

# Pandemic Influenza

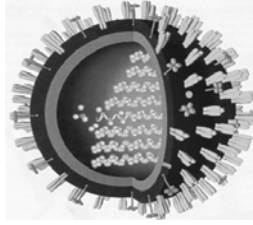
## Dr. Stephano Lazzari, WHO, Lyon

### A Webber Training Teleclass

## Pandemic Influenza

**Dr. Stefano Lazzari**

Director, WHO - Lyon  
Department of Epidemic and  
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Hosted by Paul Webber  
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## Outline

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

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## THE INFLUENZA VIRUS

- Family: Orthomyxoviridae
- Genus: Influenza A, B, C and Thogotovirus
- 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



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#### 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, influenza A viruses are associated with both flu epidemics and pandemics.
- Influenza B viruses infect man and birds; they cause human disease but generally not as 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.

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#### Antigenic variation of Influenza viruses

##### ● Antigenic drift

- Influenza viruses have only little RNA repair mechanisms
- Accumulation of point mutations in the HA and/or NA genes resulting in minor changes in HA and NA surface proteins
- Occurs under selective pressure (naturally or artificially immunized patients)
- New antigenic variants still possess the same HA and NA subtypes and there is linear succession as each new subtype replaces the previous strain

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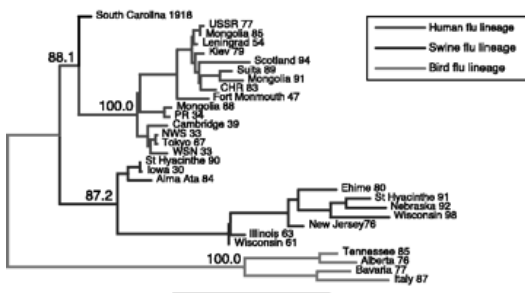
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**B** Nucleotide sites 1-150 and 921-1695



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**Orthomyxovirus: Classification**

● **How to name a new influenza virus?**

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

(Example: A / HongKong / 03 / 1968 / H3N2)

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**Antigenic variation of Influenza viruses**

● **Antigenic shift**

- Sudden appearance of a new type influenza A virus with different HA or NA subtype or changes in both subtypes.
- Different potential mechanisms:
  - **Reassortment** of viral RNA segments during maturation of progeny viruses when a single cell is infected with two or more animal and human viruses
  - Gradual **adaptation** of animal viruses to human transmission
  - **Recirculation** of existing (*dormant*) subtypes

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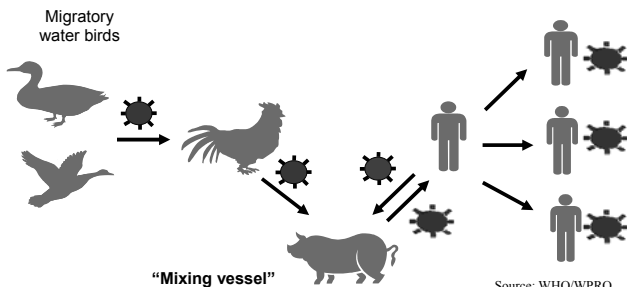
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**Reassortment (in pigs)**



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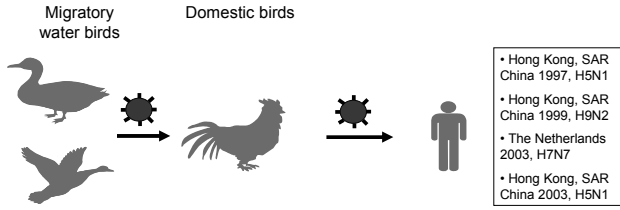
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## From birds to humans



Source: WHO/WPRO

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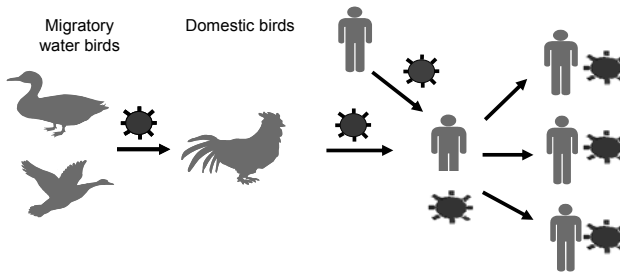
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## Reassortment (in humans)



Source: WHO/WPRO

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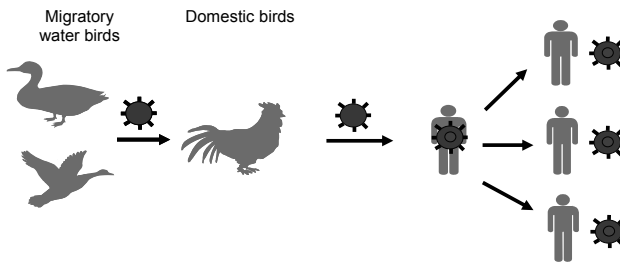
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## Mutation (in humans)



Source: WHO/WPRO

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#### 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. Attack rate: 10-20% overall, 40-50% in selected populations (5-19 years old).
- Peak of infectivity 1-2 days before and 4-5 days after the clinical signs.
- Seasonal epidemic trends (in temperate climates)
  - November-April in Northern Hemisphere
  - May-October in Southern Hemisphere

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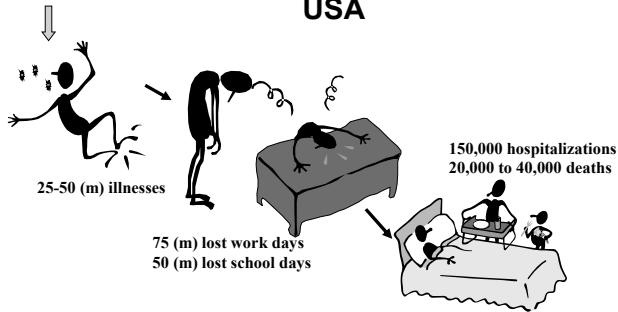
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#### Influenza Associated Morbidity & Mortality USA



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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
- The economic costs of influenza is estimated at several hundred billion US dollars

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#### Laboratory Diagnosis of Influenza

- The optimal specimen is a nasopharyngeal aspirate obtained within 3 days of the onset of symptoms, although nasopharyngeal swabs and other specimens can also be used
- Immunofluorescence assay (IFA) can be used for the detection of influenza A and B antigens in either clinical specimens or cell cultures
- Virus Isolation is a sensitive technique with the advantage that virus is available both for identification and for further antigenic and genetic characterization, drug susceptibility testing, and vaccine preparation.
- Polymerase chain reaction (PCR) is a powerful technique for the identification of influenza virus genomes
- Serological tests available for the measurement of influenza A-specific antibody include the haemagglutination inhibition test, the enzyme immunoassay, and the virus neutralization tests.

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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 composition:
  - two A subtypes (H3N2 and H1N1)
  - one type B virus

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#### Inactivated Influenza Vaccines

- 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 lower within 6 months)
- Reduction in laboratory confirmed illness and deaths
  - 70-90% efficacy in young healthy adults
  - 58-62% efficacy in persons >60 years of age
- Need for good strain match!

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#### WHO Influenza Surveillance Network



- 1 Laboratory
- > 1 Laboratory
- National network

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

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#### 2 day analysis, discussion and decision



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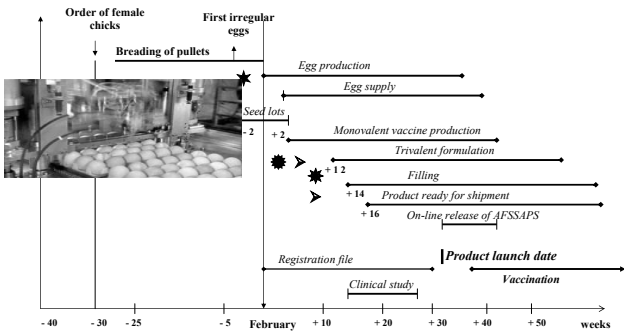
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#### Vaccine Production Schedule



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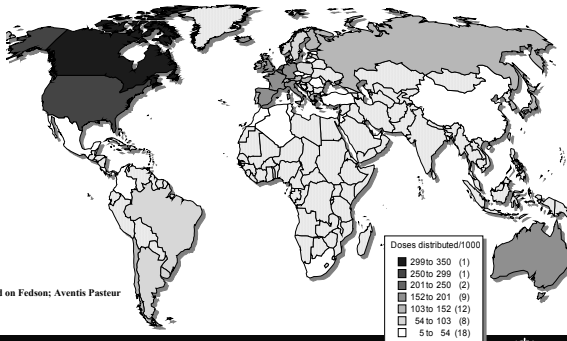
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**Influenza Vaccine Consumption (2000)**  
Estimated 350 million doses



Based on Fedson; Aventis Pasteur

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### Priority groups for vaccination

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

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### WHO targets for vaccination

FIFTY-SIXTH WORLD HEALTH ASSEMBLY, May 2003

- where national influenza vaccination policies exist, to establish and implement strategies to increase vaccination coverage of all people at high risk, including the elderly and persons with underlying diseases, with the goal of attaining vaccination coverage of the elderly population of at least 50% by 2006 and 75% by 2010;



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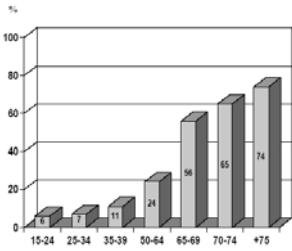
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### Influenza Vaccination Coverage

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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### Antiviral Treatment

#### ● 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, can be given orally. Shown to be effective and devoid of significant side effects in clinical trials. Recommended for treatment for influenza A and B in persons 18 years or older. Approved for prophylaxis in persons 13 years or older. High cost.

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### Avian Flu



- First described in poultry in Italy in 1878
- Influenza A recognized as cause in 1955
- Detected in more than 90 species of wild birds
- Wild waterfowls are the most frequent (asymptomatic) carriers
- Pathogenic in other birds, including domestic poultry
  - Low-pathogenic form (*ruffled feathers and reduced egg production*)
  - Highly pathogenic form (HPAI (*chicken Ebola*) 100% mortality within 48 hours)
- HPAI is caused only by H5 and H7 subtypes. No natural reservoir, it emerges usually by mutation in poultry
- HPAI was considered rare until 2004. Only 24 outbreaks since 1959, but 14 in the past 10 years!

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#### 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.
- Control measures include:
  - Culling of all infected or exposed birds
  - Proper disposal of carcasses
  - Quarantining and disinfection of farms

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#### Avian Influenza Infection in Humans

- Avian influenza A viruses do not usually infect humans. Of the four subtypes (H5N1, H7N3, H7N7 and H9N2) known to have infected humans, only H5N1 can cause severe disease and death
- 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.
- Transmission is usually through inhalation of infectious droplets and droplet nuclei, by direct contact, and perhaps, by indirect (fomite) contact following exposure to infected animals
- Highly pathogenic viruses can cause:
  - Sustained fever (> 38°C)
  - Shortness of breath and dry, non-productive cough
  - Rapid progression of severe respiratory distress



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#### Recorded human infections with animal flu viruses (since 1968)

- 1976: H1N1 Swine influenza USA (1 †)
- 1986: H1N1 Swine virus derived from avian source: one severe pneumonia
- 1988: H1N1 Swine virus USA: pregnant woman died after contact to sick pigs
- 1993: H3N2 Swine virus recombinant with avian H1N1 Netherlands: 2 children, mild disease
- 1995: H7N7 duck virus UK: adult mild conjunctivitis
- 1997: H5N1 avian influenza Hong Kong: 18 cases/6 †
- 1999: H9N2 quail virus: 2 mild cases
- 2003: H5N1 avian virus Hong Kong: 1 †; 1 disease +1 related † from pneumonia
- 2003: H7N7 avian virus Netherlands: 1 †; 80+ conjunctivitis; few respiratory symptoms
- 2003: H5N1 avian virus Guangdong: 1 †
- 2003: H9N2 avian virus Hong Kong: 1 mild upper respiratory symptoms
- 2003: H7N2 avian virus New York: 1 pneumonia (HIV-coinfection)
- 2004 H5N1 disease and death in Vietnam and Thailand (35 cases/24 †)
- 2004: H7N3 avian virus Canada: 2 cases (conjunctivitis)
- 2004 H5N1 disease and death in Vietnam and Thailand (9 cases/8†)
- 2005-6: H5N1 disease and death in Vietnam and Cambodia, Indonesia, China, Turkey and Iraq.

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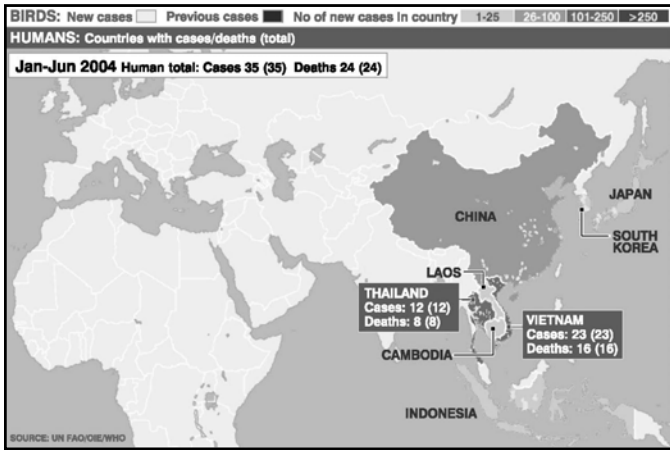
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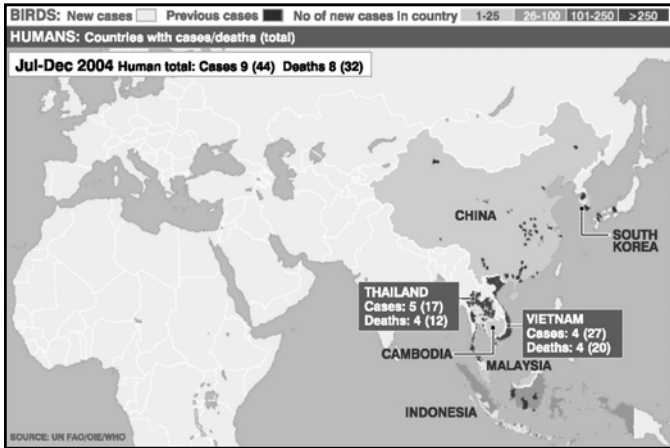
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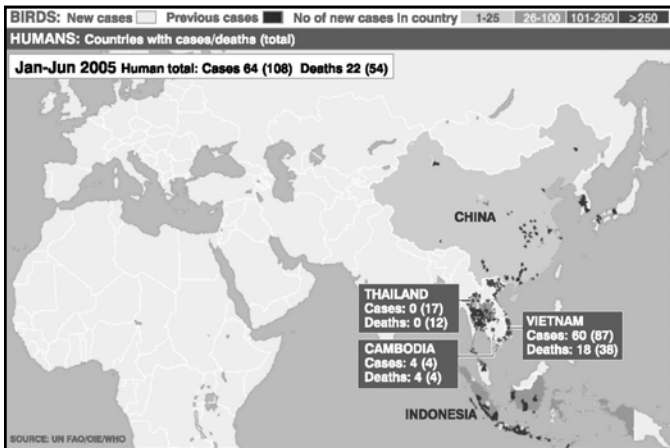
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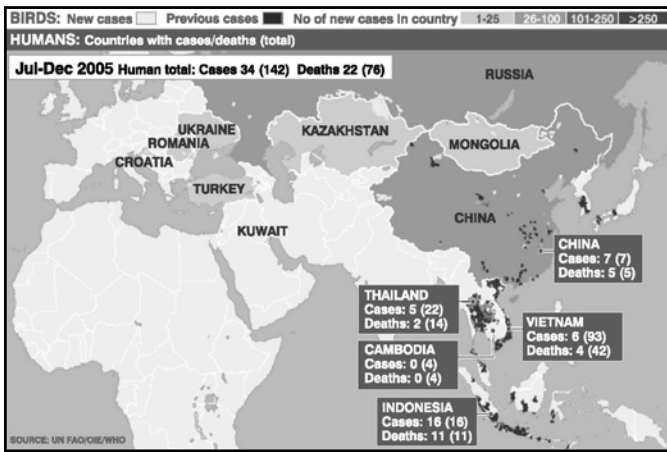
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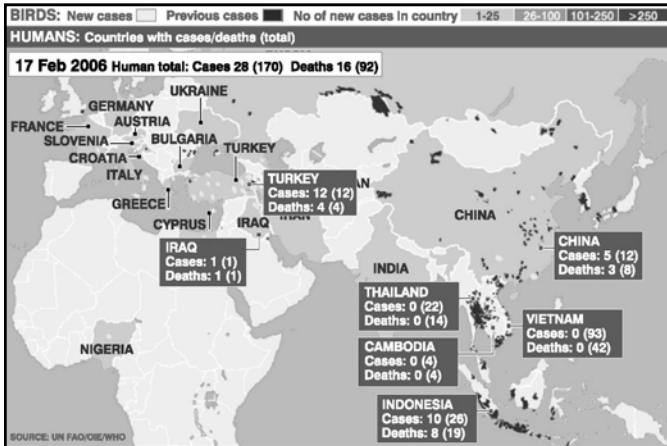
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Cumulative Number of Confirmed Human Cases of Avian Influenza A(H5N1) as of 1 March 2006

Country/ Territory	Total cases	Deaths
Cambodia	4	4
China	14	8
Indonesia	27	20
Iraq	2	2
Thailand	22	14
Turkey	12	4
Viet Nam	93	42
Total	174	94

• Total number of cases includes number of deaths. WHO reports only laboratory-confirmed cases.

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#### CONSTRAINTS AND CHALLENGES TO HPAI CONTROL (FAO/OIE)

- Inadequate veterinary services
- Stamping out and biosecurity are difficult to implement
- Inadequate disease information systems
- Domestic ducks are an important H5N1 reservoir
- Disease has become endemic in several countries
- Wildlife reservoirs are a source of HPAI infection
- Financial resources remain inadequate

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#### Prevention of human infection

- Elimination of animal reservoir
  - Rapid detection
  - Culling
  - Quarantine
  - Disinfection
- Vaccination (humans and/or poultry)
- Antivirals
- Basic hygiene measures
- Personal protective equipment
- Proper practices during slaughtering and preparation for cooking



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#### Poultry vaccines

- Vaccination protects against clinical signs and mortality, reduces virus shedding, increases resistance to infection, protects from diverse viruses with same haemagglutinin subtype, reduces contact transmission.
- However, the virus is still able to infect and replicate in clinically healthy vaccinated birds.
- Inactivated vaccines or recombinant vaccines are available
- Detection of infection in vaccinated flocks and birds:
  - sentinel birds left unvaccinated in each vaccinated flock
  - vaccine containing a virus of the same haemagglutinin (H) subtype but a different neuraminidase (N) from the field virus.

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#### H5N1:

#### Why are we so concerned?



- H5N1 is endemic in poultry in Asia
- H5N1 is more deadly in poultry and can kill at least some wild migratory birds
- H5N1 is expanding its host range. New animals (cats and tigers) are becoming infected for the first time.
- Asymptomatic domestic ducks are excreting large quantities of virus
- H5N1 can survive longer in the environment
- Large human exposure to H5N1, with human cases and deaths

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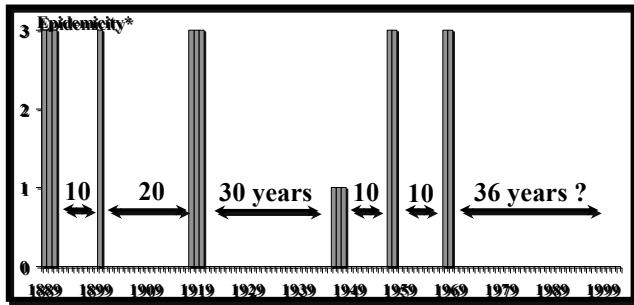
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#### Recorded Influenza Pandemics



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

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

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#### Prerequisites for the start of a pandemic

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

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### Influenza pandemics 20th century



Credit: US National Museum of Health and Medicine



#### 1918: "Spanish Flu"

20-40 million deaths

A(H1N1)

#### 1957: "Asian Flu"

1-4 million deaths

A(H2N2)

#### 1968: "Hong Kong Flu"

1-4 million deaths

A(H3N2)

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### Lessons from the past pandemics

- Great variations in mortality, severity of illness and patterns of spread
- Rapid surge in the number of cases in a short time
- Progression in waves, different groups, increased severity.
- Most pandemics originated in Asia
- Quarantine and travel restriction have little effect. Banning of public gatherings and closure of schools may be helpful.
- Delaying spread is desirable. Less people ill at the same time.
- Limited impact of vaccines, only for producing countries.

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### Next Influenza Pandemics- Impact

- Influenza pandemics are a true global public health emergency
- Impact 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

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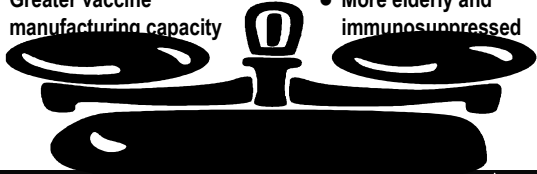
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### Next Pandemic Influenza

- Expanded global and national surveillance
- Better healthcare, medicines, diagnostics
- Greater vaccine manufacturing capacity
- Increased global travel and commerce
- Greater population density and movement
- More elderly and immunosuppressed



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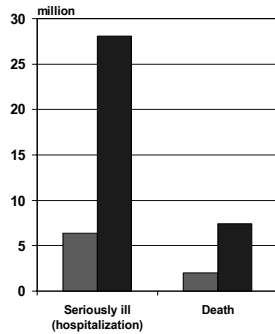
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### Influenza Pandemics

#### Global Health Implications

- **Disease and death** (attack rate 35%)
  - 1253 - 500 million ill
  - 875 - 1601 require medical care



Extrapolated by Meltzer 2003 from Meltzer et al 1999

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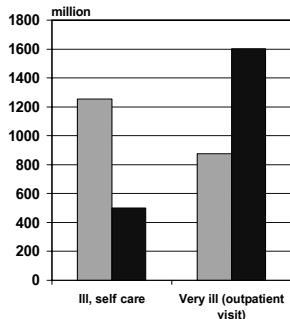
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### Influenza Pandemics

#### Global Health Implications

- **Disease and death** (attack rate 35%)
  - 1253 - 500 million ill
  - 875 - 1601 require medical care
  - 6.4 - 28.1 hospitalizations
  - 2-7.4 million death
    - Case fatality rate 0.6%
    - 1918: mortality was 2.2%
- **During few weeks**
- **Several waves**



Extrapolated by Meltzer 2003 from Meltzer et al 1999

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#### Influenza Pandemic Other implications



- Will affect medical care services and other 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/control efforts
  - Indirect disease consequences and impact of travel/trade recommendations/restrictions

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#### WHO Global Influenza Preparedness Plan



- Revised in 2005
- Describes new pandemic phases
- Lists goals, objectives and actions for each phase
- Identifies roles and responsibilities of WHO and Member States before and during a pandemic

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NEW PHASES	OVERARCHING PUBLIC HEALTH GOALS
<p><b>Interpandemic period</b></p> <p><i>Phase 1.</i> No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered to be low.</p> <p><i>Phase 2.</i> No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.</p>	<ul style="list-style-type: none"> <li>● Strengthen influenza pandemic preparedness at the global, regional, national and sub-national levels.</li> <li>● Minimize the risk of transmission to humans; detect and report such transmission rapidly if it occurs.</li> </ul>

Epidemic and Pandemic Alert and Response




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# Pandemic Influenza

## Dr. Stephano Lazzari, WHO, Lyon

### A Webber Training Teleclass

NEW PHASES	OVERARCHING PUBLIC HEALTH GOALS
<p><b>Pandemic alert period</b></p> <p><i>Phase 3.</i> Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact.</p> <p><i>Phase 4.</i> Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans.</p> <p><i>Phase 5.</i> Larger cluster(s) but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk).</p>	<ul style="list-style-type: none"> <li>● Ensure rapid characterization of the new virus subtype and early detection, notification and response to additional cases.</li> <li>● Contain the new virus within limited foci or delay spread to gain time to implement preparedness measures, including vaccine development.</li> <li>● Maximize efforts to contain or delay spread, to possibly avert a pandemic, and to gain time to implement pandemic response measures.</li> </ul>

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NEW PHASES	OVERARCHING PUBLIC HEALTH GOALS
<p><b>Pandemic period</b></p> <p><i>Phase 6.</i> Pandemic: increased and sustained transmission in general population.</p>	<ul style="list-style-type: none"> <li>● Minimize the impact of the pandemic.</li> </ul>

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<b>Objective 1: Early Warning</b>
<ul style="list-style-type: none"> <li>● Objectives                             <ul style="list-style-type: none"> <li>– Rapid detection of disease and virus</li> <li>– Vaccine prototype strain development</li> <li>– Assessment of pandemic potential of virus (transmissibility; pathogenicity; morbidity/mortality; affected age groups)</li> <li>– Initiation of public health interventions at early stage of pandemic</li> </ul> </li> <li>● Prerequisite                             <ul style="list-style-type: none"> <li>– Capacity for isolation and characterization of virus</li> <li>– Epidemiological surveillance for respiratory diseases</li> </ul> </li> </ul>

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#### Objective 2: Delay initial spread

- For the first time in history, delaying the spread of a pandemic can be envisaged, though its feasibility cannot be stated with certainty.
- Prerequisites
  - Early detection of clusters of diseases and isolation of virus
  - Initial reduce human-to-human transmission efficiency
  - Aggressive containment measures
    - Prophylactic use of antiviral drugs for the entire communities where initial spread is detected
    - Non-medical interventions (personal hygiene, masks, quarantine, ban of public gatherings, travel bans, etc.)

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#### Objective 3: Ensure early availability of pandemic vaccines

- Rapid virus identification and development of “seed” vaccines using modern technologies (e.g. *reverse genetics*)
- Clinical trials and registration
- Increase production capacities and expand access to vaccines:
  - Advance stockpiling is not possible
  - Increase use of seasonal vaccines (*long-term solution*)
  - Using monovalent vaccines and reducing the antigen needed by the use of adjuvants can increase number of doses available
  - Expand manufacturing capacities (now only present in a few developed countries);
  - Reduce costs (vaccine; shipment; use and application)
- Contingency plan for vaccine production and distribution

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#### Objective 4: Mitigate impact

- Use of antiviral stockpiles for prophylaxis in selected groups to maintain essential services
- Public health measures to reduce transmission, “flatten” the epidemic curve and reduce the peak in disease burden
  - ban on gatherings, closing of schools
  - temporary travel restrictions
  - masks, personal hygiene, etc
- Hospital and medical services emergency plans
- Appropriate “risk communication” to the public
- Ensure access to vaccines, as soon as they become available.

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# Pandemic Influenza

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#### Research priorities

- Understand the potential for H5N1 to reassort or mutate
- Clarify the role of animal influenza in the emergence of pandemic viruses
- Improve clinical knowledge of human disease
- Find ways to economize on antigen content in vaccines
- Improve vaccine production

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#### Pandemic preparedness: where are we?

- Surveillance and rapid detection are insufficient
- Limited national capacities for epidemic alert and response (*International Health Regulations 2005*)
- Very few countries have adequate pandemic preparedness plans or national policies for vaccination and antiviral use
- Severe vaccine and antiviral shortage are expected. Absence in developing countries
- National and international agreements on vaccine production and distribution to countries without domestic vaccine production are not in place
- Limited collaboration between the animal and public health sectors

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#### For more information

- WHO Influenza website
  - <http://www.who.int/csr/disease/influenza/en/>
- CDC Influenza website
  - <http://www.cdc.gov/flu/>
- MEDLINE Plus influenza site
  - <http://www.nlm.nih.gov/medlineplus/flu.html>
- FAO Influenza website
  - [http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/special\\_avian.html](http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/special_avian.html)
- OIE Influenza website
  - [http://www.oie.int/download/AVIAN%20INFLUENZA/A\\_AI-Asia.htm](http://www.oie.int/download/AVIAN%20INFLUENZA/A_AI-Asia.htm)

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**Pandemic Influenza**  
**Dr. Stephano Lazarri, WHO, Lyon**  
**A Webber Training Teleclass**

Teleclass ... August 16, 2006



# Avian Influenza

Presented by Dr. Lance Jennings, PhD  
Virologist, Avian Influenza Specialist

Recent Publications (2005)

JENNINGS L.C. "World Health Organisation (WHO) recommendations on the use of rapid testing for influenza diagnosis." *WHO*

JENNINGS L.C., Fekunda K., Plant A., "Assessment of Avian Influenza Situation." *WHO*

JENNINGS L.C. "Avian Influenza and Influenza Surveillance.", *WHO*

JENNINGS L.C. "Influenza Update.", *The Practice Nurse*.

Broadcast live from the  
National Division of Infection Control Nurses conference  
Christchurch, New Zealand

For NDICN conference information refer to:  
[www.infectioncontrol.co.nz/files/events-detail.asp?EventID=27](http://www.infectioncontrol.co.nz/files/events-detail.asp?EventID=27)

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