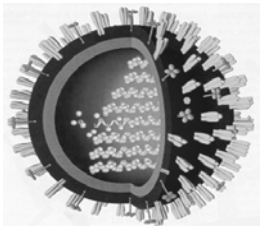
Endemic Influenza, Pandemic Influenza, and Avian Flu



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A Webber Training Teleclass
www.webbertraining.com

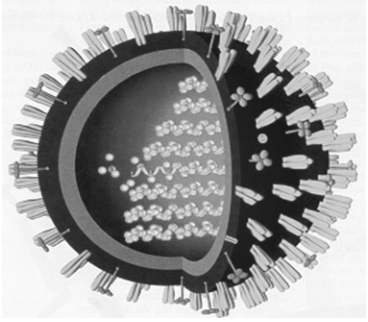
Outline

- The virus
- The disease
- Epidemic influenza
- Avian influenza
- Pandemic influenza

THE INFLUENZA VIRUS

- Family: Orthomyxoviridae
- Genus: Influenza A, B, C and Thogotovirus (Tick transmission)
- Virions are usually roughly spherical and 80-120nm in diameter.
- The viral genome is composed of eight segmented negative sense single stranded RNA.
- The outer surface of the particle consists of a lipid envelope from which project prominent rigid glycoprotein spikes of two types, the haemagglutinin (HA) and neuraminidase (NA)
- There are 15 different hemagglutinin subtypes and 9 different neuraminidase subtypes

Structure of Influenza viruses



Host Range

- Influenza A viruses infect a wide variety of mammals, including man, horses, pigs, ferrets and birds. Pigs and birds are believed to be particularly important reservoirs. The main human pathogen, is associated with both epidemics and pandemics.
- Influenza B viruses infect man and birds; they cause human disease but generally not a severe as A types.
- Influenza C viruses infect man alone, but do not cause disease. They are genetically and morphologically distinct from A and B types.

Antigenic variation of Influenza viruses

- Antigenic drift
  - Influenza viruses have only little RNA repair mechanisms
  - Accumulation of point mutations in the HA and/or N genes resulting in minor changes in HA and N surface protein
  - Occurs under selective pressure (immunized patients)
  - New antigenic variants still posses the same HA and N subtypes and there is linear succession as each new subtype replaces the previous strain
- Antigenic shift
  - Caused by the segmented nature of influenza virus genome
  - Sudden appearance of a new type influenza A virus possessing a distinctly different HA or NA subtype or changes in both subtypes.

Antigenic shift

- Reassortment of viral RNA segments during maturation of progeny viruses when a single cell is infected with two or more viruses
- Recirculation of existing subtypes
- Gradual adaptation of animal viruses to human transmission

Orthomyxovirus: Classification

How to name an influenza virus?

Type ABC / City / strain # / year isolated /glycoproteins HA(1-15) NA (1-9)

e.g. A / HongKong / 03 / 1968 / H3N2

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Pathogenesis

- Primary infection involves the cilliated epithelial cells of the U.R.T. Necrosis of these cells results in the common symptoms of the acute respiratory infection (fever, chills, muscular aching. headache, prostration, anorexia).
- Normally self-limited. Infection usually lasts 3-7 days.
- In epidemic influenza death from primary influenza infection is very rare and appears to be determined by host factors rather than 'virulence' of virus.
- Damage to respiratory epithelium predisposes to secondary bacterial infections which account for most deaths.

Influenza epidemiology

- Influenza viruses are spread by aerosols and occasionally by fomites.
- Transmission is very efficient. There are usually 3-9 new infections per clinical case.
- Seasonal epidemic trends (temperate climates)
- Peak of infectivity 1-2 days before and 4-5 days after the clinical signs.
- Epidemics usually last from 3-6 weeks and the highest attack rates are for 5-19 years old

Clinical Signs and Symptoms of Influenza

- Incubation period of 48 hours
- The onset is abrupt with
  - marked fever, continuous, lasting around 3 days
  - headache
  - photophobia
  - shivering
  - a dry cough
  - malaise
  - myalgia
  - a dry tickling throat.

Complications

- Tracheobronchitis and bronchiolitis
- Primary viral pneumonia (uncommon)
- Secondary bacterial pneumonia - usually occurs late in the course of disease, after a period of improvement.
- Myositis and myoglobinuria
- Reye's syndrome
- Other complications - influenza infection have been implicated in acute viral encephalitis and Guillain-Barre syndrome.

Laboratory Diagnosis

- Virus Isolation - Throat swabs, NPA and nasal washings may be used for virus isolation. The specimen may be inoculated in embryonated eggs or tissue culture.
- Rapid Diagnosis by Immunofluorescence - cells from pathological specimens may be examined for the presence of influenza A and B antigens by indirect immunofluorescence.
- Serology - Virus cannot be isolated from all cases of suspected infection. More commonly, the diagnosis is made retrospectively by the demonstration of a rise in serum antibodies. A 50% increase is evidence of recent infection.

Treatment

- Usually symptomatic. Salicylates should be avoided in children because of the link with Reye's syndrome.
- M2 Inhibitors
  - Amantidine is only effective against influenza A, and some naturally occurring strains of influenza A are resistant to it. The compound has been shown to have both therapeutic and prophylactic effects.
  - Rimantidine is similar to amantidine but has fewer side effects. It is used both for treatment and prophylaxis of influenza A infection in persons one year or older. Amantadine and rimantadine resistant viruses are readily generated in the laboratory.
- Neuraminidase inhibitors
  - Zanamivir, the first neuraminidase inhibitor available for clinical use, is effective against both influenza A and B. It must be administered by inhalation. It is used as treatment for influenza A and B in persons 12 years or older but not for prophylaxis.
  - Oseltamivir, unlike zanamivir, can be given orally. It has been shown to be effective and devoid of significant side effects in clinical trials. It is used as treatment for influenza A and B in persons 18 years or older. It is also approved for prophylaxis in persons 13 years or older. High cost.

Outline

- The virus
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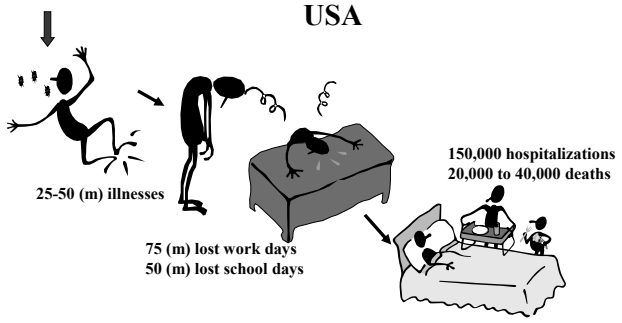
Influenza epidemics

- Seasonal epidemics:
  - November-April in Northern Hemisphere
  - May-October in Southern Hemisphere
- In tropical and subtropical climates no seasonality or bi-phasic
- Increase in morbidity, hospitalizations & mortality
- Due to minor changes in HA or NA (Antigenic drift)
- Caused by influenza A or B viruses
- Attack rate: 10-20% overall, 40-50% in selected populations
- Localised outbreak or widespread epidemic

Impact of Influenza

- Frequency
  - Between 1 to 4 in ten fall ill every year
  - One in 25 will consult a doctor
- Consequences
  - 5-6 day of reduced physical activity
  - 3-4 day immobility
  - 3 or more days of absenteeism from workplace or school
  - Almost every second case requires medical care

Influenza Associated Morbidity & Mortality USA



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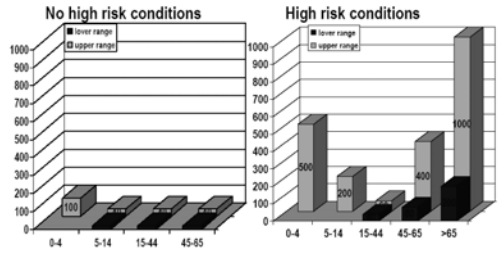
Influenza hospitalization rates
(per 100 000 population)



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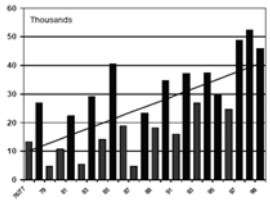
Estimated annual influenza associated death during influenza seasons (USA)

- Number of death during influenza season with underlying respiratory and circulatory disease
- Higher mortality during H3N2 epidemics (blue)
- Increase due to :
  - Aging of population
  - ↑#H3 epidemics



WHO Global Influenza Programme

Flu burden in developing countries

- Madagascar 2002
  - 27,519 cumulative cases
  - 838 cumulative deaths
  - 13 / 111 districts affected

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Yearly global burden of influenza

- 5-15% of the world population affected (mainly children 5-9 years of age)
- 3-5 million severe illnesses
- 250,000 to 500,000 deaths, mainly in elderly >65 years and high-risk groups

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Estimated cost of an influenza epidemic
(Germany, 1996-97)

Costs	DM (million)	$ US (million)
Outpatient data (observed)		
Direct medical costs:		
- consultation & exam.	50.03	29.43
- diagnosis	3.51	2.06
- medication	23.25	13.6
Total Direct medical costs	76.79	45.09
Indirect costs:		
- loss of productivity	1591	936
Total costs for outpatients	1,668	981
Inpatient data (modelled)		
Direct costs	72	42
Indirect costs	37	22
Total costs for inpatients	109	64
Overall total costs	1,777	1,045

Source: Szucs, 1999

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Influenza vaccines

- 3 types of inactivated vaccines:
  - whole virus vaccines consisting of inactivated viruses;
  - split virus vaccines consisting of virus particles disrupted by detergent treatment;
  - subunit vaccines consisting essentially of haemagglutinin and neuraminidase from which other virus components have been removed.
- Live, Attenuated Influenza Vaccines (LAIV, nasal application)
- Current trivalent compostion:
  - two A subtypes, H3N2 and H1N1
  - one type B virus

Inactivated Vaccines

Vaccine efficacy

- Rapid systemic and local immune response
  - 90% healthy young adults develop protecting serum HI titres of >1 in 40 within 2 weeks
  - Antibodies levels peak within 4-6 weeks; wane over time (two fold lover within 6 month)
- Reduction in laboratory confirmed illness
  - 70-90% efficacy in young health adults
  - 58-62% efficacy in persons >60 years of age
    - » Need for good strain match!

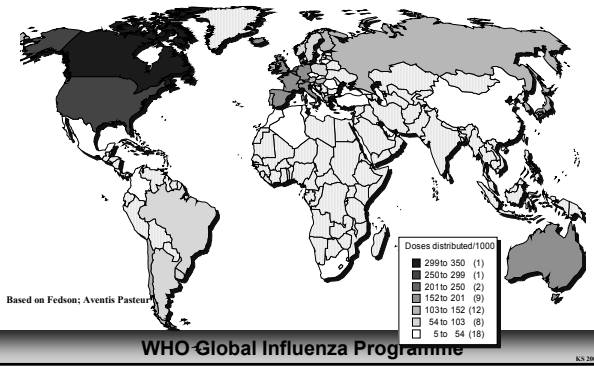
W. P. Edmondson, Am.J.Epidemiol. 93 (6):480-486, 1971; T. M. Govaert, JAMA 272 (21):1661-1665, 1994.

Vaccination efficacy - summary

- Healthy adults
  - Preventing respiratory illness and sick leave (30-89%)
- Elderly non-institutionalized
  - Preventing hospitalization (L and ARI: 25-39%; PI: 31-49%)
  - Preventing mortality (all causes 39-75%; Influenza associated: 41%)
- Elderly in nursing homes
  - Preventing respiratory illness (56%), pneumonia (58%), hospitalization (all causes: 48%), death (all causes: 68%), death from pneumonia (32-45%)

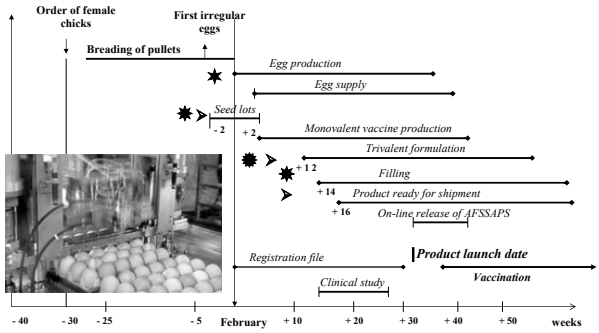
Influenza Vaccine Consumption 2000

Estimated 350 million doses



Based on Fedson; Aventis Pasteur

Vaccine Production Schedule



C. Gerdil International Symposium - Annecy : Dec. 13 - 15, 2000

WHO Influenza Surveillance Network

- 110 National Influenza Centres in 82 countries
- 4 WHO Collaborating Centres for Reference and Research on Influenza (Atlanta, London, Melbourne and Tokyo)

Assessment of National Influenza Centres

Virus submission to WHO CCs, 2001

52,200k samples
13,600 isolates
65 NICs
57 countries
2,500 strains

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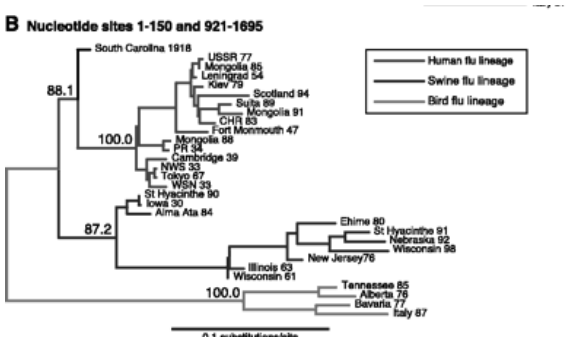

WHO Global Influenza Programme

2 day analysis, discussion and decision

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Immediate communication

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Priority groups for vaccination

1. **Residents of institutions for the elderly or the disabled.**
2. **Elderly non-institutionalized individuals suffering from chronic heart or lung diseases, metabolic or renal disease, or immunodeficiencies.**
3. **All individuals >6 months of age suffering from any of the conditions listed above.**
4. **Elderly individuals above a nationally-defined age limit (usually >65) irrespective of their medical risk status.**
5. **Other groups defined on the basis of national data.**
6. **Health care workers in contact with high-risk persons.**
7. **Household contacts of high-risk persons.**

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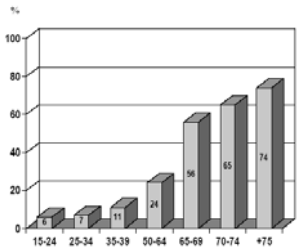
Influenza Vaccination Coverage

France



- **79 % of Health Care Personal was not vaccinated against Influenza in 2001**
- **66% has never been vaccinated in their life**

GROG Newsletter N2, 2002-2003, 9 October

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Outline

- The virus
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Avian Flu

- First described in chickens in Italy in 1878
- Influenza A recognized as cause of avian flu in 1955
- Detected in more than 90 species of wild birds, the natural host for all subtypes of influenza A virus
- Asymptomatic in most wild species (ducks, gulls, etc)
- Pathogenic in other birds, including domestic poultry
  - Low-pathogenic form
  - Highly pathogenic form

Highly pathogenic Avian Flu (HPAI)

- Only H5 and H7 subtypes
- No natural reservoir
- Emerges usually by mutation in poultry
- Rare until 2004. Only 24 outbreaks since 1959, but 14 in the past 10 years!
- Control measures include:
  - Culling of all infected or exposed birds
  - Proper disposal of carcasses
  - Quarantining and disinfection of farms

Spread of Avian Influenza Viruses among Birds

- Domesticated birds may become infected through
  - direct contact with infected waterfowl or other infected poultry,
  - contact with contaminated surfaces (such as dirt or cages) or materials (such as water or feed).
- People, vehicles, and other inanimate objects such as cages can be vectors for the spread of influenza virus from one farm to another.
- Low pathogenic forms of avian influenza viruses are responsible for most outbreaks, resulting usually in either no illness, mild illness (e.g., fewer or no eggs), or low mortality.
- When HPAI (H5 or H7) viruses cause outbreaks, 90% - 100% of poultry can die from infection.

Avian influenza outbreaks

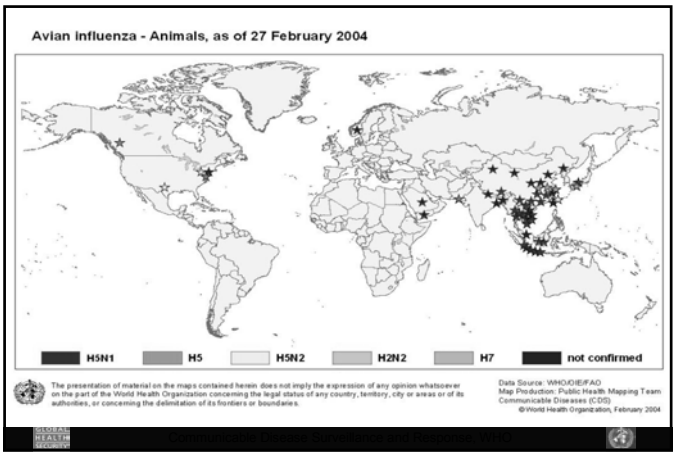
- Avian influenza outbreaks in domestic birds must be monitored for several reasons:
  - the potential to evolve into highly pathogenic forms.
  - the potential for rapid spread and significant illness and death among poultry
  - the potential economic impact and trade restrictions
  - the possibility that avian influenza could be transmitted to humans.
- Quarantine and depopulation (or culling) and surveillance around affected flocks are the preferred control and eradication options

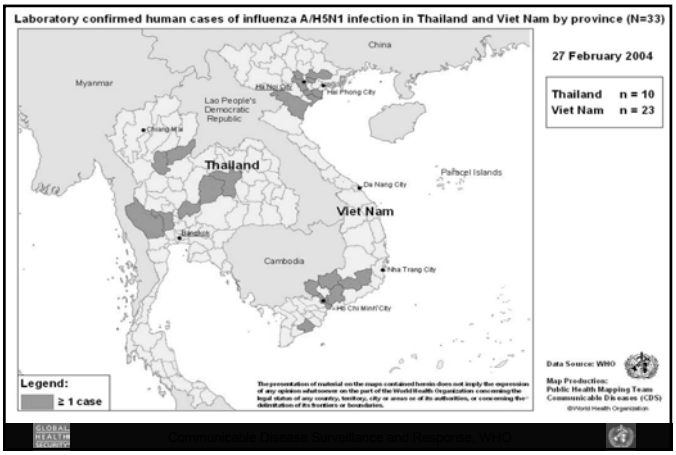
Avian Influenza Infection in Humans

- Avian influenza A viruses do not usually infect humans
- Avian influenza viruses may be transmitted to humans in two ways:
  - Directly from birds or from contaminated environments to people.
  - Through an intermediate host, such as a pig.
- Most human cases are thought to have resulted from contact with infected poultry or contaminated surfaces
- Illnesses caused by highly pathogenic viruses appear to be more severe
- Symptoms of avian influenza in humans have ranged from typical influenza-like symptoms (e.g., fever, cough, sore throat, and muscle aches) to eye infections (conjunctivitis), pneumonia, acute respiratory distress, viral pneumonia, and other severe and life-threatening complications

Confirmed instances of Avian Influenza Infections in Humans since 1997

- H5N1, Hong Kong, 1997 : Avian influenza A (H5N1) infections occurred in both poultry and humans. 18 people were hospitalized and six of them died. This was the first time an avian influenza virus had ever been found to transmit directly from birds to humans To control the outbreak, authorities killed about 1.5 million chickens to remove the source of the virus. The virus spread primarily from birds to humans, though rare person to person infection was noted.
- H9N2, China and Hong Kong, 1999 : Avian influenza A H9N2 illness was confirmed in two children.
- H7N2, Virginia, 2002: outbreak of H7N2 among poultry, one person had serologic evidence of infection.
- H5N1, China and Hong Kong, 2003 : Two cases of avian influenza A (H5N1) infection occurred among members of a Hong Kong family that had traveled to China. One person recovered, the other died. Another family member died of a respiratory illness in China, but no testing was done.
- H7N7, Netherlands, 2003 : Outbreaks of influenza A (H7N7) in poultry on several farms. Infections were reported among pigs and humans (89 people confirmed, mostly among poultry workers). There was one death in a veterinarian who visited one of the affected farms and developed acute respiratory distress syndrome.
- H9N2, Hong Kong, 2003 : H9N2 infection was confirmed in a child in Hong Kong. The child recovered.
- H7N2, New York, 2003: A patient was admitted to a hospital with respiratory symptoms, recovered and went home after a few weeks. Subsequent tests showed that the patient had been infected with an H7N2 avian influenza virus.
- H5N1, Thailand and Vietnam, 2003: In January 2003, first reports to WHO of outbreaks of highly pathogenic influenza A (H5N1). From December 30, 2003, to March 17, 2004, 12 confirmed human cases were reported in Thailand and 23 in Vietnam, resulting in a total of 23 deaths.
- H7N3 in Canada , 2004: Human infections of H7N3 among poultry workers were associated with an H7N3 outbreak among poultry. The H7N3 associated illnesses consisted of eye infections.
- H5N1, Thailand and Vietnam, 2004: Beginning in late June 2004, new lethal outbreaks of H5N1 among poultry were reported by several countries in Asia.





Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1)
since 28 January 2004

Country/ Territory	Total cases	Deaths
Cambodia	1	1
Thailand	17	12
Viet Nam	37	29
Total	55	42

- As of 2 February 2005
- Total number of cases includes number of deaths. WHO reports only laboratory confirmed cases.

Prevention of human infection

- Elimination of animal reservoir
  - Rapid detection
  - Culling
  - Quarantine
  - Disinfection
- Vaccination
- Antivirals
- Personal protective equipment

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Prerequisites for the start of a pandemic

- A novel influenza virus subtype must emerge to which the general population will have no or little immunity
- The new virus must be able to replicate in humans and cause serious illness
- The new virus must be efficiently transmitted from one human to another

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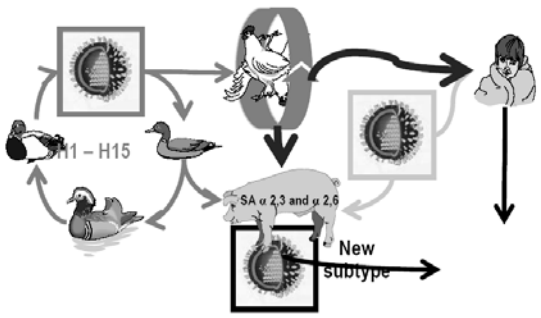
Emergence of a new virus



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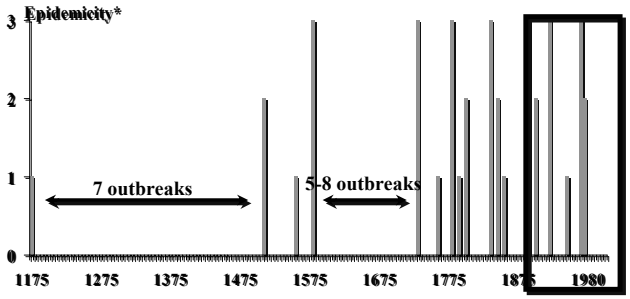
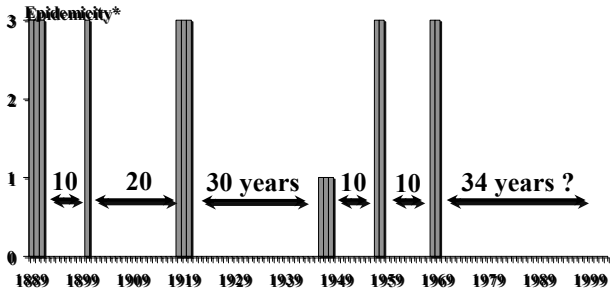
Recorded Influenza Pandemics



1: epidemic, 2: probable pandemic, 3: pandemic

Potter, C.W: Textbook of Influenza by Nicholson, Webster, Hay, Blackwell Science 1998

Recorded Influenza Pandemics



1: epidemic, 2: probable pandemic, 3: pandemic

Potter, C.W: Textbook of Influenza by Nichols, Webster, Hay, Blackwell Science 1998

Pandemic Influenza Today

Despite . . .
- Expanded global and national surveillance
- Better healthcare, medicines, diagnostics
- Greater vaccine manufacturing capacity

New risks:
- Increased global travel and commerce
- Greater population density
- More elderly and immunosuppressed
- More daycare and nursing homes

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Influenza Pandemic: impact (1)

- Will depend upon many factors
  - Virulence of the strain
  - Affected age groups
  - Gross attack rate
  - Rates of adverse effects
  - Speed of spread from country to country
  - Effectiveness of pandemic prevention and response efforts
- Expected Morbidity and Mortality
  - 25-30% clinically ill
  - 6% pneumonia
  - Hospitalization rate 1%
  - Case fatality rate 0.6% (1918→2%)

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Influenza Pandemic: impact (2)

- Will affect medical service and essential disease control function
- Will equally affect other essential community services
  - Public transport, police, fire brigade, grocery stores, air traffic control, petrol stations, …, teachers, politicians, …
- Social and political disruption
- Considerable economic losses
  - Health consequences of disease and prevention and control efforts
  - Indirect disease consequences and impact of travel/trade recommendations/restrictions

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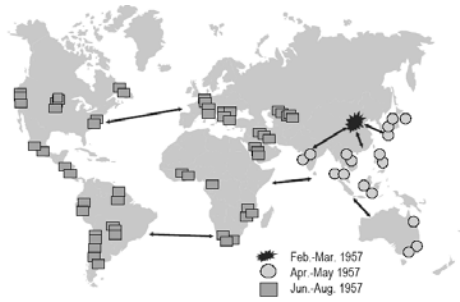
Spread of H2N2 influenza in 1957 "Asian influenza"



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Preparedness for Pandemic Influenza

- Surveillance
- Vaccines
- Antivirals
- Public health measures to reduce transmission
- Travel/trade recommendations/restrictions
- National and global Pandemic Preparedness Plans

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Surveillance

- Objectives
  - Rapid detection of disease and virus
  - Vaccine prototype strain development
  - Assessment of pandemic potential of virus (transmissibility; pathogenicity; morbidity/mortality; affected age groups)
  - Initiation of public health interventions at early stage of pandemic
- Prerequisite
  - Capacity for isolation and characterization of virus
  - Epidemiological surveillance for respiratory diseases
    - » But communicable disease surveillance is weak in many countries

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Pandemic vaccines

- Stockpiling in large quantities impossible
- Access to vaccines:
  - 4-6 month before production can begin
  - Vaccine production capacity will be insufficient
  - Influenza vaccine produced only in a few developed countries;
  - Costs (vaccine; shipment; use and application)
- Lack of contingency plan for vaccine production and distribution under emergency situations

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Vaccine production capacities

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Long Wait for Vaccine

1947 New York Times photograph

Antivirals

Stockpiling possible but…many issues remain:

- **Access**
- **Production and surge capacities**
- **Costs**
- **Shelf-life**
- **Treatment versus prophylaxis**
- **Anti-viral resistance**
- **Side affects and toxicity**

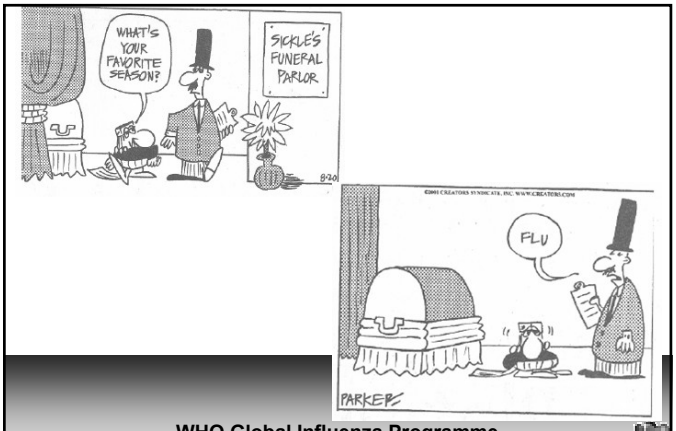
Pandemic preparedness: where are we?

- **Severe vaccine and antiviral shortage expected. Absence in developing countries**
- **Very few countries have pandemic preparedness plans or national policies for vaccination and antiviral use**
- **Overall lack of national, regional and local contingency planning**
- **National and international agreements on vaccine production and distribution to countries without domestic vaccine production are not in place**
- **Surveillance and rapid detection insufficient**

Pandemic Planning in Europe, November 2000

	Country	Pandemic Plan Accepted: National	Pandemic Plan Accepted: Regional	Domestic influenza vaccine company	Arrangement made for pandemic vaccine supply	Priority groups for vaccination identified
European Union	Austria*	—†	—	—	—	—
	Belgium	Yes	—	—	—	Yes
	Denmark	Pending	—	—	—	—
	France	Yes	—	Yes	—	Pending
	Finland*	—	—	—	—	—
	Germany	Pending	—	Yes	Pending	Pending
	Greece*	—	—	—	—	—
	Ireland	Pending	—	—	—	Pending
	Italy	Pending	—	Yes	—	—
	Luxembourg*	—	—	—	—	—
	Netherlands	Pending	Pending	Yes	Yes	Pending
	Portugal	Yes	—	—	—	Yes
	Spain	Pending	—	—	Yes	Yes
	Sweden	Pending	—	—	—	—
	United Kingdom	Yes	Yes	Yes	Yes	Yes
Non-EU	Iceland*	—	—	—	—	—
	Norway*	—	—	—	—	—
	Switzerland	Yes	—	Yes	—	Yes
Future EU ‡	Czech Republic	Yes	—	—	Yes	Yes
	Slovenia	—	—	—	—	—

Adapted from Paget WJ, Aguilera J-F. *Eurosurveillance* 2001; 6: 136-40.
*** Not included in the survey.**
† Indicates no or no information provided
‡ Future EU countries not included in the survey were Cyprus, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Bulgaria, Romania and Turkey.



Other 2005 Teleclasses

For more information, refer to www.webbertraining.com/schedule.cfm

- *February 17* – **Sad Cows and Englishmen, Predicaments and Predictions for Spongiform Encephalopathies** with Dr. Corrie Brown
- *February 24* – ***Sneezes, Coughs and Drips: Respiratory and GI Outbreaks in Long Term Care*** with Dr. Chesley Richards
- *March 10* – ***Biocide Use in a Healthcare Environment*** with Dr. Jean-Yves Mailard
- *March 17* - ***WHO's Global Patient Safety Challenge 2005/2006 Preventing Healthcare Associated Infection; A Worldwide Strategy*** with Dr. Didier Pittet
- *March 31* – ***Voices of CHICA*** (a free teleclass)
- *April 7* – ***Root Cause Analysis for the Infection Control Professional*** with Dr. Denise Murphy

Questions? Contact Paul Webber paul@webbertraining.com