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Aquatic birds are the reservoir of avian influenza. In birds, the influenza viruses in circulation are a combination of virus A subtypes comprising 16 haemagglutinins (HA) and 9 neuraminidases (NA), i.e. 144 - 2 circulating in humans = 142 potentially endemic viruses in the animal reservoir. From this reservoir, epidemics in animals and sometimes in humans have been observed.

Human and avian influenza viruses are significantly different. Specific avian or human genomic "signatures" exist (51 signatures, including 6 on HA). HA enables the virus to enter the host cell via receptors comprising of sialic acids. However, sialic acids are different in humans and in birds, creating at least a partial species barrier. In birds, the influenza virus receptor comprises alpha 2-3 sialic acids and, in humans, alpha 2-6. The transition from alpha 2-3 to alpha 2-6 requires modification of amino acids at positions 183, 190, 225 and 226.

How did the pandemics in the 20th century come about?

In 1918, an avian virus was probably transmitted directly from a domesticated bird to humans. Of the 51 signatures, only 16 had changed from "avian" to "human". By observing the signatures borne by HA in the "sialic acid receptor" region, it was demonstrated that a single mutation had occurred, causing the direct transmission of the avian virus to humans. Therefore, the barrier to be overcome is not that great and the virus is particularly flexible.

In 1957 (A/H2N2) and 1968 (A/H3N2), the virus transited via pigs. A genetic reassortment phenomenon occurred in these animals: the same cell was co-infected by a bird virus and a human virus. During the viral assembly to produce the bud, three segments of genes particularly coding for avian virus surface proteins were mixed with human segments. As alpha 2-3 sialic acids and alpha 2-6 sialic acids are present in pigs, the resulting hybrid virus had an HA able to recognise the for-

mer and capable of learning how to recognise the latter. Therefore, pigs acted as the "mixing" animal.

New data

The detailed study of the H5N1 strains demonstrated that the accepted truth that birds = alpha 2-3 sialic acids and humans = alpha 2-6 sialic acids was incorrect. In humans, ciliated cells with alpha 2-3 receptors have been found in the deep lung. This explains why some children who have inhaled very large quantities of H5N1 viral particles have developed pulmonary forms of influenza as these viruses were able to enter the host cells via the lungs.

The study of the location of different types of sialic acids in humans has demonstrated that alpha 2-6 type receptors essentially existed in the nasal fossae and in the lung and alpha 2-3 receptors in the throat and lungs.

In practice, this means that, at the present time, in order to diagnose H5N1 infection, it would be preferable to take a sample from the throat, as that is where the virus multiplies. On the other hand, if this virus adapts to human alpha 2-6 receptors (which would be the case if a genuine pandemic broke out), it will also be found in the nasal fossae. This is why it is recommended in the "Pandemic Plan" to take rhino-pharyngeal samples.

Viral strategies for next pandemic

Transmission can occur directly, as in the 1918 Spanish influenza pandemic [influenza A (H1N1) virus], or following genetic reassortment in pigs or possibly in humans as we also have both types of sialic acids. Therefore, we are on our guard against human virus/avian virus co-infections; for this reason, it has been recommended to vaccinate subjects in contact with H5N1 with "conventional" human influenza vaccines. The aim is not to protect these subjects against H5N1 virus, but rather to prevent them from becoming a melting-pot of genetic reassortment. In this way, the vaccine would prevent co-infection which could facilitate virus transmission via gene exchange.

History of avian influenza: alert timeline

- **1977** : swine influenza, USA, A/H1N1
- **1997** : avian influenza, Hong Kong A/H5N1
- **1999** : 1999: avian influenza, Hong Kong A/H9N2
- **2003** : avian influenza, Hong Kong A/H5N1 (different virus to that currently in circulation)
- **2003** : avian influenza, Netherlands A/H7N7
- **2003-05** : avian influenza, Vietnam-Thailand A/H2N1 (bird-pig transmission)
- **2004** : avian influenza, Canada A/H7N2
- **2004** : avian influenza, USA A/H7N3
- **2004** : avian influenza, Egypt A/H10N3
- **2006** : avian influenza, Asia, Europe, Africa, A/H5N1

In 1997, chicken influenza in Hong Kong was controlled by slaughtering the entire stock (2 million chickens slaughtered in one week). To date, over 450 million birds worldwide have died due to this virus. In spite of this, we are currently experiencing a panzootic situation. A/H5N1 avian influenza virus has been found on at least three continents and has been detected in wild birds, domesticated birds, and mammals (pigs, cats, dogs, tigers). The spread of the epidemic in birds is considerable and uncontrolled. As of 31 December 2006, 265 human cases had been detected on three continents and had accounted for 160 deaths.

Progression of epidemic in birds

The epizootic emerged in South Korea in 2003. It then spread to Japan, China and the Indochinese peninsula (where the first cases in humans were reported). In May 2006, more than 3000 farms (including approximately 2300 in Vietnam) had been contaminated.

Hypothesis: migratory bird migration corridors

The hypothesis of transmission via bird migration corridors makes sense with the appearance of epizootic outbreak sites. There is one such corridor between Japan, Korea and Central China. However, migratory birds are not the only cause: there is also a major migration corridor between Asia and the USA and no cases have been reported in the USA. A study of the kinetics of the appearance of cases in the Russian provinces reveals that Trans-Siberian Railway passes through all the provinces in which cases have been reported. Therefore, the epizootic has been spread by the transportation of birds by people. Similarly, in Turkey, outbreak sites have progressively appeared from East to West, along the main road (role of bird transportation). Finally, the introduction of cases of H5N1 in Africa would appear to be the consequence of imports of Chinese and Turkish birds into Nigeria (one minister purchased these birds at a very low price, even though exports had already been prohibited).

Situation in humans

As of early January 2006, all the reported cases had been in Asia. Cases were then reported for the first time in Turkey, indicating the spread of the epizootic and the exposure of human populations to diseased birds. In April, Egypt, Azerbaijan and Iraq reported human cases. As of 11 October, the majority of cases had been reported in Indonesia, the virus had been detected in humans in 10 countries, and three (China, Indonesia and Egypt) were continuing to report cases.

To date, only one case of human-to-human transmission has been reported in Indonesia: one person subject to severe coughing contaminated seven family members during a meal eaten in a tiny room. However, none of these people contaminated any others. The virus remains "avian"; there is no chain of transmission to humans.

Genetic evolution of H5N1 viruses

At the present time, there is not one but several H5N1 viruses in circulation and two groups (or clades) have been identified: clade 1 and clade 2. Three subgroups have been isolated in the latter clade: Indonesian, European-African and "Fujian-like" (Chinese).

Significant variations exist particularly with respect to haemagglutinin between these lineages which are all currently in circulation. Producing a vaccine against clade 1 would not protect against clade 2 virus infection, etc.

Solution: pandemic plan

On the basis of our historical knowledge, we know that there will be another pandemic, probably (but not necessarily) caused by H5N1. The only possible solution is to decide to get organised. The pandemic plan provides for an organisation diagram for private practices and hospital medicine. Antiviral treatments are effective. Thirty-seven million doses are currently stored by the military and hospitals. All the necessary arrangements have been made to supply these medicinal products to the population, in pharmacies (delivered in 48 hours with a protective "military cordon"). They will also be administered on a preventive basis to medical staff (Tamiflu®: preventive treatment: one half-dose/day for 1 to 2 months; curative treatment: 2 capsules/day for 5 days). If the treatment is dispensed within 6 hours of the onset of symptoms, the mortality will be reduced to 10-15,000 subjects ("only" 5 times more than a conventional influenza epidemic).

For more information, visit: www.who.int or www.grippeaviaire.fr.

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