

## Preparedness for potential avian influenza pandemic in developing countries

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Since the beginning of history, human being has been fighting against contagions. Contagions (plagues) have taken the toll of billions of lives and wrecked splendid ancient civilizations such as Roman, Maya, and Inca. In China, the earliest inscriptions recorded on oracle bone dated back more than 3,000 years ago, had already mentioned diseases such as "worm", "poisonous insect", "impaludism".

Among all contagions, influenza virus, a respiratory pathogen, had in the past caused periodical pandemics worldwide. And it is still a formidable enemy even today.

It is believed that the current H5N1 virus strain can be readily mutated in its natural environment and become infectious to human without reassorting with existing human influenza viruses. Once passed the generic barrier, it will cause a new round of human influenza pandemic worldwide. If happens, an estimated 2 million to 7 million people could die from the outbreak of influenza pandemic.

Early in October, 2005, US Department of Health has held an international meeting on "avian influenza" at Washington. The US congress then passed 7 billion dollars bill to support research on prevention and treatment for avian flu. United Nations, on the other hand, has also created International Coordinating Institution for preventing and controlling influenza pandemics. WHO has called on the world to make the best preparations for possible influenza pandemic. Even though we cannot predict accurately when the next worldwide influenza pandemics will occur, it will be unavoidable.

### Human influenza virus and its link to avian virus

Human influenza virus belongs to the family of Orthomyxoviridae. It has three different serotypes, i.e. A, B, and C. Among them, only influenza A can trigger worldwide pandemics.

Influenza A virus can be further divided into different subtypes based on their antigenicity differences of the viral surface proteins: hemagglutinin (HA) and neuraminidase (NA). So far 16 subtypes of HA (H1-H16) and 9 subtypes of NA (N1-N9) have been identified. Combination of these subtypes of HA and NA could possibly produce 144 subtypes of influenza virus, such as H1N1 and H5N1.

Birds are natural host of human influenza. Human influenza A viruses are likely all come from avian. Therefore, human influenza pandemics are inseparable from avian influenza. During the 20th century, mutations of influenza viruses had led to three worldwide pandemics. The so-called “Spanish influenza” of 1918-20 was caused by H1N1 subtype. Influenza of 1957 was caused by H2N2 subtypes which had three genetic segments (HA, NA, PB1) originated from virus found in duck. The Hong Kong influenza of 1968 was caused by H3N2 subtype which had two genetic segments (HA, PB1) originated from bird virus. In addition, the influenza virus responsible for the 1918 pandemic has been proved similar to H5N1 that is very likely to be the origin for the next influenza pandemic.

Asian, particularly China has been seen by many as the source of new avian virus subtypes. Since 1957, most subtypes of influenza viruses that caused global influenza pandemics came from China. The reason for that is still unclear. Therefore, China is publicly recognized by the world as a place frequently threatened by influenza. The situation of influenza in China has drawn attention from WHO and researchers worldwide and made China the region of focus of many studies.

In China, 60% of poultries, including 15 billion chickens and about 4 billion ducks, are dispersedly raised, where poultries have close contact with people and livestock. Genetic studies indicate that influenza viruses have strict host-specificity and it is not easy for avian and human influenza viruses to transmit mutually. However, the virus strains behind human influenza pandemics do have genetic segments from both human and avian influenza viruses. Researchers believe that livestock such as pigs may be crucial for the transition. Pigs are known to sensitive to both human and avian influenza viruses. Pig possesses cell receptors for both human flu virus (NeuAc $\alpha$ 2, 6Gal) and avian flu virus (NeuAc $\alpha$ 2–3Gal). Therefore, pigs may act as a “gene mixer” when simultaneously infected by both human and avian viruses, and create a new re-assortment subtype virus which can cause pandemic in human.

Extensive spread of avian influenza in Asia has become a public-health-concerned emergency event and avian influenza has been listed as class A contagion by International Veterinary Bureau, class-A monitoring contagion by Chinese Ministry of Agriculture, and one of the major contents for counter-bioterrorism intentionally.

*WHO global influenza preparedness plan*

### Recent outbreak of bird flu and human infection

Up to the end of 2003, highly pathogenic avian influenza (HPAI) was a rare disease. There were 21 reported epidemic outbreaks globally since 1959 and mainly happened in Europe and America. However, since mid-December of 2003, 9 Asian countries have found epidemics of highly pathogenic avian influenza H5N1. Since then, hundreds of millions of poultries died from this disease. Spread of H5N1 virus has also reached Mongolia, Russia, Kazakhstan, Turkey, Romania, Greece, and other European countries, even in Africa and America.

Several Institutes and Universities in China conducted whole-genome sequencing of isolated samples. The results indicated that they were not precisely the same as the known H5N1 strain. It is likely that the virus genomes have been reassorted and are in constant process of mutation. This new H5N1 virus is far more virulence than those found earlier in North China. (Science: 2005,7)

Under normal conditions, avian influenza virus cannot infect animals other than poultries and pigs. Recently, it has been shown that avian influenza viruses can infect human beings directly. In early 2003, The University of Hong Kong isolated two H5N1 virus strains from two SARS patients. Up to Dec 30, 2005, there are 142 patients infected with highly pathogenic avian influenza virus H5N1 and 74 died. Persistent transmission among human beings has not happened yet. However there were some cases deserving suspicion. For example, during the autumn of 2004 in Thailand, a report (Ungchusak 2005) showed that a child patient has apparently transmitted the virus to his/her mother and aunt. Genetic analysis of the epidemic virus strain indicated that the avian influenza virus had not been re-assorted with the genes of human influenza virus yet. But it was proved that the virus had the power to get across the barrier and infect cat, pig, tiger, and catamount.

Whole genome sequence analysis of 4 strains of H5N1 virus isolated from patients in China(China CDC) also indicated that these viruses also belong to the avian viruses according

Inter-pandemic phase new virus in animals on human cases	low risk of human cases	1
	higher risk of human cases	2
pandemic alert new virus causes human cases	no or very limited human-to-human transmission	3
	evidence of increased human-to-human transmission	4
	evidence of significant human-to-human transmission	5
pandemic	efficient and sustained human-to-human transmission	6

to whole genome sequence homology with the H5N1 virus isolated from fowls, especially the cell receptor specificity and poly basic amino acids between the HA1 and HA2 connection site. (Shu et al 2005 personal communication)

World Health Organization (WHO) uses a series of six phases of pandemic alert as a system for informing the world of the seriousness of the threat and of the need to launch progressively more intense preparedness activities.

Each phase of alert coincides with a series of recommended activities to be undertaken by WHO, the international community, governments, and industry. Changes from one phase to another are triggered by several factors, which include the epidemiological behavior of the disease and the characteristics of circulating viruses.

The world is presently in phase 3—It means that a new influenza virus subtype (H5N1) is causing disease in humans, but is not yet spreading efficiently and sustained among humans.

### **Strategies to prevent and control worldwide influenza pandemics**

Experts at WHO and elsewhere believe that the world is now closer to another influenza pandemic than at any time since 1968, when the last of the previous century's three pandemics occurred. WHO and other international public-health-related organizations and health sectors in all the countries have conducted considerable studies on how to prevent influenza pandemics and to establish corresponding prevention and control systems. Should pandemic happens, rapid responses will be available, we will briefly discuss a few key issues here.

#### *Advancing medical science and technologies in developing countries*

The most effective measures to control virulent contagions are vaccination and use of antiviral drugs. Under the instruction of WHO, smallpox has been eliminated worldwide and poliomyelitis from most regions in the world through effective vaccination. However, prevention of influenza is different. It is very difficult to control the origin of influenza virus since birds and domestic poultries are natural host for human virus. It is also difficult to predict the new strain since the virus undergoes constant reassortment. Even if the new strain is identified, large population can still be infected if large quantity of vaccine cannot be made available in a very short period.

On the other hand, based on WHO report, prevention through antiviral drugs must also covers 80% of the initial infected population within about three weeks after symptoms appear to stop influenza epidemic within a group or a country.

So far, that kind of conditions can only be partially met even in the most technically advanced and wealthiest countries. For example, the U.S. government has stored enough antiviral drugs for about 7 million people and that supplied by private organization can protect 33 million people. The experimental production of vaccines against avian influenza H5N1 for 2 million people has just begun. (www.nature.com Dec 15, 2004). Situation in developing countries is far behind.

Developing countries urgently need technologies and production facilities that will help them to develop new vaccines, new anti-viral drugs as well as to develop quicker method for monitoring viral mutations and to establish an early warning system. Chinese scientists are now developing a new trivalent nasal spray inactivated influenza vaccine and efficacy of the new vaccine has been demonstrated in animal studies. If succeed, the new vaccine will have broad protection spectrum and can be applied easily by the general population.

#### *Improving rural social and economic structures and livestock industry*

As mentioned, the animal farming conditions may be a key factor that contributes to the breed of new subtypes of human influenza virus. Taking China as an example, since the influenza virus was confirmed in 1933, several worldwide influenza pandemics started from China. China is the most populated country in the world and still is largely a society of small-scale peasant economy where the farming household is the unit of rural economy. Besides farming, almost each household raises chickens, pigs, and ducks all living in close contact with humans. Most of the household breeding industry in developing countries lacks scientific management, preventive measures against zoonosis, and general knowledge about sanitation. Such ecological environment provided advantageous conditions for reassortment of human influenza virus and avian influenza virus.

Therefore, to prevent and control the creation and spread of new influenza subtypes, such small-scale farming economy must be reformed. Chinese government is devoted to build a well-off society including a better living and working conditions in rural areas, which would lead to a more specialized animal farms with modern technology, facility and management and reduced direct human-animal contact.

*Build preventive systems against zoonosis*

Prevention of animal influenza should be prior to prevention of human influenza.

International organizations (WHO, Food and Agriculture Organization of the United Nations) need to establish an international influenza prevention and control center to monitor all kinds of influenzas related to human beings such as birds and pigs. The international influenza prevention and control centers should analyze the influenza virus strains appearing in different countries, publish the vaccine strains of human and animal influenza, and inoculate human beings and relevant animals annually.

*Prevent possible bioterrorist attacks*

Even though more than 160 countries and regions have signed the international pact against researches on bio-weapons in 1972, the rapid development of biological technologies could provide hostile forces or terrorist organizations the opportunities to develop bio-weapons. To prevent terrorists from developing and applying possibly deadly influenza virus, any study on recombined influenza viruses should be monitored closely and all the countries around the world should register all recombined influenza viruses as pathogens that could be used for bio-terrorism. The influenza virus subtypes that disappeared from public (such as H2N2) should be conserved by international labs uniformly to prevent any possible leaking.

*WHO and International Effort*

WHO has begun coordinating the international plan for influenza detection as early as 50 years ago. In 1999, WHO published *Influenza Pandemic Preparation Plan* that specified responsibilities of WHO and all countries during a possible influenza pandemics. WHO's Global Outbreak Alert and Response Network includes over 20 collaborative institutions all over the world. From 2000 to 2004, WHO has been requested to assist the control of 62 epidemics of contagions and from 2001 to 2003, there have been 636 requests, involving 136 countries. Among them, 482 (78.5%) have been verified.

**Summary**

Rapid changes in global economy and environment have increased the difficulties in preventing influenza pandemic. In Southeastern Asia, increase of demand for animal food has resulted in increasing quantity of pigs, chickens, and ducks, as well as high-density breeding operation. This operation is often conducted without biological security, leading to direct

contact between feeders and animals and propelling the virus evolution. In addition, rapid increasing population raises the possibility of spread of new and old contagions faster and broader ever. Therefore, international organizations need to work together to help developing countries to improve preventive systems against contagions. After all, influenza pandemics are borderless and fighting them is necessary for the health and existence of all human beings.