

## INFLUENZA DEVELOPMENT, INCLUDING H1N1, SURVEILLANCE AND POST-VACCINATION MONITORING OF H5N1

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**Summary:** Recent outbreaks of highly pathogenic avian influenza (HPAI) have spread from South-East Asia to sixty-two Asian, Middle East, African and European countries. H5N1 viruses isolated from dead water birds in Mongolia and Hokkaido, Japan on the way back to their nesting areas in Siberia in April to May 2005, 2006, 2008, and 2009 were genetically closely related to those isolated from birds in China, Iraq, Croatia, Nigeria, Korea, and Japan, but different from those from poultry in Vietnam, Thailand, and Indonesia. It is a serious concern that these HPAI viruses may perpetuate in the lakes where migratory water birds nest in summer. In the intensive surveillance studies on avian influenza fulfilled in autumn from 2004 to 2009 in Mongolia and Japan, no HPAI virus was isolated from migratory water birds that flew from Siberia, indicating that the virus has not yet dominantly perpetuated in their nesting lakes in Siberia. Careful surveillance of avian influenza in migratory water birds is to be continued as far as HPAI viruses are circulating in Eurasian countries.

These H5N1 HPAI virus strains have caused severe disease with high mortality in a few humans who appear particularly susceptible to infection with the virus strain in Asia, Middle East, and Africa since 2003. In 15 countries, a total of 262 died out of 442 confirmed cases in 5 years in the world (as of 24 September 2009).

The second concern is that the H5N1 avian influenza virus alone has been assumed to cause next pandemic influenza in humans. Since each of the known subtypes of influenza viruses perpetuates among migratory ducks and their nesting lake water in nature, and avian viruses of any HA subtype should contribute genes in the generation of reassortants in pig, none of the 16 HA and 9 NA subtypes can be ruled out as potential candidates for future pandemic strains. Surveillance of swine influenza is, thus, extremely important, as well as that of avian influenza for the preparedness for the emergence of pandemic strains in humans.

Avian influenza virus strains isolated from migratory ducks in our global surveillance studies have been stored for the use of vaccine and diagnosis. Influenza virus isolates of 62 combinations of HA and NA subtypes have been isolated from fecal samples of ducks and viruses of 82 other combinations have been generated by the genetic reassortment procedure in chicken embryos. Thus, 246 avian influenza virus strains of 144 combinations of HA and NA subtypes have been stocked in the library of a panel of influenza virus strains and their genes. Their pathogenicity, antigenicity, genetic information and yield in chicken embryo have been analysed, registered in the database, and opened for the member countries of WHO and OIE through internet.

**Key words:** natural reservoir – perpetuation – host range – interspecies transmission – antigenic and genetic variation of influenza virus – vaccine

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## Introduction

Although many infectious diseases have been eradicated or controlled in the last century, influenza remains to be overcome, since influenza A viruses cause occasional catastrophic pandemics in poultry and mammals including humans. In addition, recent outbreaks of highly pathogenic avian influenza (HPAI) in the world alarm to realise that there is no border for infections and give a rise to concern for human health as well as for livestock industry. H5N1 avian influenza virus strains have jumped the species barrier and caused severe disease with high mortality in humans —although the number of cases remains very small—, first in Hong Kong in 1997 and in Vietnam, Thailand and Cambodia until 2004. It is obvious that live bird markets have played important roles in the generation and supply of HPAI virus strains. Then the HPAI virus strains returned to feral water birds and have spread throughout 62 countries. It is also obvious that the reason why the H5N1 HPAI virus strains have been persisting for 12 years in Asia is attributed to the failure of control measures, and that inactivated vaccines were used and made it difficult to proceed the basically essential stamping-out strategy. In addition, vaccination accelerated selection of multiple antigenic variants [10]. Moreover, these countries are ranked as the top 4 for the number of human cases of H5N1 virus infection.

To elucidate the origin and evolution of pandemic influenza viruses, the OIE Reference Laboratory for Highly Pathogenic Avian Influenza at Hokkaido University has conducted global surveillance of influenza in birds, animals and humans. On the basis of antigenic and genetic analyses of influenza virus isolates from migratory ducks, domestic ducks, pigs, and humans and experimental infection studies of birds and mammals with those viruses, the OIE Reference Laboratory proposed that the hemagglutinin (HA) gene of A/Hong Kong/68 (H3N2) strain was introduced into the precedent human H2N2 Asian influenza virus by genetic reassortment, that occurred in the epithelial cells lining the upper respiratory tract of pigs, through domestic ducks from an H3 influenza virus circulating in migratory ducks in southern China [4, 5, 6, 11].

Ecological studies have revealed that a vast influenza virus gene pool for avian and mammalian influenza exists in migratory ducks. Each of the known subtypes of influenza A viruses perpetuates among migratory ducks and their nesting lake water in nature [1, 7]. Experimental infection studies established that influenza viruses preferentially replicate in the columnar epithelial cells in the colon, causing no disease signs and excreted in high concentration in ducks [3]. Influenza viruses have been isolated from freshly deposited fecal materials and from lake water, indicating that migratory ducks have an efficient way to transmit viruses, i.e. via fecal material in the water supply.

In comparison with influenza viruses in humans, influenza viruses in ducks are in evolutionary stasis [4]. The remarkable lack of amino-acid changes among influenza viruses isolated from migratory ducks suggests that the virus genes in this host are subject to stringent stabilizing selection. The genetic and antigenic conservation of influenza viruses in ducks suggests that the virus and host have reached a long established adaptive optimum. Such a stasis in migratory ducks is further evidence that duck population is the natural reservoir of influenza viruses.

In experimental infection of pigs, most tested strains of each of the known HA subtypes of avian influenza viruses replicated in the upper respiratory tract of the animals. Co-infection of pigs with a swine virus and with an avian virus unable to replicate in this animal generated reassortants, whose polymerase and HA genes were entirely of avian origin, that could be passaged in pigs [6]. The results indicate that avian viruses of any subtype can contribute genes in the generation of reassortants and so that none of the 16 HA and 9 neuraminidase (NA) subtypes can be ruled out as potential candidates for future pandemics in humans and poultry. The direct transmission of H5N1 influenza viruses from domestic poultry to humans in 15 countries in Asia, Middle East, and Africa in recent years further emphasized the need to have information on all influenza A subtype viruses circulating in avian species in the world.

To provide information on the influenza viruses in the natural host, virological surveillance of avian influenza was carried out in Alaska and Siberia during their breeding season, i.e. summer. A number of influenza viruses of different subtypes were isolated from fecal samples of ducks and surprisingly also from fresh water samples of the lakes where they nest. Even in autumn when the ducks had left for migration to the south, viruses were still isolated from the lake water, indicating that influenza viruses are maintained in duck population by water-borne transmission in nature and revealed the mechanism of year-by-year perpetuation of the viruses in the frozen lake water while ducks are absent in winter. Phylogenetic analysis of the isolates from Alaska indicates that ducks carrying these viruses migrate to the south through the continent of North America and not to Asia [1]. Influenza virus isolates from fecal samples of ducks in their nesting areas in Siberia phylogenetically belonged to Eurasian lineage and were closely related to those from birds, pigs, and horses in Asia. It was noted that these isolates closely correlated to the H5N1 influenza virus isolates from chickens and humans [7]. Phylogenetic analysis of the HA of H5 influenza virus isolates from ducks in Japan revealed close relationship with those of H5N1 influenza viruses from Hong Kong, southern China, Thailand, Vietnam and Japan, indicating that the H5HA of these viruses is originated from influenza viruses maintained in migratory ducks

nesting in Siberia. These results indicate that the precursor genes of pandemic influenza viruses are perpetuated in water in the lakes where ducks nest in northern territory. Vaccine strains should be antigenically closely related to the pandemic strain, avirulent for humans and chicken embryos, of high yield in chicken embryos, and immediately prepared when the causative virus is characterised. The OIE Reference Laboratory at Hokkaido University tested immunogenicity to mice of inactivated avirulent H5N4 influenza viruses isolated from reservoir host ducks. The results showed that they were potent enough to protect animals from challenge with lethal dose of the highly pathogenic H5N1 virus [9].

### **Influenza is a zoonosis**

Influenza A viruses are widely distributed in birds and mammals including humans. Among those, viruses of each of the known HA and NA subtypes (H1-H16 and N1-N9, respectively) have been isolated from migratory ducks. Ecological studies have revealed that a vast influenza virus gene pool for avian and mammalian influenza exists in migratory ducks and their nesting lake water and that influenza is a typical zoonosis. Influenza viruses in ducks are in evolutionary stasis, suggesting that the virus and host have reached a long established adaptive optimum.

### **Perpetuation of influenza viruses in nature**

Ducks are orally infected with influenza viruses by water-borne transmission at their nesting lakes in Siberia, Alaska and Canada around the Arctic Circle during their breeding season, i.e. summer. These viruses then replicate in the columnar epithelial cells, forming crypts in the large intestine, and are excreted together with faeces. The viruses in the lake water become frozen after ducks migrate to the south, and are preserved there over the winter. That is, northern nesting lakes for migratory ducks serve as influenza virus gene pools in nature.

### **Mechanism of the emergence of new pandemic influenza viruses in humans**

The phrase “a new virus” describes an influenza A virus of a subtype of the HA or the NA other than H1N1, H2N2 and H3N2, which have spread among humans in the last century, that transmits to humans and causes pandemic. The OIE Reference Laboratory for Highly Pathogenic Avian Influenza at Hokkaido University has revealed that the A/Hong Kong/68 (H3N2) pandemic influenza virus emerged in 1968 via genetic reassortment in pigs concurrently infected with an H3Nx influenza virus circulating in migratory ducks through domestic ducks and the H2N2 virus, which was circulating among humans at the time, in southern China. Furthermore, experimental infection studies revealed that pigs are highly susceptible to avian influenza viruses of all HA subtypes, and that since epithelial cells lining the upper respiratory tract of pig have receptors for both human and avian viruses, genetic reassortment takes place and new viruses are thus produced in pigs. These findings indicate that genetic reassortants of any HA subtype will be generated in pigs, and new viruses will emerge as a result.

### **Highly pathogenic avian influenza viruses**

Since late 2003, the HPAI virus of H5N1 subtype has seriously affected poultry in Asia. Well over 400 million birds have died from infection or have been killed for control purposes. A HPAI virus is generated when a non-pathogenic virus brought in by migratory birds from nesting lakes in the north is transmitted to chickens via domestic ducks, geese, quails, turkeys, etc. and acquires pathogenicity for chickens with repeated multiple infections in the chicken population. This pathogenicity does not mean for other kinds of birds and mammals, nor does it to humans.

### **Do the highly pathogenic avian influenza viruses that were conversely transmitted from poultry to feral water birds perpetuate in the lakes where migratory birds nest?**

During over-wintering, some migratory birds were conversely infected with the highly pathogenic H5N1 virus from poultry and are found dead at lakes in northern China, Mongolia, Russia, Europe and Africa in May on the way back to their nesting lakes in northern territory. It was found that all viruses isolated from these birds were HPAI virus strains isolated from poultry in China. Since it is concerned that this H5N1 virus may perpetuate in the lakes in Siberia where migratory ducks nest in summer, intensive surveillance of avian influenza have been carried out in autumn when migratory birds fly from Siberia to the south in Mongolia, China, and Japan. In the four-year investigation, no highly pathogenic avian influenza virus has been isolated, indicating that the highly pathogenic H5N1 avian influenza virus strain has not yet perpetuated in the lakes where the migratory birds nest in summer.

## Transmission of highly pathogenic avian influenza viruses to humans

It was confirmed that more than 442 people have been infected with the H5N1 virus, 60% of whom died in Asia, the Middle East and Africa since 2003. Against this backdrop, it is assumed that H5N1 virus will acquire the ability to transmit among humans and wreak havoc as a new virus. The World Health Organization (WHO) has warned for the past decade that this avian influenza virus is in the final stages of acquiring the ability to infect humans. In response, industrialised nations have formulated emergency plans, including measures such as stocking an inactivated H5N1 vaccine for humans.

The world is now confused to the extent that avian influenza passes as a human disease. Both avian influenza and human influenza are infections with influenza A virus. Although the potential for a virus with the H5HA gene to cause an influenza pandemic in humans cannot be denied, we should not focus on the H5N1 virus alone. Rather, we should keep in mind the possibility of influenza viruses of other subtypes emerging as new pandemic influenza virus strains.

Research to date has revealed that all the genes of influenza viruses for birds and mammals including humans are derived from non-pathogenic viruses maintained in migratory ducks. The basics of practical avian influenza control measures involve minimising damage and protecting human health and food safety by stamping-out policy to contain avian influenza within poultry.

Efforts should also be made to conquer human influenza through prediction and prevention. It is necessary to establish and implement a preemptive strategy to control HPAI and human pandemics by investigating mechanisms of the emergence of human pandemic influenza virus strains and the acquisition of pathogenicity of avian influenza viruses. To this end, the OIE Reference Laboratory at Hokkaido University has completed a library of all HA- and NA-subtype virus strains and genes that exist in nature, and have created a database and provided it over the internet<sup>2</sup>. It has already been used for vaccine production and diagnosis by 36 research institutions in 12 countries.

## Zoonosis control measures

The strategy fostered in influenza research has been applied to combat other zoonotic infections. First of all, it is necessary to identify the natural host of the causal agent and clarify the root of transmission. That is to say, the ecological elucidation of wildlife and agents in nature leads to fundamental control of infections.

The Research Center for Zoonosis Control, inaugurated at Hokkaido University in 2005, conducts global surveillance studies and engages in research and education toward the establishment of methods for diagnosis, prevention and control. Its aim is to predict and prevent the outbreaks of influenza, the West Nile fever, Ebola-Marburg haemorrhagic fever, hantavirus infections, rabies and some unknown infections.

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.../Appendix



Appendix I

**Summary of the answers received to a questionnaire on  
“influenza development, including H1N1, surveillance and post-vaccination monitoring of H5N1”**

This is a summary of the answers received from Members of the OIE Regional Commission for Asia, the Far East and Oceania to a Questionnaire on “influenza development, including H1N1, surveillance and post-vaccination monitoring of H5N1”, to be presented during the 26th Conference of the OIE Regional Commission for Asia, the Far East and Oceania, in Shanghai, People's Republic of China.

A total of 23 Members, out of 34 Members of the OIE Regional Commission for Asia, the Far East and Oceania answered to the questionnaire.

### **Section A: General information**

1. 11 Members (out of 23 responding Members) informed on initial location of highly pathogenic avian influenza (HPAI) outbreaks caused by H5N1 virus, and other subtypes of HPAI, and low pathogenic notifiable avian influenza (LPNAI (H5 and H7)) occurrences encountered in the country in each year since 2003.
2. Regarding HPAI virus infection in pigs, or pandemic H1N1 2009 virus infection in pigs or birds detected virologically or serologically in the country during the past 5 years, only Indonesia answered affirmatively. Indonesia provided the following information: In Sulawesi Selatan 2 of 32 samples and 1 of 18 were positive for HPAI virus infection. In Kota Tangerang, Banten, 2 of 150 samples were positive for H1N1 virus infection, and in Tangerang district, 2 of 150 were positive for H5N1 virus infection.
3. For each of the infections listed at points 1 and 2, Members provided the following information:
  - a. The infection was suspected due to: high morbidity and mortality, remarkable egg drop, production losses, respiratory clinical signs, etc.
  - b. The infection was diagnosed through: clinical signs, virological findings, serological findings, and pathological findings. Indonesia also informed having carried out screening test with rapid diagnosis test.
  - c. In reference to serological and/or virological diagnosis, Members indicated having carried out the following tests: haemagglutination inhibition and RT-PCR.
  - d. As confirmatory laboratory test, some Members have used: RT-PCR and virus isolation
  - e. Laboratory tests were carried out at: local laboratories, national laboratories, and some at international reference laboratories.
  - f. 6 Members (Bangladesh, Cambodia, China, Indonesia, Pakistan, Vietnam) have informed that the disease impacted on public health, while 9 Members noted that there was no impact in their human population, and 8 countries have not answered this point.
  - g. In 5 Members (Australia, Cambodia, Indonesia, Pakistan, Vietnam), a link between animal and human infection was established under the umbrella of the National Steering Committee for Avian Influenza Control and its mirror committees at all other levels, WHO Human/Animal Interface Network; while in 10 countries such a connection was not established and 8 Members have not answer this point.
  - h. Immediate control measures which were taken included: standard measures such as stamping out, or modified stamping out with compensation, movement control, closure of live bird markets (during the outbreak period), vaccination and communication.
  - i. China, Indonesia, Pakistan, Vietnam also applied subsequent vaccination as a complementary control measure.
  - j. 8 Members have developed respective economic studies to estimate the losses caused by the disease, ranging from 1.4 to 4,300 million USD. 2 Members have not estimated such losses and 13 countries have not answered this point.
  - k. All the countries that have detected the infection (13 Members) notified to the OIE as per their obligation.

## Section B: HPAI and LPNAI

1. a. 13 out of 23 responding Members have reported that HPAI or LPNAI have been encountered in their country.
- b. In reference to the initial location, species affected and the time of occurrence, most of affected members informed that outbreaks by HPAI H5N1 have been observed in almost every year since early 2004. All avian species have been observed affected, including chickens, ducks, Muscovy ducks, geese, pigeons, quails, turkeys, etc. (Vietnam).
- c. Other locations and times: Varied
- d. Number of outbreaks recorded as of 1 October 2009: Varied
- e. In reference to the mortality rate in each outbreak it depended on the stage of detection. Typical/average mortality was at around 65-80%.
- f. Morbidity rate in each outbreak: 90-100%
- g. Initial control measures applied can be summarised as follows: movement restrictions first, then followed by immediate culling.
- h. 4 Members have informed the application of vaccination as a subsequent control measure.
- i. Most of affected Members have notified that the disease is now under control or eradicated. Some of them informed that there are few sporadic outbreaks, occurring in different provinces.
- j. While referring to the best management practice to control the disease or to prevent its spread, the responding Members (joint analysis of answers) have ranked the following control measures in order of importance:
  - Culling of infected flocks of birds (stamping out)
  - National movement controls
  - Sanitary/bio-security measures on farms or at markets
  - Closing of markets/bird gatherings
  - International movement controls
  - Vaccination
  - Other culling policies: Selective culling is suitable for Cambodian environment since compensation policy is not applied.
- k. Different hypotheses which could explain the entry of HPAI virus to the affected Members included:
  - Legal import of live poultry,
  - Illegal import of live poultry,
  - Illegal import of other birds,
  - Wild birds.

2. In regards to the use vaccine for the controlling HPAI, answers from Members varied as follows:

a. “Yes”: 4 Members:

- China: H5N1 reverse genetics inactivated vaccines and recombinant NDV vaccine. Vaccination is applied instead of stamping-out.
- Indonesia: H5N1, H5N2, H5N9 and recombinant H5N1 inactivated vaccines. Vaccination is applied instead of stamping-out.
- Pakistan: H5N1, H5N2, H5N9, H5N3 inactivated with aluminum hydroxide, or mineral oil adjuvants. Vaccination is applied in addition to stamping-out.
- Vietnam: H5N2 inactivated vaccines for commercial industrial breeding farms and H5N1 adjuvant inactivated vaccines for national vaccination campaigns. Vaccination is applied instead of stamping-out.

“No”: 15 Members; Australia, Bangladesh, Bhutan, Brunei, Cambodia, India, Iran, Japan, Maldives, Myanmar, New Caledonia, Singapore, Sri Lanka, Chinese Taipei, Vanuatu.

No answer: 4 Members: Iraq, Nepal, New Zealand, Philippines.

- b.** For countries applying vaccination, the vaccination exit strategy varies as follows:
  - Indonesia: Vaccination in sector 3 and 4 (backyard).
  - Pakistan: Withdrawal of vaccination after 3 consecutive years on non reporting of avian influenza virus prevalence.
  - China and Vietnam have no vaccination exit strategy.
- c.** In regards to surveillance and post-vaccination monitoring:
  - China: Evaluation of antibody titers induced by vaccination and virological examination by RT-PCR and virus isolation from swab samples.
  - Indonesia: Collecting samples.
  - Pakistan: Through an established national surveillance network comprising of 40 surveillance units, 66 rapid response units, 10 regional laboratories and 1 national reference laboratory.
  - Vietnam: Conducting biannual serological surveys to measure HI titer. Monthly swab sampling of birds (focused on farmed waterfowls such as ducks and Muscovy ducks) from farms and live bird markets.
- d.** From these 4 countries that apply vaccination, only Vietnam put sentinel birds in the vaccinated poultry population.
- e.** Countries applying vaccination (China, Pakistan, Vietnam) use RT-PCR and virus isolation as diagnostic methods for the detection of virus antigen.

### **Section C: Miscellaneous**

1. 22 out of 23 responding Members informed that they notify OIE-listed diseases to the OIE regularly (Iraq has not answered this question).
  2. 19 Members notify other diseases to the OIE or to other regional or international organisations, while India, Philippines and Sri Lanka answered that they do not notify to other organizations (and Iraq has not answered to this point).
  3. 20 Members have answered that they are aware of objectives and functioning of OFFLU, while Maldives, Vanuatu and Cambodia had no information on OFFLU.
  4. 22 out of 23 answering Members have responded positively to the question whether the OIE should continue and further develop standards on Animal Influenza surveillance, prevention and control (while Brunei has not answered this point). Vietnam has also proposed that the OIE develop a technical guidance on surveillance for HPAI under vaccination circumstance.
  5. 19 out of 23 responding Members have compensation mechanisms for livestock owners in case of stamping out, while Cambodia, Myanmer, Philippines, Vanuatu have not implemented so far such a mechanism.
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