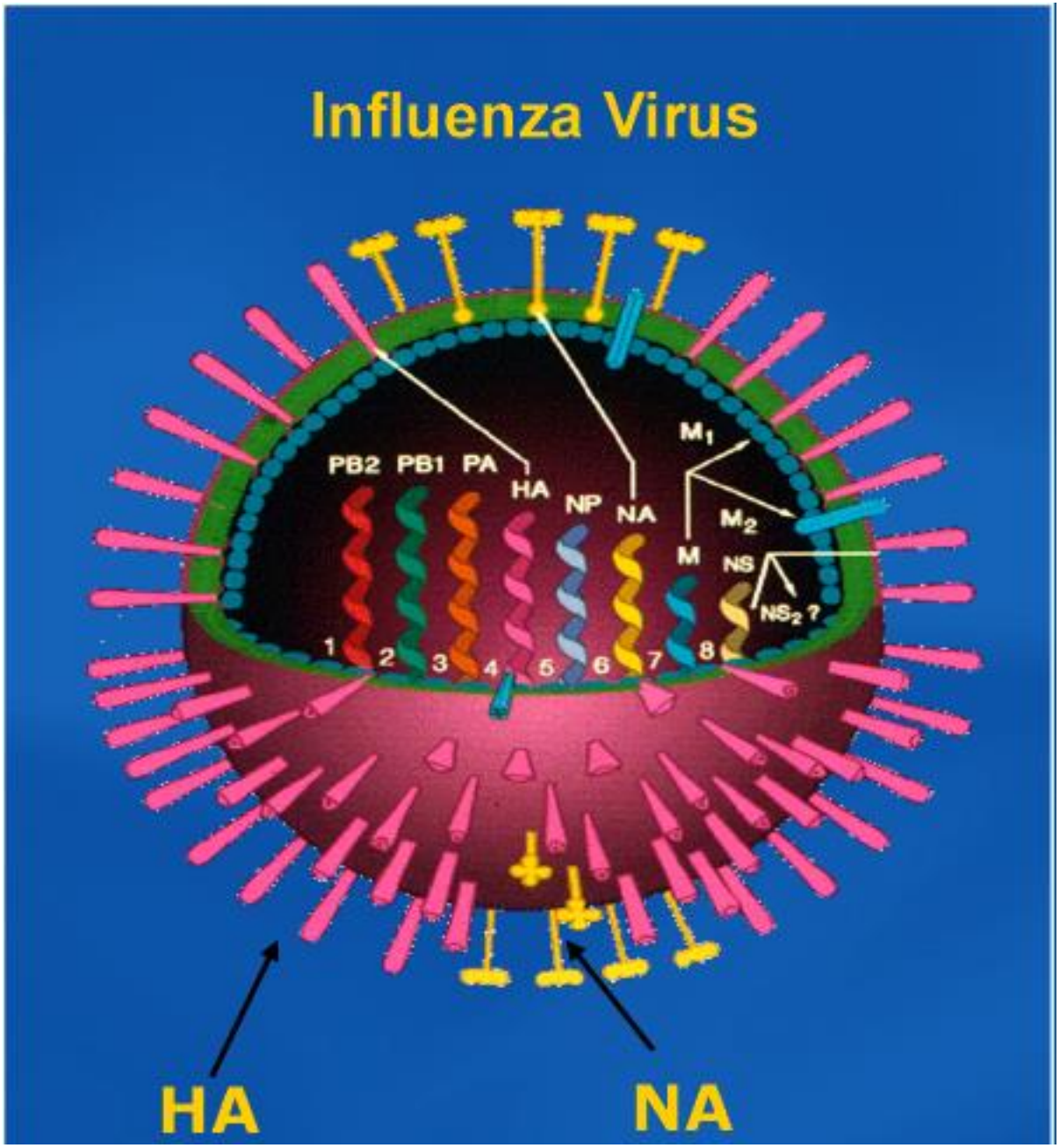
- Epidemiology of Influenza –
- Seasonal, Avian and Pandemic


Ah Quan

- What is Influenza?
- An acute Respiratory Tract Infection (RTI), caused by Influenza
- virus, characterised by sudden onset of:
- Fever/chills
- Headache, myalgia
- Sore throat
- Cough
- Coryza
- Prostration
- Range of symptoms differs by age
- Vomiting & diarrhea in children/elderly
- Fever alone in infants
- May be atypical in elderly
- Serious complications can occur among high risk groups

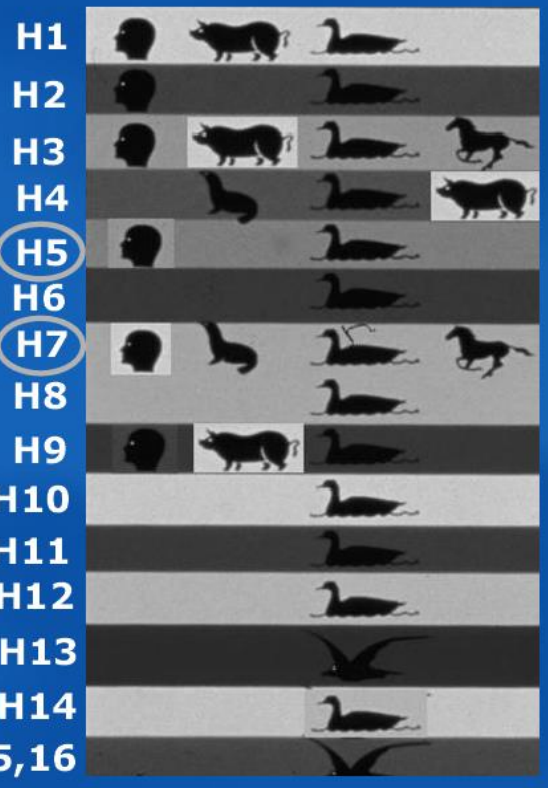
- Influenza Virus – 3 Types
- Causes significant
- disease: epidemics;
- pandemics
- Causes significant
- disease: milder
- epidemics
- Does not cause
- significant disease
- Infects both humans
- and other species
- Limited to humans Limited to humans
- Frequent antigenic
- variations
- Infrequent antigenic
- variations!
- Antigenically stable
- □ RNA virus
- □ Antigenically distinct types
- □ No cross-immunity between different types
- Type A Type B Type C

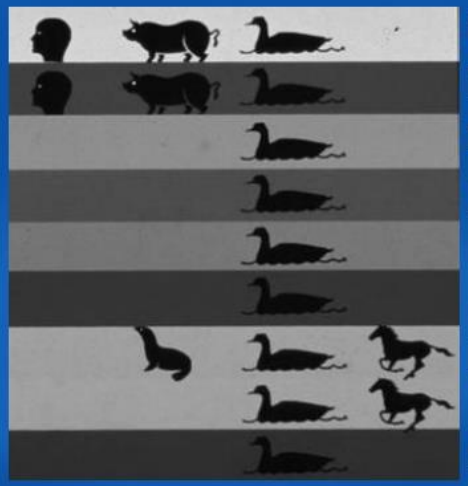
- Influenza A – Important Features
- 2 surface antigens:
- Haemagglutinin (HA)
- Initiates infection following
- attachment of virus to
- susceptible cells
- Neuraminidase (NA)
- Release of virus from
- infected cell
- 16 ‘H’ antigens (1-16)
- 9 ‘N’ antigens (1-9)
- Different combinations
- of H and N antigens


Influenza Virus
PB2
PB1
PA
HA
NP
NA
M1
M2
M
NS
NS2 ?
1
2
3
4
5
6
7
8
HA
NA

- Influenza A – Antigenic Variations
- Antigenic drift: gradual antigenic change over a period;
- Involves ‘point mutations’ in genes owing to selection pressure
- by immunity in host population
- Responsible for frequent influenza epidemics; necessitates
- reformulations of seasonal influenza vaccines
- Antigenic shift: sudden, complete or major change;
- Results from genetic recombination of human with animal/
- avian virus
- Leads to a novel subtype different from both parent viruses
- If ‘novel subtype’ has sufficient genes from HI viruses which
- make it readily transmissible from person to person, it may
- cause pandemics
- Evidence suggests that human influenza viruses responsible
- for last 3 pandemics and current H1N1 pandemic contained
- gene segments closely related to avian influenza viruses

Different Species Infected by Influenza A Subtypes





- All 16 H subtypes infect birds
- Most widespread epidemics & all pandemics: H1N1, H2N2, H3N2

- Influenza Terminology - 1
- Human seasonal influenza
- Avian influenza
- Pandemic influenza

- Influenza Terminology - 2
- Seasonal influenza:
- Occurs every year with gradual variations in previous year’s
- virus surface proteins (antigenic drift)
- Spreads around the world in seasonal epidemics, affecting 10 -
- 20% of total population
- Annual epidemics thought to result in 3-5 million cases of
- severe illness and 2.5-5 lakh deaths

- Influenza Terminology - 3
- Avian Influenza:
- Primarily a disease of birds due to large group of different
- influenza A viruses
- Rarely jumps species and infects humans
- An influenza pandemic happens when a new subtype emerges
- that has not previously circulated in humans and is adapted to
- human to human transmission
- Viruses in wild water fowl is the ultimate source of new viruses
- in humans causing pandemics

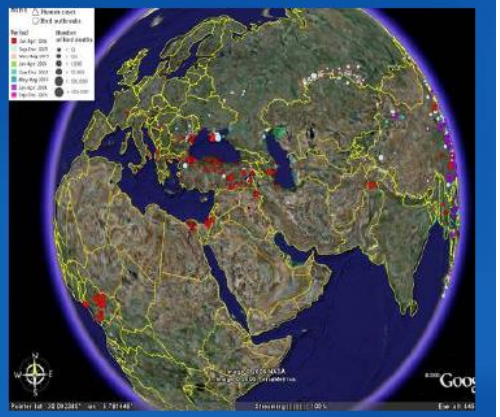
- Influenza Terminology - 4
- Pandemic Influenza:
- □ A worldwide surge in cases caused by the introduction of
- a new influenza type A surface protein (antigenic shift).

Seasonal Epidemics vs. Pandemics

Seasonal Influenza	Influenza Pandemics
A public health problem each year	Appears in the human population rarely and unpredictably
Usually some immunity built up from previous exposures to the same subtype	Human population lacks any immunity. Virulence and mortality not entirely linked to immunity
Infants and elderly most at risk	All age groups, including healthy young adults, may be at increased risk for serious complications
Result of Antigenic Drift	Result of Antigenic Shift

Magnitude of Disease Burden
(Seasonal Influenza)

World-wide in distribution:



- Sporadic cases every season/year round
- Outbreaks (primarily Influenza A): occur every year
- Major epidemics: at interval of 2-3 years
- Pandemics: rare; 10-15 years or more
- Attack rates during epidemics: 10-20% in general community; > 50% in closed populations
- Epidemics generally last 3-6 weeks

Influenza Pandemics

1918: "Spanish Flu"
50 million deaths
A(H1N1)

1957: "Asian Flu"
1 - 4 million deaths
A(H2N2)

1968: "Hong Kong Flu"
1 - 4 million deaths
A(H3N2)

2009: "Swine Flue" A (H1N1)
77201 human cases
332 deaths in 120 countries*

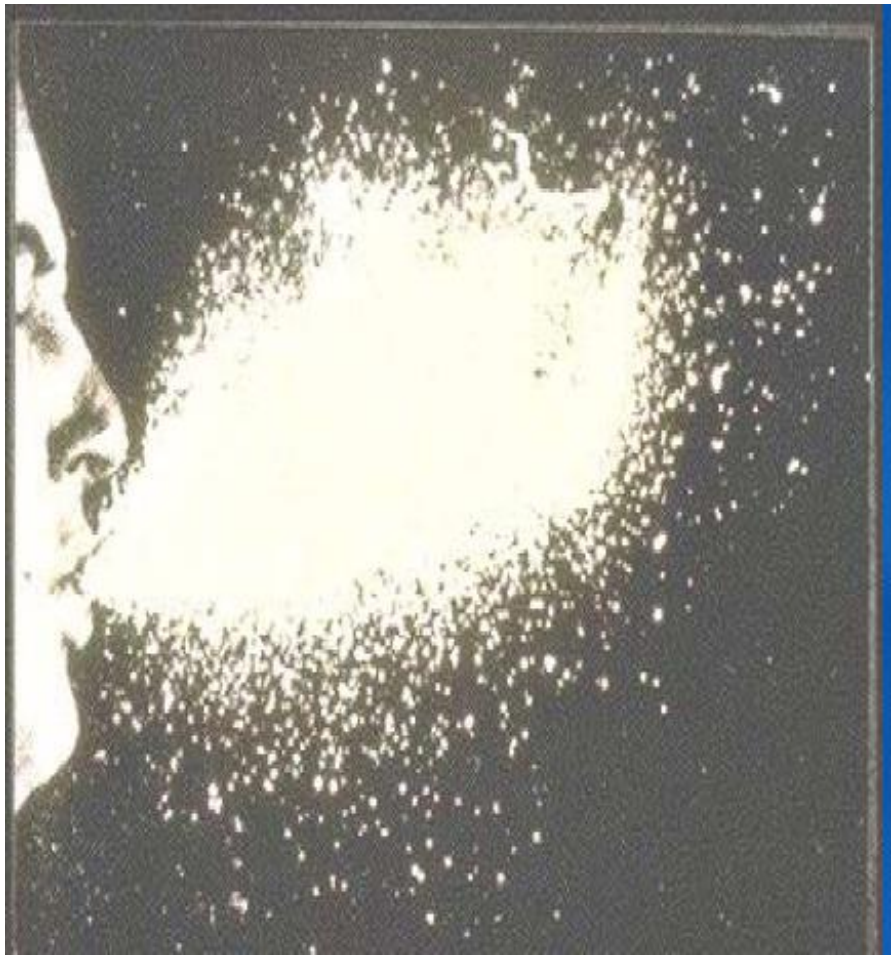
*Data as on 1st July 2009

- Influenza: Key Characteristics—
- Agent Factors
- Reservoir of Infection:
- Humans primary reservoir for human infections
- Major reservoir – animals & birds (swine, horses, dogs,
- cats, domestic poultry, water birds, wild birds etc.)
- Source of Infection:
- Usually a case or sub-clinical case
- Communicability:
- 3-5 days from clinical onset in adults;
- Up to 7 days in young children
- Peak viral shedding occurs on day 1 of symptoms

- Influenza: Key Characteristics—
- Host Factors
- Age & Sex:
- All ages, both sexes
- Attack rates lower among adults
- High Case Fatality Ratio (CFR) during epidemic in high risk
- cases: (old people; children; persons with diabetes, ch.
- heart disease, renal & resp. diseases)
- Human Immunity
- Antibodies to ‘H’: neutralises the virus
- Antibodies to ‘N’: modifies the infection
- Antibodies appear in 7 days after an attack; reach
- maximum. Level in 2 weeks; drops to pre-infection level in
- 8-12 months

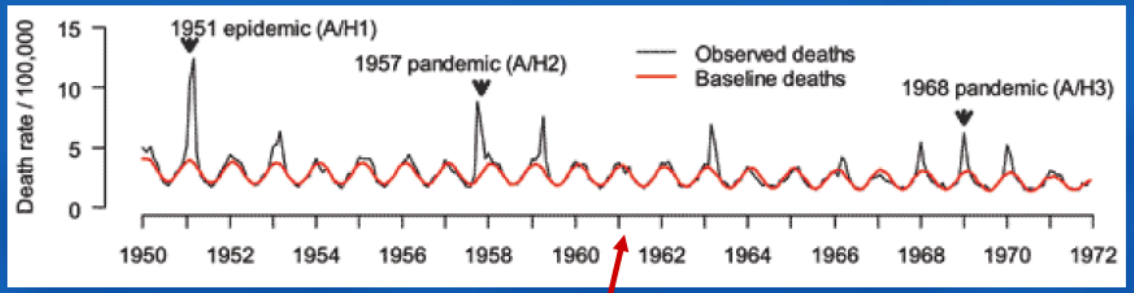
- Influenza: Key Characteristics—
- Environmental Factors
- Seasonality:
- □ Temperate zones: epidemics occur in winter
- □ Tropics: epidemics occur in rainy season
- □ Sporadic cases: any month
- Overcrowding:
- □ Enhances transmission
- □ Higher attack rates in closed popn. groups
- (schools, institutions, ships etc.)

- Influenza: Key Characteristics—
- Disease Transmission
- Mainly airborne:
- □ Droplet infection
- □ Droplet nuclei
- Through direct contact
- Transmission from objects
- possible
- Incubation period:
- □ 18 to 72 hours



Epidemiology Terms

- Endemic
  - A disease that occurs at an expected constant level in a population
  - "Background" level

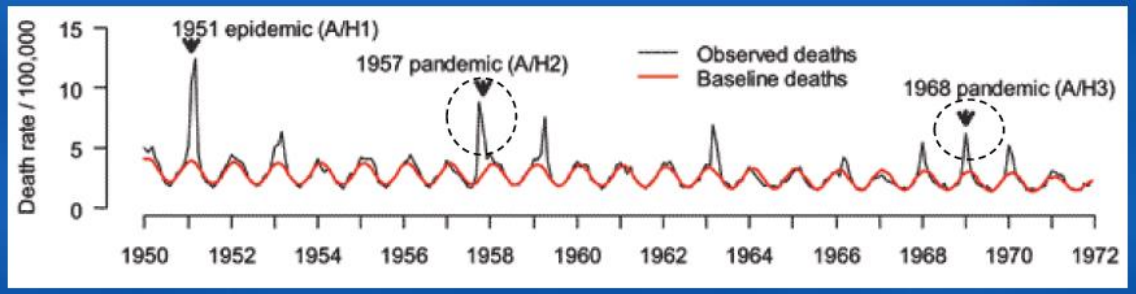


Red line: Expected deaths each year

Cécile Viboud, et al. Emerg Infect Dis [serial on the Internet]. 2006 Apr. Available from http://www.cdc.gov/ncidod/EID/vol12no04/05-0695-G2.htm

Epidemiology Terms

- Epidemic
  - When the cases of a disease exceed what is normally expected
- Pandemic
  - An epidemic that occurs over a large geographic area, or across the whole world



When does the pandemic start?

- Usually not known
- H5N1 is not the only avian influenza A virus to worry about
- Circulation of H5N1 viruses among poultry must be controlled
- WHO Pandemic alert period:
  - Phase 3 (Avian H5N1 influenza)
  - Phase 6 (Novel H1N1 influenza)

Recent Human Infections:

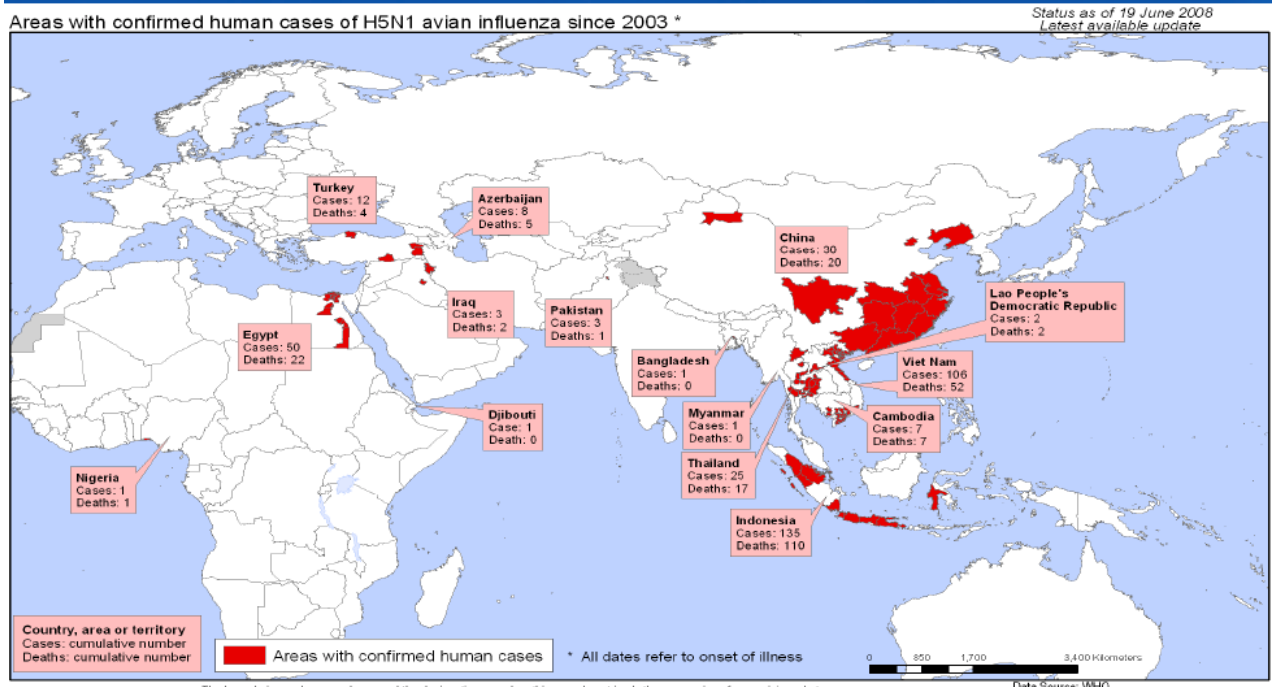
Avian Influenza

Year	Place	Subtype	Cases	Deaths
1997	Hong Kong	H5N1	18	6
1999	Hong Kong	H9N2	2	0
2003	Hong Kong	H5N1	2	1
2003	Netherlands	H7N7	83	1
2003	Hong Kong	H9N2	1	0
2004 - Feb . 2009 *	Azerbaijan, China, Cambodia, Djibouti, Egypt, Indonesia, Iraq, Lao's PD R, Myanmar, Nigeria, Pakistan, Thailand, Turkey, Vietnam Bangladesh	H5N1	436	262

* As of 1st July 2009

Emergence of Avian Influenza (H5N1)

2003 - Feb' 09: 436 human cases, 262 deaths, CRR > 60%



World Health Organization

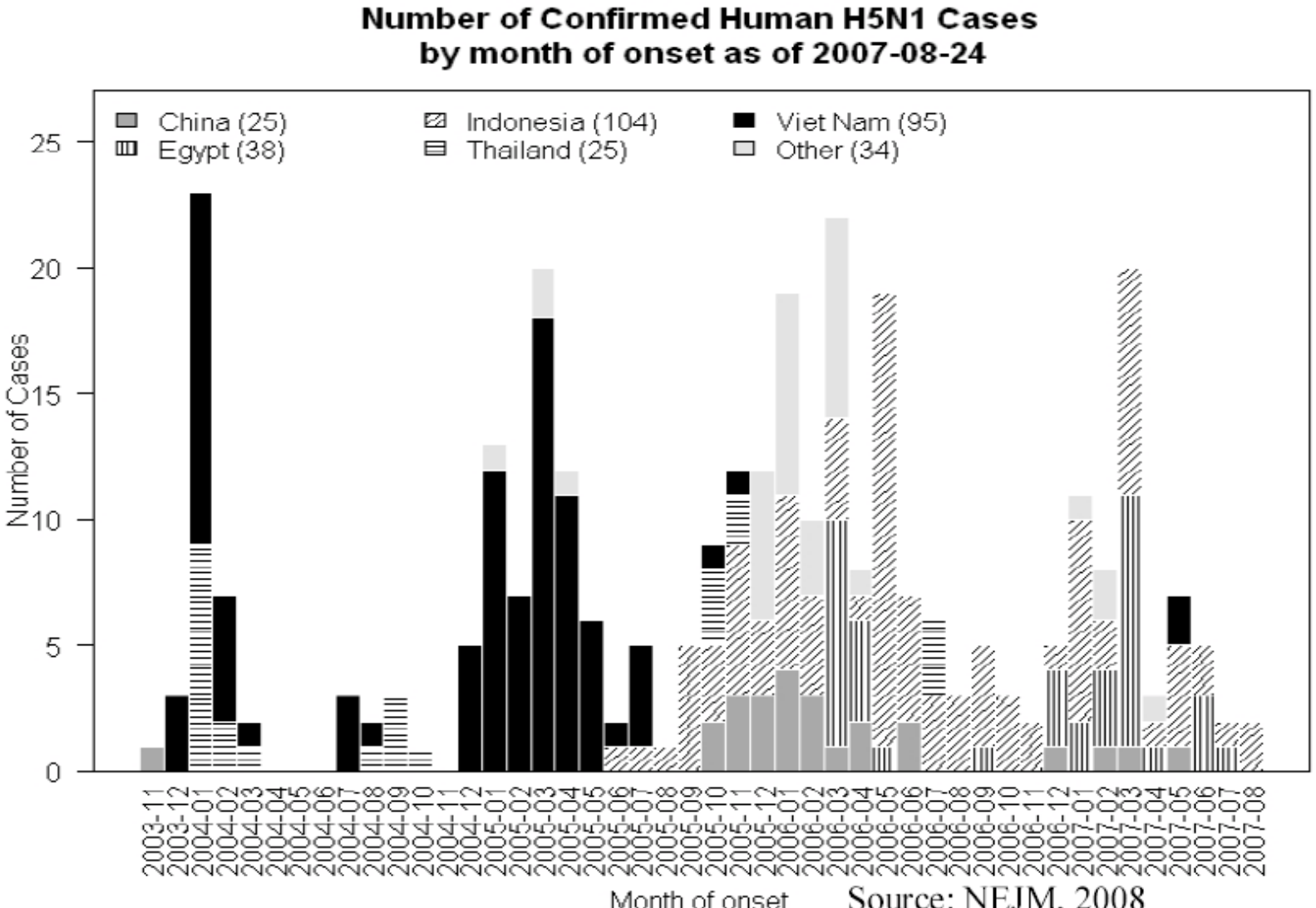
Data Source: WHO
Map Production: Public Health Information and GIS
World Health Organization

- Epidemiology of Avian Influenza
- in Humans (H5N1)
- Demographic characteristics
- Despite widespread exposures to avian influenza (H5N1)
- infected poultry, disease in humans remains rare
- Since May 2005, number. of both affected countries and
- confirmed cases of H5N1 infection (408 cases) have
- increased, in part because of the spread of clade 2.2 viruses
- across Eurasia and Africa
- Median age of patients with H5N1 infection is approximately
- 18 yrs; 90% patients 40 years or younger

- Overall Care Fatality Ratio (CFR): 63%; highest among 10
- -19 yrs; lowest among persons 50 years or older:
- pre-existing immunity
- differences in exposure or
- other factors
- Increased H5N1 human cases during cooler months:
- associated with increased poultry outbreaks
- Cases occur year-round: clinicians must be alert at any time,
- especially in countries with H5N1 poultry outbreaks
- Epidemiology of Avian Influenza
- in Humans (H5N1)
- Demographic characteristics

Epidemiology of Avian Influenza in Humans (H5N1)

Seasonality



Source: NEJM, 2008

Epidemiology of Avian Influenza in Humans (H5N1)

Transmission

Direct avian-to-human transmission: predominant route

Most common risk factor: Handling of sick/dead poultry (week before the onset of illness)

Potential risk factors:

- Slaughtering, defeathering, or preparing sick poultry for cooking
- Playing with or holding diseased/dead poultry
- Handling fighting cocks/ducks that appear healthy
- Consuming raw or undercooked poultry (products)

Epidemiology of Avian Influenza in Humans (H5N1)

Transmission

- **Human clusters:** at least 2 epidemiologically linked cases of H5N1 illness; identified in 10 countries - approximately 25% of reported cases.
- **Cluster size:** mostly 2-3; largest 8 persons
- **Possible genetic susceptibility:** more than 90% of clusters among blood-related family members; might be chance alone

Epidemiology of Avian Influenza in Humans (H5N1)

Transmission

- **Transmission in clusters:** Mostly common-source exposure to poultry, but limited, non-sustained H-to-H transmission probably occurred during very close, unprotected contact with a severely ill patient
- **Largest cluster:** probable transmission from index case to 6 blood-related family members; subsequently to another family member
- Respiratory secretions, all body fluids, incld. feces considered potentially infectious

Epidemiology of Avian Influenza in Humans (H5N1)

Transmission

- In 25% patients, source of exposure is unclear; environment-to-human transmission possible
- For some patients, only identified risk factor was visiting a live-poultry market contact with virus-contaminated fomites or fertiliser containing poultry feces
- Drinking potable water and eating properly cooked food not considered to be risk factors, but ingestion of virus-contaminated products or swimming or bathing in virus-contaminated water might be risky

- Epidemiology of Avian Influenza
- in Humans (H5N1)
- Incubation period
- □ After exposure to infected poultry:
- □ Generally 7 days or less
- □ 2-5 days in many cases
- □ Clusters with limited H-to-H transmission:
- □ Approximately 3-5 days
- □ Estimated 8-9 days in one cluster

Prevention

- Public education campaigns are used to reduce infection rates
- Isolation of infected people is desirable but not always practical
- Immunisation

Immunisation

- Vaccines are offered to people aged 65 or over (Note: Currently this group has some immunity and are not being targeted)
- Clinically at risk groups – asthmatics, immuno-compromised patients, diabetics, people with chronic respiratory disease.
- Health care workers
- Vaccine effectiveness varies between 40 – 60%

Chemotherapy

- Tamiflu (oseltamivir) – inhibits the neuraminidase and thus prevents the spread of the virus in the body
- Tamiflu can therefore be used to reduce the length of illness and its transmission within a household
- Resistance of H1N1 strain to oseltamivir has been reported at 25%

Conclusion

- Flu can be a bit of a swine!
- Prevention is better than cure!
- Avoid contact with infected people.
- Read how the population of Eyam avoided spreading the plague!
- Eyam - Plague Village - Derbyshire

- **Emergency warning signs in children that need urgent medical attention:**
  - Fast breathing or difficult breathing.
  - Bluish or grey skin discoloration.
  - Not drinking enough fluids.
  - Not fully conscious.
  - Flu like symptoms (Fever, cough, Sore throat, Body aches, Diarrhea in some cases) improve but return with fever and severe cough.

Centers for Disease Control and Prevention (CDC) Guidelines to Prevent Spread of Influenza in Children:

- Influenza vaccine to all children from 6m to 19 y.
- Vaccine to care providers to children.
- Children and care providers oriented to hand washing or use alcohol based hand cleaners (wash hands for 15-20 sec).
- Keep the child care environment clean and make sure that supplies are available.
- Cover nose and mouth during sneezing or coughing.

- Observe all children for symptoms of respiratory illness; infants and young children can become quite ill with influenza very quickly and might require urgent medical attention and hospitalization.
- Encourage parents of sick children to keep their children home.
- Encourage sick care providers to stay home.
- Consult your local health department when increases in respiratory illnesses occur in the child care sitting.

- Health care providers should stay informed on what is happening in their communities.

- Sick children may infect others up to 10 days after the symptoms start, adults may infect others while sick for 5-7 days.

- Keep a record for persons with various illnesses (e.g. respiratory, diarrhea, rash) by day or at least by week.

- Follow public health advice regarding school closures, avoiding crowds.
- Supply of over-the-counter medicines, alcohol based cleaners.

Epidemiological activities must take place:

- Active surveillance in the countries where infection in humans have been identified.
- Studies of health care workers who were exposed to patients infected with the virus to see if became infected.
- Studies of households and other contacts of people who were confirmed to have been infected to see if they become infected.
- Study of a public schools.

Preventing the Flu: Good Health Habits Can Help Stop Germs

Fact Sheet

1-Avoid close contact.

Avoid close contact with people who are sick. When you are sick, keep your distance from others to protect them from getting sick too.

2-Stay home when you are sick.

Stay home from work, child care, school, and errands when you are sick, except to seek medical care. Keep sick children at home except to seek medical care. You will help prevent others from catching the illness.

3-Cover your mouth and nose.

Cover your mouth and nose with a tissue when coughing or sneezing. Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue in the trash after you use it.

4-Wash your hands often.

Washing your hands and the hands of your children often will help protect you from germs.

5-Avoid touching your eyes, nose or mouth.

Germs are often spread when a person touches something that is contaminated with germs and then touches his or her eyes, nose, or mouth.

6- Practice other good health habits.

Get plenty of sleep, be physically active, manage your stress, drink plenty of fluids, and eat nutritious food.

Get the Facts About

Novel H1N1 Influenza

Content Source:

U. S. Centers for Disease Control and Prevention

May 2009

Novel H1N1 Influenza

Novel H1N1 (referred to a swine flu early on) is a new influenza virus that is spreading from person-to-person.

The United States government has declared a public health emergency in the U.S. in response to the H1N1 outbreak.

CDC's response goals are to:

- reduce transmission and illness severity
- provide information to help health care providers, public health officials, and the public address the challenges posed by this emergency.

Novel H1N1 Influenza

- The first cases of human infection with novel H1N1 influenza virus were detected in April 2009 in San Diego and Imperial County, California and in Guadalupe County, Texas.
- The virus has spread rapidly.
- The virus is widespread in the United States at this time and has been detected internationally as well.

Novel H1N1 Influenza

CDC expects that more cases, more hospitalizations, and more deaths from this outbreak will occur over the coming days and months.

- Influenza is always serious – each year in the United States, seasonal influenza results, on average, in an estimated 36,000 deaths and more than 200,000 hospitalizations from flu-related causes.
- This outbreak certainly poses the potential to be at least as serious as seasonal flu, if not more so, especially given the fact that there currently is no vaccine against this virus.
- Because this is a new virus, most people will not have immunity to it, and illness may be more severe and widespread as a result.

Signs and symptoms

Symptoms of novel H1N1 flu in people are similar to those associated with seasonal flu.

- Fever
- Cough
- Sore throat
- Runny or stuffy nose
- Body aches
- Headache
- Chills
- Fatigue
- In addition, vomiting (25%) and diarrhea (25%) have been

How does novel H1N1 Influenza spread?

- This virus is thought to spread the same way seasonal flu spreads
- Primarily through respiratory droplets
  - Coughing
  - Sneezing
  - Touching respiratory droplets on yourself, another person, or an object, then touching mucus membranes (e.g., mouth, nose, eyes) without washing hands

Can you get novel H1N1 Influenza from eating pork?

No. The novel H1N1 influenza virus (formerly referred to as swine flu) virus is not spread by food.

You cannot get novel H1N1 flu from eating pork or pork products. Eating properly handled and cooked pork products is safe.

What can you do to protect yourself from getting sick?

There is no vaccine right now to protect against this new H1N1 virus.

However, everyday actions can help prevent spread of germs that cause respiratory illnesses like influenza.

Take these everyday steps to protect your health

- Wash your hands often with soap and warm water, especially after you cough or sneeze. Wash for 15 – 20 seconds.
- Alcohol-based hand wipes or gel sanitizers are al effective.

Take these everyday steps to protect your health

- Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue in the trash after you use it.
- Avoid touching your eyes, nose or mouth. Germs spread this way.
- Avoid contact with sick people.

If you get sick…

- Stay home if you're sick for 7 days after your symptoms begin or until you've been symptom-free for 24 hours, whichever is longer.

- If you are sick, limit your contact with other people as much as possible.

Watch for emergency warning signs

Most people should be able to recover at home, but watch for emergency warning signs that mean you should seek immediate medical care.

In adults:

- Difficulty breathing or shortness of breath
- Pain or pressure in the chest or abdomen
- Sudden dizziness
- Confusion
- Severe or persistent vomiting
- Flu-like symptoms improve but then return with fever and worse cough

Emergency warning signs in children

If a child gets sick and experiences any of these warning signs, seek emergency medical care.

In children:

- Fast breathing or trouble breathing
- Bluish or gray skin color
- Not drinking enough fluids
- Severe or persistent vomiting
- Not waking up or not interacting
- Irritable, the child does not want to be held
- Flu-like symptoms improve but then return with fever and worse cough

What is CDC doing?

- CDC has implemented its emergency response.
- CDC continues to issue new interim guidance for clinicians and public health professionals.
- CDC's Division of the Strategic National Stockpile (SNS) has sent 25% of the SNS stockpile of antiviral drugs, personal protective equipment, and respiratory protection devices to all 50 states and U.S. territories to help them respond to the outbreak.

What is CDC doing?

- CDC is working closely with state and local officials nationwide.
- CDC teams are deployed and many other activities and studies are underway or are being planned.
- CDC also is coordinating closely with the World Health Organization and other international partners.

Summary

- CDC anticipates that there will be more cases, more hospitalizations and more deaths associated with this new virus in the coming days and weeks because the population has little to no immunity against it.

- We must all work together to limit and control the transmission of novel H1N1 influenza.

Summary

- For the most current information on the H1N1 influenza outbreak, visit http://www.cdc.gov/h1n1flu/
- CDC, WHO, and public health officials worldwide are carefully monitoring the situation.
- Follow all recommendations for preventing the spread of influenza.
- For local guidance, contact your state, local, or county health officials.

Resources

- http://www.cdc.gov/h1n1flu/
- http://www.cdc.gov/h1n1flu/espanol/
- 1-800-CDC-INFO ()
- http://www.who.int/csr/disease/swineflu/en/index.html

Pandemic planning

- An influenza pandemic will be unlike other public health emergencies or common disasters.
  - Inevitable
  - Will arrive with very little warning
  - Locally explosive epidemics
  - Widespread, not focused like a bio-terrorism event
  - Will put an extraordinary strain on human and material resources
  - Effect will be relatively prolonged –weeks to months

Laboratory issues

- Laboratory safety
- Tissue culture techniques
- Rapid test kits
- HA/HI sub-typing
- Immuno-fluorescent testing
- Real time PCR analysis
  - Molecular typing and sub-typing

Laboratory/Epidemiology Topics of Discussion

- Reviewing current Influenza surveillance testing algorithm
- Brief comments on alternative Influenza surveillance algorithms and the ability of this laboratory to support them.

Current testing algorithm

- Inoculation of specimens into cell culture; one diploid, one Hep-2, one Viromed Rhmk and two Diagnostic Hybrid Rhmk
- In the absence of CPE, “blind” Hemadsorption (HAD) at days 7 and 14.
- In the absence of CPE “blind” passage of Hep2 with “blind” FA for RSV at day 14 for all patients ≤5 years old
- Identification of Influenza isolates:
  - Immuno-fluorescent testing to identify type (A or B) followed by Hemagglutination Inhibition (HI) testing to identify sub-type

Alternatives to be considered

- The use of shell vials for more rapid isolation and identification of Influenza
  - Studies by Wisconsin and Iowa suggest that MDCK shell vials are more sensitive for Influenza than Rhmk cell culture
  - MDCK shell vials inoculated, incubated, and “blind” stained at day 5 for Influenza A and B with supernatant saved and used for HI testing (if necessary).
    - Things to consider:
      - Cost: purchase shell vials commercially with goal of preparing our own shell vials once the cell culture preparation method has been established.
      - The CDC provides the FA reagents as part of the WHO/CDC Influenza Kits received each year. In addition, commercial sources are available.
      - Time and labor requirements; Not an issue once Arbovirus season is over.

Alternatives to be considered

- The use of Immuno-fluorescence (IFA) for Influenza A sub-typing
  - The CDC/WHO kit provides staining reagents for H1N1 and H3N2
  - Cost: We would have to purchase additional anti-mouse IgG conjugate commercially.
  - This procedure would decrease turn-around-time
  - Has the potential for allowing us to test for 2 sub-types at once by using different conjugates, I.e. FITC and Rhodamine

Alternatives to be considered

- Use of Rapid Test kits
  - Things to consider
    - Cost: These kits are very expensive and have relatively short shelf-lives
    - Poor positive predictive values in the absence of an outbreak (high sensitivity but low specificity)
    - These kits are probably more effective for use at a primary care setting <u>during influenza season</u>

Alternatives to be considered

- PCR: The CDC has provided the sequence data for the primers and probes for Influenza A (group) and Influenza B (group). In addition, it has provided the data for H1, H3, and H5 (avian considered as possible candidate for next pandemic).
  - Things to consider
    - Cost: While the cost of primers is probably manageable, probes are very expensive.
    - There will be a lag time as we will have to obtain all the probes and primers and do validation studies. This includes validation for H5; Note, we do not have any controls for that agent. The CDC has indicated they will provide a Proficiency set sometime next year.
    - The CDC primer sets are for H1, H3, and H5, not H1N1, H3N2, and H5N1 (no neuraminidases). The CDC is not overly concerned about this because it is the "H" (Hemagglutinin) that is related to pathogenicity but, if we choose to report based on PCR we will only be able to report on the Hemagglutinin result.

Suggested algorithms

- It is not the intent of the CDC to replace culture with PCR but rather to allow the States to have PCR testing available as a surveillance/rapid diagnostic tool
- Isolation will still be needed for vaccine related surveillance and production efforts
- Consider the purpose of this surveillance effort

Next Steps

- Laboratory Management and the State Epidemiology will have to meet to more carefully review and discuss the options available to us in terms of surveillance enhancement.

Items to consider

- It has been 20+ years since our Influenza algorithm has been changed
- A number of exciting new methods and tools are available to us including
  - The use of shell vials
  - Immuno-fluorescent sub-typing including multiplexing
  - PCR

Final algorithm

- Should allow for the most rapid response possible
- Cost considerations
- Sensitivity and specificity of the tests
- Validation studies, not just to satisfy CLIA requirements but also to ensure that the tests being performed are providing accurate information.