influenza and vaccine reformulation updates antigenic profile<sup>2</sup>
- Responsible for annual epidemics<sup>2</sup>

1. Oshida, S. *Journal of Virology* 1992;66:1211-1215.  
2. CDC. *Current Influenza Virus* May 2001 50(9):1-14.



### Antigenic Shift

- Influenza type A only
- Profound variation in hemagglutinin or neuraminidase structure
  - reassortment of genomic material
- New virus with novel antigenic profile
  - compromised vaccine and immune system efficacy
- Pandemic consequences

Orlowski, Subbarao K. *Lancet*. 1999;354(1):277-1292.

The huge population of viruses, combined with their rapid rates of replication and mutation, makes them the world's leading source of genetic innovation: they constantly invent new genes.

### Species-to-species transfer

- Studies have indicated that pigs, seals, whales, mink, and ferrets are susceptible to natural infection with purely avian flu viruses.
- But only **pigs** are significant for human health, because they **can harbor both avian and human flu viruses**, setting the stage for potential combination of the two to form a dangerous new strain

### And flu probably starts in the Orient because of the close proximity of pigs and chicken to people



### Avian flu jumping the species barrier

- 1997 – Influenza A (H5N1) caused **18 cases and 6 deaths** in Hong Kong
- February, 2003 - H5N1 resurfaced infecting **2 people and killing 1**
- 2003 – Netherlands H7N7 strain from a poultry farm caused 80 minor illnesses and at least 1 death ( in a vet), slaughtered ~26 million birds at some 250 farms
- 2003 – South Korea
- 2003 – Hong Kong (H9N2) – 1 child (last 1999)

### The current status of Avian Flu (H5N1)

- A total of 44 cases (32 deaths) have now been reported in Thailand (n=17) and Vietnam (n=27) since January, 2004.
- Most confirmed cases have occurred in children and young adults who had exposure to sick or dead poultry.
- The 44 cases include a family cluster of 4 cases (2 confirmed as H1N1; 1 probable; 1 pending) from Thailand, prompting concern of possible human-to-human transmission – at least one of the ill family members reportedly had no exposure to live or dead poultry but provided bedside care to an ill child.

### The current status of Avian Flu (con't)

- Affected poultry flocks in eight countries in East Asia
- In Thailand, avian flu killed two house cats and a clouded leopard, and infected a tiger at a zoo near Bangkok
- There has been no evidence of wider transmission in the community.
- The most recent case was reported from Thailand on 10-25-04.

### Transmission

- In the current poultry outbreaks, the virus grows in the intestines as well as the respiratory tract of birds, so that birds are spreading the virus in their droppings and causing widespread contamination
- The extreme virulence of some strains (e.g., highly pathogenic avian influenza virus) is determined by the susceptibility of the hemagglutinin of virulent strains to cleavage and activation by specific proteases present in vulnerable internal tissues.

### The Current Flu Status in North America (not H5N1)

- The Texas Animal Health Commission reported an **H5N2** outbreak in a chicken flock. The virus appears to be a low-pathogenic strain that causes low mortality in chickens and poses no threat to humans.
- **H7N2** outbreaks were reported at two chicken farms in Delaware
- **H7N2** in 4 live-bird markets in New Jersey
- **H2N2** strain was found at a farm in Pennsylvania.
- Canadian Food Inspection Agency reported an **H7** influenza virus at a poultry farm in British Columbia

### Treatment of flu



### Reckless Early Treatment

- Typhoid vaccine
- Quinine
- Morphine
- Opium
- Heroin
  
- Put them to bed and keep them there
- Nurses > doctors

## Drugs & Vaccines

- Prevention
- Killed flu vaccine
- Live flu vaccine
- Amantidine (Symmetrel)
- Rimantidine
- Oseltamivir (Tamiflu)
- Amantidine (Symmetrel)
- Rimantidine
- Oseltamivir (Tamiflu)
- Zanamavir (Relenza)
- Treatment
- Amantidine (Symmetrel)
- Rimantidine
- Oseltamivir (Tamiflu)
- Zanamavir (Relenza)



**IMPORTANT NOTICE TO ALL PATIENTS**  
Please tell staff immediately if you have flu symptoms

*(Flu symptoms include fever, headache, sore throat, dry cough, runny nose, muscle aches and body aches)*

**1** **Cover Your Cough and Sneeze**

- Use a tissue to cover your mouth and nose when you cough or sneeze.
- Grip your used tissue in a waste basket.
- You may be asked to wear a mask if you are coughing or sneezing.

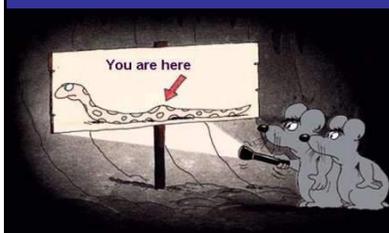
and

**2** **Clean Your Hands**

- Wash your hands with soap and warm water or clean with gels or wipes with alcohol.
- Cleaning your hands often helps you from spreading germs.

For avian flu we would have to add or substitute an H5N1 component and get it through the FDA.

## Where are we today?



## So what can we do about all this?

- Global and domestic surveillance
- Drugs and vaccines for prevention & Rx
  - WHO has recommended as part of its Pandemic Preparedness Plan that countries establish stockpiles of antiviral treatments such as Tamiflu, which are effective against all strains of the influenza virus.
- Infection control practice
  - At home and at work
  - In crowded places
  - In the hospital

## Making the infectious diseases market more attractive to industry

- Tax credit incentives
- Strengthened intellectual property rights
- Liability protections
- Some type of federally guaranteed purchase program

## Sweetening the Pot

- A proposed Senate bill would guarantee government purchase of unused doses and offer tax breaks to encourage investment in vaccine production and research.
- But bear in mind that:
  - drug companies reported a 17% overall profit last year while the rest of the economy reported a 3-4% profit.
  - Drug price increases substantially outpace inflation
  - We have the highest drug prices in the world

## So Why Worry About Avian Flu?

- There are very few human cases worldwide and none here in the US
- No clear consistent evidence of human-to-human transmission
- It hasn't done any serious harm (yet)
- There are vaccines to prevent it and drugs to treat it

### But consider...

- Vietnam reported H5N1 activity in 57 of the country's 64 provinces
- This resulted in the death or destruction of 43 million poultry
- Fortunately humans were not culled

### Why did we kill all those chickens?

- Given enough time and exposure it could mutate
- The genetic material from an old flu virus mixes with genetic material from the new virus producing a new virulent virus that is rapidly transmissible
- We would be virtually defenseless

**Antigenic Shift!**

### H5N1: Summary

- Present in 8 SE Asian countries (Vietnam, China, Thailand, Korea, Cambodia, Indonesia, and Laos )
- Vietnam has had 22 cases with 15 deaths
- There could be further dissemination by water sources contaminated with droppings from wild birds
- Is killing wild birds an appropriate control method vs. monitoring contact between wild birds and poultry?
- Hiding and smuggling of valuable birds such as fighting cocks can prolong or worsen avian flu outbreaks
- The triumvirate: Humans, birds and pigs

### The Federal Pandemic Influenza Preparedness & Response Plan

- a coordinated strategy to prepare for and respond to an influenza pandemic
- provides guidance to state and local health departments and the health care system

### The plan will

- assure and expand influenza vaccine production capacity and use
- stockpile influenza antiviral drugs in the Strategic National Stockpile (SNS)
- enhance U.S. and global disease detection and surveillance infrastructures
- expand influenza-related research
- support public health and laboratory planning
- improve health care system readiness at the community level.

### More things to do

- Development & enhancement of stockpiles & reserves
- Streamlining the regulatory process
- Strengthening liability protection
- Improving communication among stakeholders
- Assessing the financial incentives for the manufacturer

### CDC's 7 Components of Influenza Surveillance

- World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System (NREVSS) Collaborating Laboratories
- U.S. Influenza Sentinel Providers Surveillance Network
- 122 Cities Mortality Reporting System
- State and Territorial Epidemiologists Reports
- Influenza-associated pediatric mortality
- Emerging Infections Program (EIP)
- New Vaccine Surveillance Network (NVSN)

### Worldwide WHO Influenza Surveillance Collaborating Laboratories



### Phases of Pandemic Influenza

- Phase 1
  - confirmation that the novel influenza virus is causing outbreaks in one country
  - Confirmation that it has spread to others
  - disease patterns indicating that serious morbidity and mortality are likely to occur

## Phase 2

- Outbreaks and epidemics occur in **multiple countries** with global disease spread
- Response activities depend, in part, on the extent of disease internationally and in the U.S.
- **Community-level interventions** like activation of emergency response plans to preserve community services
- **travel restrictions** may decrease disease spread
- Once **vaccine** becomes available, immunization programs will begin.
- **antiviral prophylaxis** and therapy targeted to maximize impact, local coordination of hospital and outpatient medical care and triage, and
- **Federal** agencies and personnel will support response activities, monitor vaccine effectiveness and adverse events following vaccination and antiviral drug use, conduct surveillance to track disease burden, and disseminate information.

## Phase 3

- signals **the end** of the first pandemic wave but may be followed by a second seasonal wave
- activities include recovery, assessment and refinement of response strategies, ongoing vaccine production and vaccination and restocking supplies such as antiviral drugs.

## Phase 4

- A second seasonal wave

## Phase 5

- as population immunity to the pandemic strain becomes high due to disease or vaccination, the virus changes, and/or another influenza strain becomes predominant.



Experience is a wonderful thing.  
It enables you to recognize a  
mistake when you make it again.

# The End