Grippe en 2005: les risques et les armes, dont la vaccination et les antiviraux.



Dr R.Snacken Scientific Institute of Public Health Bruxelles, 27/10/2005

Influenza





Types	A/H1-3 N1-2	A/H1-16 N1-9
Host-range	Human	Mammals : birds, pigs horses, seals, whales, minks
Transmission route	Aerosolized droplets	Faeco-oral, droplets
Intermediate host		Pig, (human?)
Natural reservoir		Aquatic birds

- Interpandemic influenza (antigenic drift) : human disease
- Pandemic Influenza : (antigenic shift) : zoonosis



Interpandemic Human Influenza



Respiratory infection associated with a high morbidity and mortality, and with an important societal cost as well

- The burden of the disease can be avoided by vaccination
- Anti-viral drugs can help to reduce the morbidity
- Influenza Pandemic Preparedness Plan must be ready in case of emergence of a novel human-to-human transmissible A strain

Clinical Course



Inter-Pandemic Human Influenza Burden of the Disease

High incidence (up to 20%)

- Lower incidence in the elderly
- But attack rate as high as 60% in nursing homes

La Force M et al. Immunization in Medical Education, 1994

- High rate of complications
 - 9.5% in general population
 - 73% in 70 year and more Betts RF et al. Principles and practice in infectious diseases, 1990



Mortality related to Inter-Pandemic Influenza

USA : 21.000 deaths / year

Simonsen L et al. Am J Publ Health, 1997

> 1989 UK : 26.000 excess deaths

Curwen T et al. BMJ,1990

> 1989 Belgium 4.900 excess deaths

Snacken R. et al. Eur J Epidemiol, 1992

> 80% of deaths in 65 year and more



Complications

Interpandemic Influenza	Belgium
0 % incidence rate	10 ⁶
10 % complications	10 ⁵
10 % hospitalizations	10 ⁴

10% deaths 10^3

Belgium today :

> Annual influenza : 1.000 deaths / year

If Spanish-like pandemic in Belgium: 100.000 deaths if we are not prepared Spanish Flu

50 % incidence rate

2 % CFR



Control and management of Interpandemic Influenza

Not eradicable disease
(animal reservoir)
→ objective: to reduce the impact by

Surveillance

Vaccination





Chemoprophylaxis

Treatment



Clinical and Virological Data Sentinel Practices

GP's notify Acute Respiratory Infections

GP's perform swabs in suspect cases

Swabs are sent to the IPH for identification, typing and sub-typing



Evolution du pourcentage de grippes et d'infections respiratoires aigués (IRA) totales enregistrées par les médecins sentinelles chez leurs patients

Seuil épidémique

des IRA totales

Semaines

16 | 17 |



Influenza B 0 0





EISS : Collection of Outstanding Events in the World (Promed) 2003

•Hong Kong SAR (Feb 4th) : precautionary slaughter of H5-type influenza virus infected birds (10,000)

•Congo : (Feb 13th) 14 medical institutions in Kinshasa reported 3,963 influenza cases including 126 deaths (case-fatality rate of 3.2 percent) and 33 health zones reported 27,211 cases including 170 deaths (case-fatality rate of 0.6 percent). The Institut Pasteur from Paris confirms that influenza virus A(H3N2) is involved in the current outbreak.

•China (Feb 14th) : Pneumonia outbreak in southern China kills five, prompts panic buying of antibiotics. According to the Guangzhou City's Director of the Municipal Health Bureau, the causative agent has been identified : Mycoplasma pneumoniae

Recommendations for Preventing Influenza

Current recommendations are essentially targeted to :

- Persons at high risk of complications (>65 y, institutionalized persons, underlying chronic condition from the age of 6 month : heart, lung, liver, kydney, diabetes and other immunologically frail people)
- Persons who can transmit the disease to high risk persons (medical staff, households, ...)
- Anywhone who whishes to be vaccinated
- •These recommendations were recently extended (Sept 2005)

Transmission Routes of Influenza

1. Droplets





2. Airborne droplet nuclei

3. Fomites



NB: SARS: not 2.

Rationale for Reinforcing Vaccination Policy

Medical staff

Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients.

10-17% reduction of mortality

Potter J et al. J Infect Dis, 1997

Effects of influenza vaccination of health-care workers on mortality of elderly people in longterm care: a randomised controlled trial

odds ratio 0.58



Carman WF et al. Lancet 2000

Take care, she is not vaccinated

She is an inter-pandemic serial killer

Herd Immunity : Flu Vaccination in children and mortality all ages in Japan



Treatment

Inhibitors of Neuraminidase

Oseltamivir efficacious if early treatment

•34.0% reduction lower tract infection in high risk patients

•26.7% reduction overall antibiotic use for any reason

•59% reduction of hospitalizations

Kaiser L et al. Arch Intern Med, 2003

Rapid diagnosis test not helpful and not cost-effective for presumptive treatment during influenza epidemics

Schwarzinger M et al. PharmacoEconomics, 2003

Chemoprophylaxis

Oseltamivir was effective in reducing the incidence of secondary complications

Matheson NJ et al. Cochrane Database Syst Rev, 2003

- Long-term prophylaxis (4 weeks) for high risk persons or households even if vaccinated
- Contact prophylaxis essentially in nursing homes

Indications could be extended, but further evidence is needed for supporting this practice

Influenza Pandemic

- New influenza virus with a hemagglutinin (Ha) different from that contained in strains circulating in man for many years
- 2. No or low antibodies titres to the HA of the novel virus in the population
- 3. High person-to-person transmissibility with accompanying human disease



Influenza A Virus Shift

 $H_w N_x$



This representation of the flu virus shows a cutaway of the virus shell, coated with protein (blue) inside a lipid bilayer, to reveal the virus's eight genes. Pink and yellow spikes represent hemagglutinin and neuraminidase respectively. These components control the virus's ability to attach to and release from a cell, and they constantly change -- making a new vaccine necessary each year.

 H_3N_2

 $H_Y N_Z$

 H_7N_7

 H_5N_1

Evolution of Influenza A viruses



Influenza A Pandemics

1889-90	A/H2N8	3.8.2.1	
1900-03	A/H3N8		
1918-19	A/H1N1	Spanish Flu	
1957-58	A/H2N2	Asian Flu	Australian Red Cross 1918
1968-69	A/H3N2	Hong Kong Fl	u
(1977-78)	A/H1N1	Russian Flu	

Best candidates for the next pandemic :

H2 or a HA (H5 or H7) with a human receptor binding protein H9N2?

The Spanish Flu (1918) Death Toll : 20-40 million deaths



High mortality in both developing and developed countries

- High pathogenicity in young adults
- Importance of basic nursing and care
 support
- Efficacy of community-based efforts
- Inefficacy of closing borders
- Five waves in 18 months

The Influenza Pandemics that might have been

1976 : Fort-Dix (EU) (1 fatal case)		H1N1
1986 : The Netherlands (1 severe pneumonia)		H1N1
1988 : Wisconsin (EU) (1 fatal case)		H1N1
1993 : The Netherlands (2 mild infections)		H3N2
1997 : UK (1 conjonctivitis)		H7N7
1997 : Hong Kong SAR (18 cases/6 deaths)	<u>A</u>	H5N1
1999 : Hong Kong SAR en China (7 cases)		H9N2
2003 : Hong Kong SAR (3 cases, 2 deaths)		H5N1
2003 : NI-Be : > 100 cases, 1death		H7N7

Lessons learned from Fort Dix, A/H1N1, USA, 1976

One lethal case suspected to have been infected by a virus similar to the A/H1N1 responsible for the Spanish Flu

→ Monovalent vaccine prepared in emergency and administered to 45 millions people

→ The program was stopped as the virus did not spread. Moreover more than 100 cases of Syndrome de Guillain-Baré, a direct side effect of the vaccine, were observed



The Bird Flu A/H5N1 Hong Kong, 1997

- March : several thousand chicken die in 3 farms
- May 1997 : 1 child of 3 year dies
- Summer 1997 : similarity between H5N1 avian and human viruses confirmed
- December 1997 : 17 human cases from which 5 deaths



Lessons learned from Hong Kong, 1997

- Transmission by poultry
- Human to human transmission not observed
- 1.6 millions chicken slaughtered
- No human case was observed after culling

→ It was the right time because seasonal flu had started with the likelihood of a reassortment between circulating and avian strains with a possible emergence of a pandemic strain

Fowl Plague

- First description in Italy in 1878
- The name HPAI (Highly Pathogenic Avian Influenza) was first used in 1959 and 1961(A/H5N1 in chicken in Scotland and A/H5N3 in terns in South-Africa)
- Outbreaks of HPAI viruses (H5 et H7) were observed in Pennsylvania in 1983-84. More recently, outbreaks were detected in Australia, Pakistan and in Mexico.
- HPAI are uncommon and must be distinguished from LPAI which can also be caused by H5 or H7
- Low pathogenic H5 virus can mutate and become high pathogenic

<u>OIE Liste A</u> : Maladies transmissibles qui ont un grand pouvoir de diffusion et une gravité particulière, susceptible de s'étendre au-delà des frontières nationales, dont les conséquences socio-économiques ou sanitaires sont graves et dont l'incidence sur le commerce international des animaux et des produits d'origine animale est très importante

Fowl Plague

Since 1955, there have been 18 cases of HPAI



It is important not to allow the mildly pathogenic viruses circulate in populations as a way of preventing it's evolution into highly pathogenic avian influenza.

Avian Influenza 2003 The Netherlands

Date outbreak : Feb 28 th ~ 100 farms confirmed cases

- 1 vet died (H7N7)
- 349 conjunctivitis
- 90 Influenza-like infection



Koopmans M et al. Lancet 2004; 363: 587-93

- \rightarrow Culling of > 20 million chickens
- \rightarrow Hygienic measures (gloves, masks, ...)
- → Prophylactic use of oseltamivir (compulsory)
- \rightarrow (re)vaccination with the current influenza vaccine

Avian Influenza 2003 Belgium



More strict checks for stillstands Preventive culling in 129 farms Total waterfowl slaughtered 3.171.000



- Preventive use of oseltamivir but not compulsory
- Use of influenza vaccine

Current Asian Bird Flu Outstanding Observations



Unprecedented geographical spreading Unprecedented high number of outbreaks at the same moment Concomitant LPAI in neighbouring countries and elsewhere Bird to humans infection remains sporadic Children seem to be at high risk Very high CFR Wild birds sick New species infected : pet cats, tigers, leopards, civet cats Genes of A/H5N1 are all of avian origin Current A/H5N1 different from 1997 strain Primary resistance to M2 inhibitors Prevalence in swine unknown Role of migratory birds? Only 2 AA are needed for acquiring tropism to human respiratory receptors

Human Cases of H5N1 in S-E Asia in 2004-2005

Human cases / deaths (as of Oct 24th)

62

- Viet Nam
 Thaïland
 Thaïland
 19
 13
 Cambodia
 4
 4
 Indonesia
 7
 4
 - 121

WHA resolutions Global Agenda on Influenza



Third recommendation : Expand animal influenza surveillance and integrate with human influenza surveillance

- Expand and formalise the WHO Animal Influenza Network (AIN)
- Establish close interactions between OIE (Office International des Epizooties) and WHO influenza networks
- Encourage studies at the human/animal and at the domestic/wild bird interfaces and provide training to carry out studies
- Develop and distribute reagents for identifying influenza viruses of all subtypes and establish the total gene pool among influenza viruses

Rationale: Extension of animal influenza surveillance and integration with human influenza surveillance is essential for understanding and preparing for threats to human health posed by animal influenza viruses.

Influenza Pandemic Preparedness Plan

The Role of WHO and Guidelines for National and Regional Planning

Geneva, Switzerland, April 1999

http://www.who.int/emc-documents/influenza/whocdscsredc991c.html



Preparedness Levels

Today

- Level 0 : inter-pandemic period
- Level 1 : novel virus sub-type confirmed
- Level 2 : human infection confirmed
- Level 3 : high human-to-human transmission confirmed
- Phase 1 : onset of a pandemic
- Phase 2 : multi-(regional) outbreaks
- Phase 3 : end of the first wave
- Phase 4 : next waves
- Phase 5 : end of the pandemic

N.B. Phasing was recently changed

National Influenza Pandemic Plan Committee (Belgium) Membership

- Public Health Authorities
- Other administrations involved
- Universities and scientific institutions
- Pharmaceutical companies

→ The Minister of Public Health runs the process (Chain of command)

Sub-Committees

- Scientific
- Case
 management
- Surveillance
- Logistics
- Communication
- Animal Protection



Actions to be taken (I)

- <u>Phase 0</u>: Preparedness and update
- <u>Phase 1</u>: Monitoring enhancement, acceleration of pneumococcal vaccination, stockpiling, provision of adequate information
- <u>Phase 2</u>: Preparation of vaccination and use of antiviral drugs

Actions to be taken (II)

- <u>Phase 3</u>: additional human resources, delaying non urgent hospitalizations, cohorting patients, diagnosis and hospitalizations criteria for GP's,
- <u>Phase 4</u>: limiting transport, wearing masks in public and Health care facilities, closing hospitals and nursing homes to visitors, closing non essential public places, handling of corpses, ...

Actions to be taken (III)

 <u>Phase 5</u>: WHO will declare the pandemic to be over, monitoring for the detection of an additional wave, serum surveys, socio-economic and demographic assessment, lessons to be learned,...

Stockpiling of Antivirals



Objective : 30% Belgian population should have access to treatment in 2008

A/H5N1 Human Vaccine





A/PR8/34 (H1N1) (master donor) A/H5N1 (Circulating strain)

6 matrix genes

2 antigenic genes (HA and NA)

Attenuation of highly pathogenic residues



Re-assortant vaccine virus

Vaccination

- No vaccination
- Vaccination of selected groups (5-10%)
- Vaccination of high risk groups (25%)
- Vaccination of the population (>90%)

Advantages and disadvantages according to the identification of risk groups

Scientific and Medical Issues

- Hazards for laboratory workers
- Criteria for initiating levels of response
- Target groups for vaccination and antiviral drugs
- Criteria for hospitalization
- Instructions for medical staff
- Other preventive measures (masks) FFP2

Pharmaceutical and Logistical Issues

- Steps to licence the vaccine (Fast track procedure)
- Timetable for procuring vaccines, antiviral drugs, antibiotics, pneumococcal vaccines
- Ancillary supplies (syringes, masks,...)
- Health care facilities
- Implementation of mass vaccination
- Transportation of corpses

Surveillance Issues

- Case definition
- Transport of swabs
- Laboratory procedures
- Indices to be monitored
- What sub-groupings (e.g. age groups)
- Surveillance of vaccine and antivirals drugs use + resistance

Health Care Facilities : An Unavoidable Issue





Conclusions

In case of an Influenza A pandemic exceeding the usual ways for control and management of a widespread outbreak, the national committee must initiate a national response. The main issue will be the supply of antiviral drugs and the implementation of vaccination (if any). Home care of sufferers has to be the rule. Hospitalization must be the exception. Equity in access to medicines must be guaranteed, especially in case of shortage. Collaboration with developing countries has to be enhanced for integrating stockpiling and counter measures in a global development process