Avian Influenza Virus: The Threat of A Pandemic

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The 1918 influenza A virus pandemic caused a death toll of 40~50 million. Currently, because of the widespread dissemination of the avian influenza virus (H5N1), there is a high risk of another pandemic. Avian species are the natural hosts for numerous subtypes of influenza A viruses; however, the highly pathogenic avian influenza virus (HPAI) is not only extremely lethal to domestic avian species but also can infect humans and cause death. This review discusses why the avian influenza virus is considered the most likely candidate for the first flu pandemic of the 21st century. *(Chang Gung Med J 2006;29:130-4)*

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The avian influenza A virus (the so-called bird flu) which belongs to the *Orthomyxoviridae*, was first characterized as early as 1900. Like other influenza A viruses, bird flu contains eight-segmented single-stranded RNA with negative polarity (Fig. 1). Influenza viruses have been named on the basis of the antigenic relationships of the surface glycoproteins (HA and NA) since 1971. The avian influenza virus was originally thought to be highly species-specific and only to infect avian species. However, humans were found to be infected by avian influenza A (H5N1) in Hong Kong in 1997.[1] Avian influenza virus generally enters host cells through the receptor which contains sialyloligasaccharides (SAs) in the sialic acid α2,3-Gal linkage form. This form of the receptor comprises the majority found on avian cells. While most of the receptors on human cells contains SAs in the sialic acid α2,6-Gal linkage form, scientists found that avian influenza virus, in a high viral titer can also bind to trace amounts of human receptors containing SAs in the sialic acid α2,3-Gal linkage form. Waterfowl are the natural reservoir of all subtypes of influenza A viruses, and these viruses are normally relatively nonpathogenic to waterfowl. In the H5N1 outbreaks of 1997 to 2005, the evolutionary stasis somehow changed, and some waterfowl became sources of infection, allowing the highly pathogenic H5N1 virus to spread to new areas.[2] Although transmission from birds to humans is rare, the possibility exists that the virus may mutate, and person-to-person transmission is still a threat to human beings. This paper reviews the three influenza pandemics that occurred in 1918, 1957, and 1968. Here we also update the current status of avian influenza infections and discuss why avian influenza threatens humans.

The 1918 influenza A virus pandemic

The 1918 "Spanish" influenza pandemic killed at least 40 million people during 1918~1919. The most notable feature of the 1918 pandemic was its high transmissibility and lethality. The 1918 pandemic killed over 2% of those infected, and especially affected young adults in the 15~34-year-old age group. Infection rates were also high, with up to 30% of populations infected by the virus.

In 1997, Dr. Taubenberger and his colleagues obtained viral RNA from the preserved lung tissues of victims of the 1918 pandemic.[3] Scientists subsequently sequenced the full genome of the viral seg-

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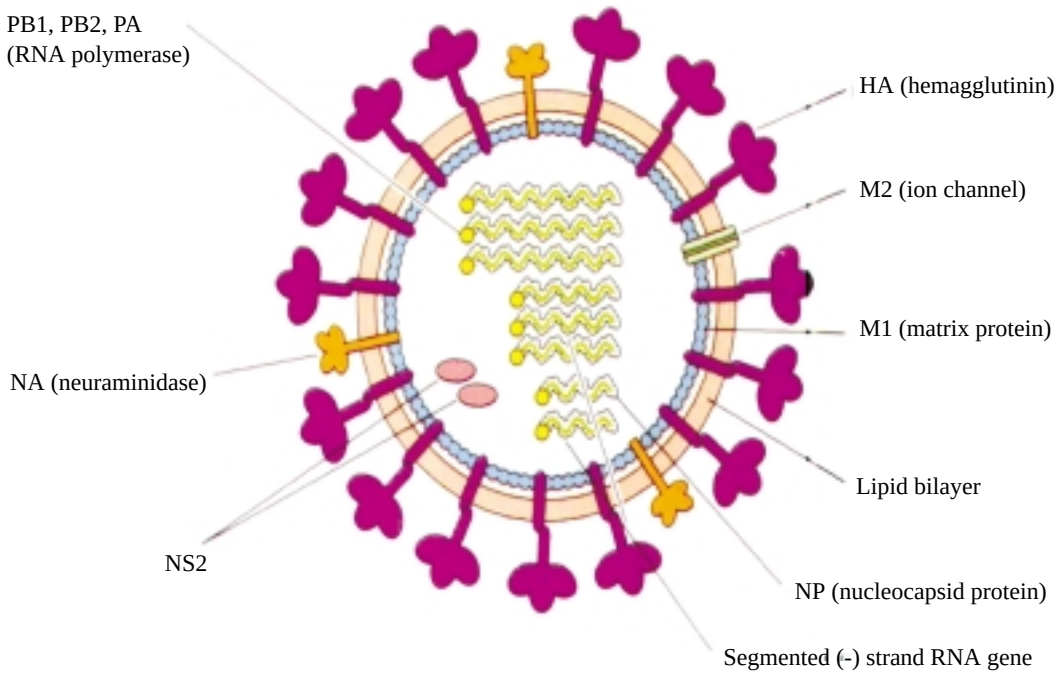

Fig. 1 Genome structure of influenza A virus

ments and applied reverse genetics to identify the most important genetic products causing its high virulence. In October 2005, Taubenberger's group published the sequences of the polymerase (PA, PB1, and PB2) genes of the 1918 pandemic virus, and their results support the hypothesis that the 1918 pandemic virus was not directly derived from an avian influenza virus.[4] However, the 1918 pandemic virus is more closely related to the avian influenza A virus than other influenza viruses which have infected mammals. Influenza experts speculated that the 1918 pandemic virus must have circulated in mammals (in an unknown host or even in humans) before the 1918 outbreak.[5]

Last year, a team led by James Stevens compared the crystal structure of 1918 HA with that of other human, avian, and swine influenza viruses. The comparison showed that the cavity size of the receptor binding site of the 1918 hemagglutinin (HA) approximates that of human influenza, although its shape resembles an avian influenza virus. A single amino acid mutation at position 190 of HA changed the binding affinity.[6] Variations in the HA structure are a key factor in the ability to expand the host range and enhance the infection virulence. It is one possible reason why the 1918 pandemic virus was transmitted among humans and was able to efficiently replicate in humans.

Darwyn Kobasa et al. applied a recombinant viral approach to prove that viral virulence was enhanced when HA was replaced by the 1918 pandemic virus HA. Mice infected with the recombinant virus containing the 1918 HA were observed to have severe lung infection syndromes, similar to those in humans caused by the 1918 pandemic virus. Furthermore, the high levels of cytokine expression in lung tissues of infected animals indicates that the 1918 HA activates macrophages and causes acute lung injury.[7]

The 1957 influenza A virus pandemic

The 1957, the pandemic "Asian flu" first appeared in February in the southern China province of Guizhou. In March, the flu spread to Hunan Province, and by April it had reached Singapore and Hong Kong.[8] This pandemic virus had completely different HA and NA antigens to previously circulating H1N1 viruses. The 1957 virus was comprised of HA (H2), NA (N2), and a viral RNA polymerase gene segment, polymerase basic 1 (PB1), from an

avian virus, with the other gene segments being derived from a previously circulating human virus.[9] The 1957 virus was more lethal than other H1 strains circulating at the time because no human had previously encountered the H2 protein, and thus humans lacked immunity against the new strain. Although H2N2 viruses were isolated in the UK and US as early as June or July 1957, the peak incidence of influenza caused by the new pandemic strain did not occur until October. The pandemic had spread worldwide by November 1957. At the start of 1958, H1 flu in humans disappeared, being replaced by H2 strains. This first wave of disease in the UK and US was followed by a second wave in January 1958, with both waves being accompanied by excess mortality. The highest rates of infection during this pandemic, of > 50%, occurred in children aged 5~19 years.[10] The estimated total influenza-associated mortality of this pandemic was 4 million worldwide.[11]

The 1968 influenza A virus pandemic

A similar process occurred again in 1968, with the emergence of another hybrid virus. The 1968 virus, "Hong Kong flu," were first isolated in Hong Kong in July 1968 and spread to the US later that year. However, in some other countries, including the UK, the pandemic did not arrive until the winter of 1969~1970. The influenza A H3N2 pandemic had avian HA (H3) and PB1 segments, with the remaining genes being derived from H2N2 human viruses.[9] The acquisition of avian surface antigens permitted these viruses to circumvent the human immune response. The rates of infection were highest (40%) among 10~14-year-old children. The total influenza-associated excess mortality for this pandemic was estimated to be two million deaths worldwide.[11] Many experts believe that the severity of the Hong Kong pandemic was reduced because much of the population by this time had antibodies to the N2 surface protein, thus moderating the infection severity.

Human infections by avian influenza A H5N1 virus

The highly pathogenic avian influenza (HPAI) H5N1 virus infections in both poultry and humans first occurred in 1997 in Hong Kong, and these were the first reports of human infections with avian influenza.[12] In total, 18 people were hospitalized, six of whom died. The authorities responded by slaughtering all chickens, and thus successfully eradicated the source of the virus. The primary means through which the virus spread was from birds to humans, but rare person-to-person infections also occurred.[13] Clinical signs of H5N1 infection included fever, upper respiratory tract infection, and other typical symptoms of classical influenza. Some patients suffered severe complications, primarily pneumonia, gastrointestinal manifestations, increased levels of liver enzymes, and renal failure.[14] All viral genes of human H5N1 isolates originated from a Eurasian avian virus, but differed from those that occurred in 1957 and 1968, which originated from reassortants.

In 2003, two cases of H5N1 virus infection occurred in a Hong Kong family. The son developed severe respiratory illness, while the father died. Another family member, the daughter, also died of a respiratory infection in China, but the origin of the infection was not tested.[15]

During 2003 to early 2004, outbreaks of the HPAI H5N1 virus occurred among poultry in eight countries in Asia: Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand, and Vietnam. From December 30, 2003 to March 17, 2004, 12 confirmed human cases of H5N1 virus were reported in Thailand and 23 in Vietnam, resulting in 23 deaths.[16] During August to October 2004, human cases of H5N1 virus were only sporadically reported in Vietnam and Thailand.[17] However, since December 2004, H5N1 outbreaks among poultry and humans in Vietnam have surged. Moreover, Indonesia and Thailand have continued to report human cases. As of October, 2005, there have been at least 116 confirmed cases of H5N1 avian flu, including 61 deaths.[18]

Human infections by the avian influenza A H7N7 or H7N3 virus

In February 2003, the Netherlands reported outbreaks of the HPAI H7N7 virus in poultry. In total, 89 people were infected with N7H7, most of whom were poultry workers. The outbreaks of H7N7 included 78 cases of conjunctivitis, five cases of conjunctivitis and influenza-like illnesses, two cases of influenza-like illnesses only, and one fatal case of pneumonia combined with acute respiratory distress syndrome.[19] Direct contact with infected poultry was thought to be the route of transmission. However, three cases of human-to-human transmission were

reported, with probable transmission from poultry workers to family members.

In February 2004, human infections of the HPAI H7N3 virus among poultry workers occurred in British Columbia, Canada. The H7N3-associated clinical signs included mild illnesses, particularly eye infections. To date, the reason that H7, but not H5, viruses cause conjunctivitis in humans remains unclear.[20]

Human infections by the avian influenza A H9N2 virus

In 1999, low-pathogenic avian influenza (LPAI) H9N2 virus infection was confirmed in two children in Hong Kong, in whom it caused an uncomplicated influenza-like illness.[21] Direct bird-to-human transmission in poultry was assumed to have been the infection route. However, person-to-person transmission could not be ruled out. Furthermore, five human cases of H9N2 virus infection were reported in China.[22] The H9N2 viruses have now become a panzootic in poultry in Eurasia and have also been detected in pigs in Hong Kong.[23] In December 2003, human infections of H9N2 were confirmed again in Hong Kong, presenting as mild respiratory disease in a child.[24]

Conclusions

The 1957 and 1968 pandemic influenza viruses emerged from the mechanism known as "reassortment" of human and avian influenza viruses. The 1918 pandemic influenza virus, although it did not directly acquire genes from an avian influenza virus, likely originated from avian influenza but evolved in an unidentified host before emerging in 1918. The history of influenza pandemics during the last century indicates that the avian influenza virus threatens to be the first pandemic of the 21st century. Although scientists know the approximate mutation rate of influenza RNA polymerases, flu experts have difficulty in predicting the probability of emergence of a pandemic strain. The types of mutations that would enable the avian influenza virus to become a human virus (i.e., to adapt to humans) remain unclear. However, limiting avian influenza viral replication will reduce the viral mutation rate. Reducing human infection by the avian influenza virus will reduce the opportunity for the virus to adapt to human cells. Preventative measures are necessary to delay, contain, and prevent a pandemic.

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