The Two Faces of Influenza

Annual, epidemic Influenza and Pandemic Influenza

Sabine Arnoux March 2007, Eldoret, Kenya
Often misunderstood and underestimated, Influenza is not just “a bad cold”!

Annual, winter influenza epidemics

Influenza pandemics: exceptional epidemiological events occurring every few decades
Influenza virion

Capsid (type A, type B, type C)

Envelope

Neuraminidase (NA)

Haemagglutinin (HA)

Surface antigens

Protective antibodies
Influenza virus mutations

Influenza type A viruses mutate frequently, type B viruses mutate less frequently,

Mutation enables the virus to bypass the population’s acquired immunity

Both the haemagglutinin and neuraminidase surface antigens mutate

Mutation occur through two mechanisms

- **Antigenic drift**
  - Occurs continually
  - Leads to modified viruses that causes annual epidemics

- **Antigenic shift**
  - Occurs rarely
  - Leads to novel viruses that cause pandemics

Antigenic drift

Minor variations in the Haemagglutinin and/or Neuramidase

- Affects Influenza type A and B viruses
- Caused by mutations in the viral RNA
- Occurs each year within a subtype
- The resulting modified viruses cause annual epidemics

A/H3N2

Mutation

RNA segment Coding for HA or NA

Mutation(s)

Amino acid change(s)

Variations within a subtype

drift
Antigenic shift

Emergence of a novel virus

- Only affects type A viruses
- Caused by major genetic modifications to the HA or NA
- The human population has little or no immune protection against the novel virus…
- …which leads to pandemics every 10 to 40 years
Transmission

Virus is mainly spread through the air by coughing and sneezing, especially in closed public places: public transport, meeting rooms, ...

An infected person can transmit the virus to others from 1-2 days before flu symptoms start, and for 5 days afterwards.
During each annual winter epidemic:

5 to 10% of the world’s population catches influenza
i.e., 500 million people
Including 3 to 5 million serious cases
100,000 to 1,000,000 deaths each year
Influenza does not discriminate:
it affects men and women, boys and girls of all ages, in all sectors of the population, and in all countries
Typical influenza illness

- Incubation period
- Infectious period

**Incubation period**

**Infectious period**

**Time (in days)**

**LOG10 virus titre in nasopharynx**

**Temperature (°C)**

**Virus**

**Fever**

**Sore throat, Myalgia**

**Headache**

**Cough**

**Corzya (blocked/runny nose)**

**Malaise, prostration**

**Onset of illness**

**Complications**
Complications

Mainly affect the elderly and infants

Infants
- Otitis, either viral or a secondary bacterial infection
- Exacerbation of chronic asthma
- More rarely: high fever and convulsions
- Myositis

Adults
- Bronchitis, sinusitis
- Fulminant viral pneumonia (seen during influenza pandemics)

Elderly persons and those with high-risk chronic medical conditions
- Acute bronchitis
- Pneumonia: viral or bacterial secondary infection
- Respiratory (asthma), cardiac, renal or metabolic (diabetes) decompensation

Influenza in at risk patients

Asthmatics
Diabetics
At risk patients
Influenza in asthmatic patients

1. Association of respiratory viral infections with asthmatic crisis in adults
   - 138 adults with asthma
   - 10/90 to 08/92, UK
   - > 40% of symptomatic asthmatic crisis were associated with viral respiratory infections
   - 71% of the crisis were associated with cold symptoms
   - Influenza was associated with severe crisis

   *Nicholson et al., BMJ, 1993*

   **Influenza is a severe disease for asthmatics**

2. Does flu vaccination induce crisis in asthmatics??
   - 12,000 patients 65-79 years old with asthma and COPD, 3 flu seasons
   - Asthma diagnosis as well as corticosteroid prescriptions are the same after vaccination and during low risk season
   - Asthmatic crisis do not increase significantly after vaccination

   *Tata et al., Thorax, 2003*

   **Influenza vaccination does not induce asthma crisis in adults**
Flu vaccination prevents asthma crisis

1. **349 asthmatic children**
   - 0-12 years
   - 2 influenza seasons

   *Smits et al., Epidemiol Infect, 2002*

   **All children**
   - 27% reduction in acute respiratory attacks
   - 56% reduction during first influenza season

   **Children < 6 years**
   - 55% reduction in acute respiratory attacks
   - 77% reduction during second influenza season

2. **130,000 asthmatic children**
   - 1-6 years
   - 3 seasons (USA)

   *Kramarz et al., J Pediatr, 2001*

   **Asthma crisis reduction**
   - First season: 78
   - Second season: 59
   - Third season: 65
Influenza risks in diabetics

**Diabetics are**

6 times more at risk to be hospitalized with an influenza diagnosis

3 times more at risk of dying of pneumonia or influenza

Mortality rate increases by 5 to 15% during influenza epidemics

CFR for influenza: 12%

**Immune response**

Response is satisfactory in 70% of patients

Patients who don’t respond to initial immunization respond to a second dose

**Influenza consequences in diabetics are very severe**

Immunization is very valuable in these patients
Effectiveness of influenza vaccination in diabetic patients

In a case control study, influenza vaccination reduced hospitalization:

- For pneumonia and influenza by 80%
- For bronchitis
- For diabetes without mention to any complication
- For diabetic comas
- For acidocetosis

Effectiveness of influenza vaccination in the reduction of the risk of hospitalization for influenza or pneumonia, or death

- 50% in 1996-7
- 21% in 1997-8

Influenza vaccination was EFFECTIVE since it reduced hospitalizations during influenza epidemics
Influenza and cardiovascular diseases (CVD)

• In 2002, CVD represented 29.2% (16.7 millions) of worldwide deaths
• Global CVD impact increases (increase in population age, urbanization)

Flu activity and hospital admissions for heart failure in people older than 65 years, Hong Kong, 1998-2001

Obvious superposition between the flu activity peak and heart failure hospitalizations
Benefits of flu vaccination in patients with CVD

FLUVACS study (Argentina): flu vaccination and reduction of death and ischemic events in patients with Myocardial infarction

- Significant reduction in deaths (75%) and rehospitalizations
- Reduction of the triple risk (CV deaths, infarction and severe ischemia)
- Consistant results during 2 years, and with other studies

Four case control studies: reduction of:

- 49% for primary cardiac arrest risk
- 67% for the MI risk
- 55% for cerebral stroke (2 studies)

CONCLUSION: Flu vaccination is associated with a reduction in the risk of CV events
Groups at increased risk for Influenza-related complications

Influenza vaccination is the primary method for preventing influenza and its severe complications. The Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for the following groups:

Persons at high risk for influenza-related complications and severe disease, including
- Children aged 6--59 months,
- Pregnant women,
- Persons aged ≥50 years,
- Persons of any age with certain chronic medical conditions; and

Persons who live with or care for persons at high risk, including
- Household contacts who have frequent contact with persons at high risk and who can transmit influenza to those persons at high risk and
- Health-care workers.

Influenza: vaccine, vaccine production
Influenza vaccines

Influenza vaccines first available in the 1940s
- Whole virion vaccines: Connaught Laboratories (USA) in 1947 and Institut Mérieux (France) in 1968

Today’s vaccines
- **Trivalent**
  - 2 subtype A strains (H1N1, H3N2)
  - 1 type B strain
- **Two formulations per year: one for each hemisphere**
  - The WHO recommends the viral composition of each formulation, based on the predominant circulating strains
- **Different types of vaccines are available**
  - Inactivated, injectable (split virion, sub-unit and a few whole virion vaccines)
  - Live attenuated vaccine for nasal administration
- **Vaccine viral strains grown in embryonated chicken eggs**
  - Cell culture-based vaccines are in development
Influenza Vaccination: The best defence against illness for more than 50 years

Effective

- Vaccination mimics natural infection, providing protection for 6-12 months against the vaccine strains
- Protects 70–90% of vaccinated healthy adults
- Reduces complications and mortality by 70--85% in elderly persons

Beneficial to society

- Vaccination reduces the risk of transmitting the virus to others:
  - Persons at risk of complications of influenza infection (the elderly, infants…)
  - Family, friends, colleagues…
International surveillance network

Choice of vaccine strains procedure

Sentinel Doctors \( \rightarrow \) Isolation of strains

National influenza Centers (over 110 national laboratories in over 80 countries)

Collaborating Reference Centers for Research against influenza (London, Atlanta, Tokyo and Melbourne)

World Health Organization (WHO - Geneva)

Vaccine Manufacturers

Most countries in the world depend on European vaccines

- Around 300 million doses produced yearly worldwide in 2004
- Influenza vaccine-producing countries:
  - Europe (UK, France, Germany, Italy, Netherlands), Canada, USA, Japan, Australia
  - 12% of world population with 95% of global vaccine production
  - Production capacity of European countries: 190 million doses (65%)
- International Area (outside US, Western Europe, Canada, Australia & Japan): 85 M doses
  - 97% of these doses are produced in Europe
Current influenza immunization rates are very different around the world

Fig. 3. Influenza vaccine distribution in 56 developed and rapidly developing countries in 2003 indicated by the number of doses of vaccine distributed in each country per 1000 total population (adapted from\(^{(17)}\)).

Inter-Pandemic Years: Global Influenza Vaccine Distribution 1994 – 2003

292 million doses vs > 6 billion world population

Source: International Influenza Vaccine Supply Task Force 2004
# Influenza vaccine Manufacturing time-table

<table>
<thead>
<tr>
<th>Month</th>
<th>WHO (Northern hemisphere)</th>
<th>WHO (Southern hemisphere)</th>
<th>Choice of strains</th>
<th>Vaccine on the market</th>
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**INTERNATIONAL SURVEILLANCE NETWORK**

**VACCINE MANUFACTURER**
Aventis Pasteur

Influenza vaccines:

Manufacturing timetable

**Egg supply organisation**

- WHO meeting
  - D0 = mid Feb

- D0 - 6 months

**Egg supply for production**

- Seed lots
- Monovalent batches
- Blending
- Filling / Packaging
- Packaging documentation
- Pharmaceutical file
- Clinical trial

- Ref Member State Release

- Vaccine Delivery

- July/August

Reagent availability

- End of May

WHO meeting

- D0 = mid Feb
The threat of Pandemics
What is pandemic influenza?

An exceptional epidemiological event:

- Rapid worldwide circulation of a highly contagious virus
- New subtype of an influenza type A virus against which humans have little or no immunological protection
- Higher morbidity and mortality than seen with classical annual influenza

Previous pandemics affected 25–50% of the world population over a 13–23 month period

Young, healthy adults are affected by severe forms of the disease
Influenza pandemics in history

- 1889 & 1891
  - H3N8 pandemic
  - Influenza-like epidemics first reported
- 1918
  - Spanish flu H1N1
- 1933
  - Influenza virus isolated for the first time
- 1957
  - Asian flu H2N2
- 1968
  - Hong Kong flu H3N2
- 412 BC
  - Epidemic reported by Hippocrates
- 1173-1174
  - Influenza-like epidemics first reported

Spanish influenza (A/H1N1) 1918 - 1919

1 billion people affected
(25-30% of the world population)

3 epidemic waves:
- March and September 1918
- February 1919

Exceptionally virulent strain

40-50 Million deaths:
- > 200 000 in France
- 500 000 in the USA
- 1.5-2 Million in Africa
- 7-10 Million in India
Asian influenza (A/H2N2) 1957 - 1958

2 waves:
- Children
- Elderly persons

1-2 million deaths worldwide

Improved surveillance and warning compared to 1918-19 (WHO)

Vaccines and antibiotics available

Milder pandemic
Hong Kong influenza (A/H3N2)
1968 -1969

Same Asian origin as
1957-58 pandemic

Milder pandemic (possible cross-protection provided by exposure to the 1957 H2N2 strain)

0.8-1 Million deaths worldwide
Influenza Pandemic - Definition

3 conditions for a pandemic

- Emergence of a new influenza A virus with a different HA from those of recently circulating strains
- Absence of immunity in the population against the new strain
- New virus with high virulence and rapid person to person transmission
Mechanisms of emergence of novel human viruses

Adaptive mutation (e.g., Spanish flu)

The virus becomes fully adapted to humans through serial genetic modifications during successive infection in humans and other mammals.

Gene reassortment from 2 viruses co-infecting a host (e.g., Asian flu)

Strain re-emergence (e.g., Asian flu: H2N2)
Wild birds are the influenza A viral reservoir

Influenza’s main other natural hosts: Poultry, Horses, Swines, Humans


### Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO

**27 February 2007**

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Total number of cases includes number of deaths.
WHO reports only laboratory-confirmed cases.
All dates refer to onset of illness.
Avian influenza epidemics caused by highly pathogenic virus (HPV) H5N1

1959: first epidemics documented in chickens

1997 in Hong Kong
- 1.5 Million chickens culled
- 18 human cases
- 6 deaths

Since December 2003
- The H5N1 HPV progressively spread
  - From Thailand, Vietnam and Cambodia, to Laos, South Korea, China, Indonesia, Malaysia, and in 2005 to Mongolia and Kazakhs…etc
- >140 Million chickens culled
- To date (end feb 2007): 276 human cases, including 168 deaths
Current status of avian H5N1 epidemic

The epidemic is now endemic in the chickens of several Asian countries

Highly Pathogenic Avian Influenza Virus H5N1 has been also isolated from certain species of migrating birds

Ducks can carry the virus, but most of them do not develop the disease

In addition to humans, the virus has infected other mammals (felines, ferrets, pigs, New Zealand white rabbit, cynovolgus macchaque…etc)
Necessary conditions for the emergence of a pandemic influenza virus

I. Emergence of a influenza A virus against which humans have little or no protective immunity

II. The new virus is able to infect and grow in humans, causing severe disease (virulence) ➔ From December 2003 to Feb 2007, 276 persons were infected (168 deaths) in 12 countries

III. The new virus is easily and quickly spread from human to human, causing a continuous chain of infection (contagiousness) ➔ to date, human-to-human transmission is not confirmed with this virus
World pandemic preparedness
Influenza Pandemic

Why do we need planning?

It is impossible to predict when the next pandemic will occur.

WHO Weekly Epidemiological Record, November 2002: „inevitable shortage of vaccines and antivirals“

Worldwide production of influenza vaccines is currently able to cover less than 5% of the world’s population.

In case of a pandemic:

- severe pressure on health services,
- social disruption,
- interruption of commerce, economic losses, etc.
Preparedness plans of WHO, governments and private sector follows the WHO phases

<table>
<thead>
<tr>
<th>WHO Phases</th>
<th>Interpandemic period</th>
<th>Pandemic alert period (pre-pandemic)</th>
<th>Pandemic period</th>
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<tbody>
<tr>
<td>Phase 1</td>
<td>No new flu virus circulating in humans</td>
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<td>Phase 2</td>
<td>No new flu virus circulating in humans, but an animal virus poses a substantial risk of human disease.</td>
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<td>Phase 3</td>
<td>Human infection with a new virus (no person-to-person transmission, or rare and isolated cases connected to close contact)</td>
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<td>Phase 4</td>
<td>Clusters of limited and localized person-to-person transmission (virus incompletely adapted to humans)</td>
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<td>Phase 5</td>
<td>Expansion of clusters, still geographically localized (the virus is adapting to humans)</td>
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<td>Phase 6</td>
<td>Significant person-to-person transmission in the population, with rapid geographic expansion</td>
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</table>
WHO Global Agenda on Influenza Surveillance and Control

17 priority activities organized around 4 main objectives

- Strengthening surveillance
- Improving knowledge of disease burden
- Increasing vaccine usage
- Accelerating pandemic preparedness
Priority groups for vaccination

Each country will need to define its priority groups

- **Essential service providers**
  incl. health care personnel, firemen, police, persons involved in water, gas and electricity distribution, etc.

- **Groups at high risk of death and severe complications**

- **Persons without risk factors for complications**
  Healthy adults and children

„The final choice is a political one“ (Chippaux, 1994)
Pandemic preparedness and use of influenza vaccines in Interpandemic periods

Pandemic threat is a major driver for Interpandemic coverage extension

- To increase production capacities
- To avoid genetic reassortment

Resolution of the World Health Assembly, May 2003

„Better use of influenza vaccines for seasonal epidemics will help to ensure that manufacturing capacity meets demand in a future pandemic, as well as preventing numerous deaths“
Preparedness activities are in line with the WHO warnings and preparedness guidelines

1. Pandemic influenza is different from avian influenza
2. Influenza pandemics are recurring events
3. The world may be on the brink of another pandemic
4. All countries will be affected
5. Widespread illness will occur
6. Medical supplies will be inadequate
7. Large numbers of deaths will occur
8. Economic and social disruption will be great
9. Every country must be prepared
10. WHO will alert the world when the pandemic threat increases
Thank you!