

INTERNAL USE  
ONLY

# FLU NEWS

## Content :

Trends in influenza  
vaccinology ..... P1

In the press ..... P5

## Trends in influenza vaccinology

### H5N1, Asia, 2004

#### Spreading like wildfire

More than 100 million poultry have been slaughtered in 11 Asian countries since the beginning of the year, in an attempt to stop the unprecedented spread of a H5N1 virus among domestic birds ([www.oie.int](http://www.oie.int)). Up to March 17<sup>th</sup>, 34 human cases of infection by H5N1 influenza virus had been reported, with 23 deaths ([www.travelhealth.gc.ca](http://www.travelhealth.gc.ca)). In response to this situation, the WHO has raised its pandemic preparedness level to 0.2. Among the potential candidates responsible for the next pandemic, the H5N1 subtype is of particular concern. Strains of this subtype rapidly evolve among both wild and domestic birds. H5N1 is widespread in birds and pigs in Asia: since 1997, it has been regularly responsible for outbreaks in birds in Hong Kong, as well as of several fatal cases in man <sup>(1)</sup> (see FluNews4).

This time however, the avian virus has escaped control and has rapidly swept across several Asian countries (Figure1). It could take years for it to be brought under control.

#### Pandemic threat

Experts deem that under the present conditions a pandemic virus could easily spread across the globe.

2004 Asian Flu : key numbers, up to March 17th  
([www.travelhealth.gc.ca](http://www.travelhealth.gc.ca), [www.who.org](http://www.who.org), [www.oie.int](http://www.oie.int),  
[promedmail.org](http://promedmail.org))

- **More than 100 million birds culled in 10 Asian countries**
- **US\$ 965 million lost by Thailand, due to lost chicken exports**
- **34 human cases in Thailand and Viet-Nam, with 23 deaths**
- **70 % lethality associated with the current H5N1 virus strain**
- **Median age of human cases reported up now : 13 years**

The more the virus lingers, the greater the risk that the avian H5N1 virus will gain the ability to spread from person to person whilst maintaining virulence, thus giving rise to a pandemic virus. This could result either from the mixing of human and avian influenza viruses, or from the adaptation of avian H5N1 viruses (*via* genetic evolution).

For now, reports from the field indicate that this has not yet occurred. Two cases of H5N1 infection in Asia have probably resulted from human-to-human transmission

Infections due to H7 avian viruses in Canada and the US

**Two cases of infection by an avian virus of the H7 subtype were reported in Canada in March and April 2004 ([www.who.org](http://www.who.org)). These were two poultry workers involved in the culling of birds, infected during several H7-outbreaks in Canada. Both cases were mild and symptoms (conjunctivitis and nasal discharge) have fully resolved. On April 22, 2004, The Centers for Disease Control and Prevention (CDC) in Atlanta confirmed an isolated human case of H7N2 infection in New York. This case, which occurred 5 months ago, involved a patient who entered hospital with atypical symptoms for influenza, including a cough. He was discharged after 2 months, and so far there is no evidence that other members of the public have become infected. Investigations are ongoing as to determine the possible source of infection as well as to collect additional data on this avian virus.**

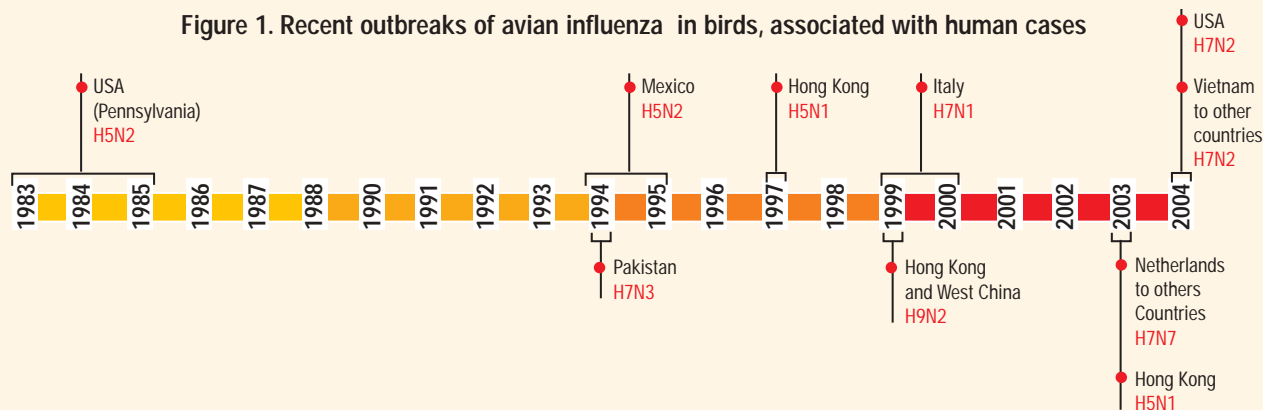


**Aventis Pasteur MSD**  
Vaccines for Life

but investigations conducted by the WHO have ruled out the possibility that the incriminated virus is a reassortant. In neither case (two women, one of whom died) there was a history of contact with infected birds and the only possible source of infection was contact with an infected

man, who had since died <sup>(2)</sup>. However, genetic analysis showed that all the genes from the H5N1 virus isolated from the women were of avian origin. This means that this virus had not acquired genes from human influenza viruses.

Figure 1. Recent outbreaks of avian influenza in birds, associated with human cases



### Controlling the animal source

Preventing the emergence of a pandemic strain is the primary aim of the H5N1 outbreak control-measures <sup>(3)</sup>. In the first phase, slaughtering of more than 100 million poultry has halted the spread of the virus in affected countries ([www.oie.int](http://www.oie.int)).

However, this does not mean that the crisis is over. In Asian countries, farming and commercial production of poultry is a source of revenue for many people <sup>(4)</sup>, who are offered poor financial compensation by their governments. As a result, some farmers may be reluctant to kill their chickens <sup>(2)</sup>. This is the case for example in Vietnam, as highlighted by Bob Dietz, the WHO's spokesman in this country: "it's going to be difficult because it's not like the large chicken farms in Holland or South Korea. Vietnam is a nation of farmers, and chickens are integrated into people's lives as a source of revenue and food" <sup>(5)</sup>.

Surveillance is also of paramount importance for the early detection of influenza outbreaks in birds <sup>(1,6)</sup>. This allowed the detection of H5N1-like viruses in chickens and other land-based poultry in Hong Kong in 2001 and 2002, before they could infect humans. Lack of awareness by the Thailand public authorities seems to have also been an important factor in the spread of the H5N1 virus across Asia ([www.promedmail.org](http://www.promedmail.org)). Live-animal markets, known as "wet markets", deserve a particular mention <sup>(1)</sup>. As part of the food consumption culture, they are widespread in Asia. As recently highlighted, wet markets are breeding grounds for viruses such as Severe Acute Respiratory Syndrome (SARS) coronavirus or avian influenza, as they provide optimal conditions

### Four measures to combat the disease

**In order to control the animal source of the H5N1 virus, the Food and Agricultural Organization of the United Nations (FAO), the WHO and the World Organization for Animal Health (OIE) have jointly recommended a global strategy relying on four measures:**

- **The rapid elimination of H5N1 infection in bird populations by culling**
- **The protection of poultry workers**
- **Improved surveillance of human respiratory disease and case detection**
- **The development and production of a vaccine**

for their transfer from animals to humans <sup>(1,6)</sup>.

### An impetus for pandemic preparedness

#### Ways to assure vaccine supply

Asian flu may give the impetus to accelerate the implementation of national pandemic planning. In Canada, most vigilant on pandemic issues, a plan has been enacted to create Vaccine Centres across the country permitting the vaccination of up to 400 people each day (Calgary Herald, 03/04/04). The government also has a contract with a manufacturing company in order to assure vaccine supplies. Such an option could serve as an example. However, this is only possible for countries with vaccine manufacturers. For those without, vaccine shortage may occur <sup>(7)</sup>.

Increasing the global vaccine coverage during the inter-pandemic period, as urged by the WHO during the 56<sup>th</sup> Health Assembly held May 28th 2003, is the path



forward towards global pandemic preparedness. The increased demand for vaccine will encourage vaccine manufacturers to invest in additional production units, thereby augmenting the global vaccine production capacity and finally vaccine output. The set objective is to be able to provide a pandemic vaccine for all. This would assure an equitable distribution of pandemic vaccines. To reach the objective, this will firstly involve increase in vaccine uptake in the currently recommended target populations and secondly, expanding vaccine recommendations to other subgroups of the population<sup>(7)</sup>. Key new sub-groups identified are the 50 years of age and older, as well as young children.

To this end, six points have been developed by the European Vaccine Manufacturers (EVM) in a Proposal

for Action Plan recently adopted by the European Commission (EC) and forwarded to the national health authorities of the fifteen Member States (box 1).

In order to ensure the possibility of producing a vaccine for all in case of a pandemic, action needs to be taken during the inter-pandemic period. In particular, the plan proposes that Member States enlarge their recommendations steadily to populations aged 50 years and over. Increasing vaccine uptake in these populations to the WHO objective will help to gradually increase vaccination coverage in Europe. The proposed step-by-step approach to implementation of these recommendations would allow the European vaccine manufacturers to increase their production capacity to a level that would enable the provision of a pandemic vaccine for all in 2010.

Box 1 Proposals for Action Plan		
Proposals	EVM Members	Member States (MSs) & EC
To prepare a flu pandemic vaccine	To develop, register and produce	EC to contribute through technical & financial support
To increase the potential influenza vaccination coverage of the EU population	To increase their production capabilities	MSs to increase vaccine inter-pandemic recommendations to populations aged 50 and over, and children
To define supply agreements between MS and EVM members for flu pandemic vaccine	To switch & to develop best efforts to maximise pandemic production capacities versus inter-pandemic	MS to plan for their pandemic needs and adapt their inter-pandemic use; EC to propose a framework
To ensure equitable distribution	To respect commitments inside & outside EU	EC coordination to ensure management of public health needs inside (MS) & outside (WHO) EU
To anticipate pricing issues	To accelerate time to market and avoid supply disruption	To anticipate price attribution & encourage for a homogeneous European price
To provide liability protection	To comply with quality requirements	To exempt manufacturers from liability & MSs to establish a national vaccine injury compensation program

**Licensing a pandemic vaccine in Europe**

Reducing delays in the licensure process is needed to make the pandemic vaccine rapidly available. To this end, "Guidelines on submission of Marketing Authorisation Applications for Pandemic Influenza Vaccines through the Centralised Procedure", have been recently established by the European Agency for the Evaluation of Medical Products (EMA). This involves the submission process of a core pandemic dossier during inter-pandemic periods, followed by a

fast-track approval of the pandemic vaccine. Approval of the core pandemic dossier will permit validation of the production process that should be used for the preparation of a pandemic vaccine (cell substrates, reagents, techniques, vaccine components...etc), as well as testing strategies, and reports for preclinical tests and clinical trials. Thus, with the fast-track procedure, when a pandemic arises, only the quality data relevant to the pandemic strain will be required for the approval of the pandemic vaccine.

## Political involvement

**In the recommendations of a consultation held by the WHO last March and attended by more than 100 experts from 33 countries, the Director General of the WHO, Dr Lee has urged “countries at the highest political level to intensify pandemic preparedness” ([www.who.int/csr/disease/avian\\_influenza/consultation/en/](http://www.who.int/csr/disease/avian_influenza/consultation/en/)). Three main objectives were identified**

- to forestall potential pandemics as they emerge
- to slow down national and international spread
- to reduce the habitually high levels of morbidity, mortality, and social disruption.

**The recommendations highlight the need to reinforce surveillance during interpandemic periods; to address the role of antivirals; to find ways to increase stockpiling to enhance public health interventions; to ensure supplies and equitable access to vaccines in both industrialized and developing countries. It also underscores that industry has to be involved very early in the preparedness process, and that the increased use of vaccines during inter-pandemic periods is the best way to increase production capacities.**

### Vaccinating children: barriers to overcome

The burden of influenza in children is now widely acknowledged. Data, showing high hospitalization rates have been reported in the US, in Asia as well as in Europe. Overall these data are in line with those previously collected (Table 1), which have conducted the US to recommend vaccination for all children aged 6-23 months. Since 2004, the American Academy of Pediatrics (AAP) has expanded these recommendations to “household contacts and out-of-home caregivers of all children younger than 24 months of age and for health care professionals” ([www.aap.org](http://www.aap.org)).

The debate now, is about how to implement these recommendations. Hurdles specific to mass vaccination of young children must be overcome. The most important being acceptability by parents and by health care providers.

For the year 2000, only 30 % of AAP fellows supported universal vaccination of infants older than 6 months of age, and 43 % opposed it <sup>(13)</sup>. Safety issues were the most important reason for opposition. Moreover, advice from the physician is the most important driving factor for parents to decide to vaccinate their child or not. This underscores the need to provide adequate education

both to physicians and to parents <sup>(14;15)</sup>.

Schedules of vaccination will also be challenged. In countries where it will be recommended, influenza vaccine will be the only childhood vaccine that must be administered yearly. Following this, it will be necessary to solve logistical issues such as vaccine supply. This should be assured via collaborations between government and vaccine manufacturers <sup>(11)</sup>. To this aim, the US government has planned to spend \$80 million over the next 2 years, in order to stockpile about 4 million doses of vaccine.

### Lessons from the winter of 2003/2004

The last influenza season was marked by the predominance of a drifted Fujian strain, associated with an early onset of epidemics, with reports of severe cases in previously healthy children and with vaccine shortage in the US <sup>(16)</sup>.

This situation however, was not so unusual. Antigenic drifts, particularly in H3 viruses, are often accompanied by a relatively early onset of the influenza season. This precocity may also have resulted from the low activity of influenza during the previous 3 years. As a

Table 1 : Hospitalization rates among young children in Europe, US and Hong Kong

Country	Study	Age	Hospitalization rates (per population)
GERMANY <sup>(8)</sup>	Analysis from various sources (sentinel, hospital-based, population-based study).	0 to 5 years	123 per 100,000
FRANCE <sup>(9)</sup>	Prospective study in a pediatric emergency department during the peak of the influenza epidemic	0-11 months	237 per 100,000
US <sup>(10;11)</sup>	19-year prospective cohort study in children	0 to 23 months	300 to 500 per 100,000
Hong Kong <sup>(12)</sup>	Retrospective, population-based study among children old hospitalized in the Hong Kong Special Administrative Region during 1998 and 1999	0-1 year 1 to 2 years	285 per 10,000 210 per 10,000



result, a large cohort of children had not been infected, and were therefore susceptible to the virus. This cohort may have promoted the rapid transmission of the Fujian strain to the rest of the community <sup>(16)</sup>.

Although several cases of severe disease have been reported in young children, no evidence exists so far to indicate that the A/Fujian-like viruses in circulation are more virulent than other influenza A viruses <sup>(17)</sup>. Retrospective data for the US suggest that death rates reported for children do not exceed those reported during other years.

Fujian strain in the 2004/2005 vaccine

**The following strains will be included in the composition vaccine for the Northern Hemisphere or the 2004-2005 season:**

- A/New Caledonia/20/99(H1N1)-like virus
- A/Fujian/411/2002(H3N2)-like virus
- B/Shanghai/361/2002-like virus

An unexpected result of the drifted strain was the increased media attention and increased public awareness of the severity of influenza for all age groups. This may partly explain the rush on vaccine early in the season in

the US, and the increase in vaccination coverage in Europe\* . In the future, raising awareness may help to increase the acceptability of the influenza vaccine and subsequently to increase the demand.

The recent global health scares on SARS and avian influenza certainly contributed to this increased awareness. In Europe, influenza vaccination coverage rate in the population 15 years and over grew almost +2% to 23.4% average. For the majority, this was due to a higher vaccination uptake in the 50-64 age group. The elderly group (65+) remains stable at a coverage of 62%, however. This study also demonstrated that coverage in people with chronic conditions and health-care professionals remains largely insufficient. Efforts will need to be made at all national and international levels to increase the coverage in all key recommended segments (elderly, chronic conditions, health-care professionals) in order to reach the set WHO objective of a 75% coverage by 2010.

Major drivers to increase vaccination in the target groups are active vaccination-recommendations from the health-care professionals and more awareness on influenza as a disease and the benefits related to influenza vaccination.

\* APMSD TNS-Sofres Influenza vaccination coverage rate study 2003-2004 ; APMSD 2004

## In the Press



### Wyeth backs out of FluMist (Scrip 28 April 2004)

Wyeth has confirmed that it is terminating its partnership with MedImmune regarding FluMist. All rights to production, marketing and sales are returned to MedImmune. MedImmune will acquire Wyeth's US distribution facility and Wyeth will provide bulk manufacturing materials and transfer all clinical trial data. Royalties will also be due to Wyeth based on future sales of FluMist and the second-generation product, cold-adapted influenza vaccine-trivalent (CAIV-T), which is in development.

FluMist's launch failed due to several reasons: prohibitive pricing, the limited age-indication, the belief that the vaccine could cause influenza and the fact that the vaccine needed to be kept frozen at all times until administration.

MedImmune will now focus on marketing CAIV-T which is not expected to be available before 2007.

### Aventis Pasteur's agreement with Crucell (USA Today, 01/08/04)

Aventis Pasteur has formed an agreement with the biotechnology company Crucell. Crucell's technology uses human cells genetically engineered to replicate infinitely. This will permit Aventis Pasteur to use the human cell technology to produce more flu vaccine according to the demand. Another expected outcome would be a flu vaccine that is faster to produce and more consistent. Currently, Aventis Pasteur grows flu virus strains in chicken eggs to develop the vaccine. The deal involves Aventis Pasteur paying Crucell about \$1.2 billion per year for the technology, and this amount is expected to double by 2010, as the demand for more flu vaccine rises.



### New US Guidelines stress flu shots for babies (Reuters – 03/11/04 – WebLink)



The American Academy of Pediatrics recommends influenza immunization for *healthy children between 6 and 24 months of age, for household contacts and out-of-home caregivers of all children younger than 24 months of age, and for health care professionals*. The academy says young children are at high risk for hospitalization when infected with the influenza virus, which killed more than 120 children during the past flu season.

#### Reference List

- (1) Shortridge KF. Severe acute respiratory syndrome and influenza: virus incursions from southern China. *Am J Respir Crit Care Med* 2003; 168(12):1416-1420.
- (2) Parry J. WHO investigates possible human to human transmission of avian flu. *BMJ* 2004; 328(7435):308.
- (3) Barclay WS, Zambon M. Pandemic risks from bird flu. *BMJ* 2004; 328(7434):238-239.
- (4) Watts J. Asian nations step up action to curb spread of avian influenza. Outbreak is spreading at an unprecedented speed, WHO says, and nowhere can be considered safe. *Lancet* 2004; 363(9406):373.
- (5) Parry J. WHO warns that avian flu could still be in the environment. *BMJ* 2004; 328(7437):426.
- (6) Webster RG. Wet markets--a continuing source of severe acute respiratory syndrome and influenza? *Lancet* 2004; 363(9404):234-236.
- (7) Fedson DS. Pandemic preparedness: a six- point agenda for inter-pandemic years. Inter-pandemic influenza : its importance for pandemic preparedness. Satellite Symposium. Options for the Control of Influenza V. Okinawa, Japon, October 7-11, 2003. 2003.
- (8) Forster J. Influenza in children: the German perspective. *Pediatr Infect Dis J* 2003; 22(10 Suppl):S215-S217.
- (9) Ploin D, Liberas S, Thouvenot D, Fouilhoux A, Gillet Y, Denis A et al. Influenza burden in children newborn to eleven months of age in a pediatric emergency department during the peak of an influenza epidemic. *Pediatr Infect Dis J* 2003; 22 (10 Suppl):S218-S222.
- (10) Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000; 342(4):232-239.
- (11) Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Jr., Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000; 342(4):225-231.
- (12) Chiu SS, Lau YL, Chan KH, Wong WH, Peiris JS. Influenza-related hospitalizations among children in Hong Kong. *N Engl J Med* 2002; 347(26):2097-2103.
- (13) Neuzil KM. Influenza vaccine for children. *Clin Infect Dis* 2004; 38(5):689-691.
- (14) Neuzil KM, Edwards KM. Influenza vaccines in children. *Semin Pediatr Infect Dis* 2002; 13(3):174-181.
- (15) Terebuh P, Uyeki T, Fukuda K. Impact of influenza on young children and the shaping of United States influenza vaccine policy. *Pediatr Infect Dis J* 2003; 22(10 Suppl):S231-S235.
- (16) Treanor J. Influenza vaccine--outmaneuvering antigenic shift and drift. *N Engl J Med* 2004; 350(3):218-220.
- (17) Update: Influenza Activity\_United States, 2003-04 Season. *JAMA* 291[52], 1197-1202. 1-7-2004.

### Flu vaccine for all? (Christian Science monitor, 03/11/04)

The Advisory Committee on Immunization Practices (ACIP) in the US is investigating whether it should recommend annual influenza vaccination for all Americans. This could further curb the spread of the disease to those at risk and could increase the country's preparedness for a major pandemic by improving vaccine production and distribution methods. This would however imply that complex logistical issues are worked out.

Catherine VERRIER-MARY, Bertrand VERWEE.

