REVIEW ARTICLE

# Influenza Pandemics: Past, Present and Future

*Yu-Chia Hsieh, Tsung-Zu Wu,[1] Ding-Ping Liu,[2] Pei-Lan Shao,[3] Luan-Yin Chang,[4] Chun-Yi Lu,[4] Chin-Yun Lee,[4] Fu-Yuan Huang,[5] Li-Min Huang[4]**

Influenza A virus is well known for its capability for genetic changes either through antigen drift or antigen shift. Antigen shift is derived from reassortment of gene segments between viruses, and may result in an antigenically novel virus that is capable of causing a worldwide pandemic. As we trace backwards through the history of influenza pandemics, a repeating pattern can be observed, namely, a limited wave in the first year followed by global spread in the following year. In the 20th century alone, there were three overwhelming pandemics, in 1918, 1957 and 1968, caused by H1N1 (Spanish flu), H2N2 (Asian flu) and H3N2 (Hong Kong flu), respectively. In 1957 and 1968, excess mortality was noted in infants, the elderly and persons with chronic diseases, similar to what occurred during interpandemic periods. In 1918, there was one distinct peak of excess death in young adults aged between 20 and 40 years old; leukopenia and hemorrhage were prominent features. Acute pulmonary edema and hemorrhagic pneumonia contributed to rapidly lethal outcome in young adults. Autopsies disclosed multiple-organ involvement, including pericarditis, myocarditis, hepatitis and splenomegaly. These findings are, in part, consistent with clinical manifestations of human infection with avian influenza A H5N1 virus, in which reactive hemophagocytic syndrome was a characteristic pathologic finding that accounted for pancytopenia, abnormal liver function and multiple organ failure. All the elements of an impending pandemic are in place. Unless effective measures are implemented, we will likely observe a pandemic in the coming seasons. Host immune response plays a crucial role in disease caused by newly emerged influenza virus, such as the 1918 pandemic strain and the recent avian H5N1 strain. Sustained activation of lymphocytes and macrophages after infection results in massive cytokine response, thus leading to severe systemic inflammation. Further investigations into how the virus interacts with the host's immune system will be helpful in guiding future therapeutic strategies in facing influenza pandemics. [*J Formos Med Assoc* 2006;105(1):1–6]

**Key Words:** avian influenza virus, influenza, influenza A H5N1 virus, pandemic

The influenza A virus, being a member of the Orthomyxoviridae family, possesses a genome make-up of eight single-stranded, negative-sense RNA segments. The specific structure allows genetic reassortment when multiple viruses co-infect the same cell. Based on the different surface glycoproteins, influenza A viruses are further classified into 16 types of hemagglutinin (HA) and nine types of neuraminidase (NA).[1] Avian hosts are the major reservoirs for all subtypes. So far, only three types of HA (H1, H2, H3) and two types of NA (N1, N2) have been widely prevalent in humans.

An influenza pandemic can develop with the emergence of a new virus with high transmission capability, and that harbors a novel HA that has not circulated for decades. In each past pandemic, a limited wave has appeared first, followed by



Section of Infection, Department of Medicine, Wan-Fang Hospital, Taipei Medical University, [1]Department of Pediatrics, Taipei City Hospital, Branch for Women and Children, [2]First Division, Center for Disease Control, Department of Health, Departments of [3]Laboratory Medicine and [4]Pediatrics, National Taiwan University Hospital, [5]Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan, R.O.C.

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***Correspondence to:** Dr. Li-Min Huang, Department of Pediatrics, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei, Taiwan, R.O.C.
E-mail: lmhuang@ha.mc.ntu.edu.tw

global spread in the following year. It has been generally believed that avian influenza virus cannot infect humans because of its inability to bind to the 2-6-linked sialic acid receptors present in the human respiratory tract. In 1997, however, 18 human cases of avian influenza A H5N1 infection occurred in Hong Kong.[2] Furthermore, extensive outbreaks of avian H5N1 infections with sporadic human spread have been ongoing in Vietnam, Thailand, Indonesia and Cambodia since 2003, although human-to-human transmission remains limited.[3,4] This particular H5N1 virus has shown increased virulence in mammals, a warning sign that it is continuously evolving to adapt to humans and mammals.[5]

The emergence of an influenza virus strain with high transmissibility among humans, either through reassortment between avian and human influenza viruses or virus mutation, is expected to occur. Given the threat of a global pandemic caused by avian H5N1 influenza A virus, we analyze the clinicopathologic manifestations in historic pandemics and compare them with recent human H5N1 infections in Asia to gain new insights into the pathogenicity of influenza viruses. Taking lessons from past experience will be useful in the development of treatment and prevention strategies in future influenza pandemics.

## Typical Influenza Syndrome—Epidemiology and Common Features

Clinically, influenza is usually a self-limiting disease characterized by abrupt onset of fever and chills accompanied by headache, diffuse myalgia, rhinorrhea, sore throat and cough. Gastrointestinal discomforts such as vomiting, abdominal pain and diarrhea are not infrequent. The most common cause of hospitalization is lower respiratory tract infection ranging from croup, bronchitis, bronchiolitis to pneumonia.[6,7] Meanwhile, manifestations involving the central nervous system may be observed, leading to encephalopathy, post-influenza encephalitis, transverse myelitis, Guillain-Barré syndrome and acute necrotizing encephalitis.[8,9] Myositis often occurs 3 days (range, 0–18 days) after influenza onset.[10,11] In young infants, influenza can mimic sepsis.[12] Myocarditis is a rare complication. Epidemiologically, excess death occurs mainly in infants and the elderly (> 65 years old) due to decreased immunity against influenza virus infection in annual influenza epidemics. The mortality curve typically presents with a U-shape when age-specific excess mortality due to pneumonia and influenza is plotted.

## 1957 H2N2 and 1968 H3N2 Pandemics—Epidemiology and Clinical Manifestations

The 1957 and 1968 pandemics were caused by Asian influenza A (H2N2) strain and Hong Kong influenza A (H3N2) strain, respectively. Both virus strains first emerged in China. Virologic study showed that these two strains were derived from genetic reassortment between human and Eurasian avian lineage influenza virus strains.[13] The HA gene segment of the human strains was replaced by those of the avian strains; human influenza virus-derived internal proteins except for PB1 were preserved.[14] In these two pandemics, common manifestations were similar to those of a typical influenza syndrome. Patients with underlying cardiovascular diseases tended to have severe complications. The U-shaped mortality curve in the 1957 and 1968 pandemics had two ends, peaking in infants and the elderly.[15]

The most frequent complication leading to death was pneumonia. Due to advances in antibacterial therapy, fatal cases caused by primary influenza viral pneumonia without secondary bacterial infections increased. Louria et al reported 33 patients with Asian influenza A infection during the pandemic of 1957–1958,[16] of whom 72.7% (24/33) had chronic diseases or were pregnant and 21.2% (7/33) had leukopenia. Liver function tests were normal except for elevated aspartate transaminase levels in 76.2%. No renal damage or hematologic abnormalities, including thrombocytopenia or abnormal blood clotting functions, were

observed. The death rate related to acute illness was 27.3% (9/33). Some rapidly progressive cases presenting with dyspnea and cyanosis resembled those observed in the 1918 pandemic.[17] Oseasohn et al reported the clinicopathologic study of 33 fatal cases caused by Asian influenza, mostly focusing on previously healthy young individuals dying rapidly during the course of the disease.[17] Postmortem examination showed pulmonary congestion, edema, intra-alveolar hemorrhage, varying degrees of consolidation and hyaline membrane formation indistinguishable from the pathologic findings of the 1918 pandemic. *Staphylococcus aureus* was the most common superimposed pathogen; 39.4% (13/33) of patients had evidence of myocarditis, and 12.1% (4/33) was diagnosed with encephalopathy.[17] There were no specific findings involving the gastrointestinal organs except in two patients: one had inflammatory changes in the esophagus and pancreas while the other had hemorrhagic congested changes in the colon.

## 1918 Pandemic—Distinct Epidemiology and Clinical Features

The geographic origin of the 1918 pandemic remains controversial, with two suspected sites of origin. One was from China, which then spread to the USA and Europe through laborer migration. Another was from the USA as the first outbreaks occurred simultaneously in Detroit, South Carolina and San Quentin Prison in March 1918, then spreading unevenly throughout the United States and Europe.[18] In the 1918 pandemic, 50% of the world's population was infected and 25% developed significant clinical infections.

The 1918 influenza pandemic occurred 28 years after the previous 1890 pandemic. The most significant difference in the epidemiology of the 1918 pandemic was the unusual W-shaped mortality pattern, with a peak of excess death among young adults aged between 20 and 40 years.[15] Excess mortality was not found among the elderly, possibly due to previous exposure to an influenza virus antigenically similar to the 1918 strain.[15] The 1918 virus strain was thought to be more virulent, causing 40–50 million deaths worldwide. In fact, recombinant viruses containing the HA gene segment of the 1918 pandemic virus were shown to exhibit high pathogenicity in mice that are not usually susceptible to other human influenza viruses.[19] The lungs of mice infected with the 1918 virus showed extensive inflammation and contained high levels of macrophage-derived chemokines and cytokines.[19,20] Gene sequencing of the 1918 influenza virus suggested that this strain was an avian influenza virus that adapted to humans.[21]

Clinical manifestations were characterized by acute onset, chills, quick and high rise in body temperature, frequent epistaxis (hemorrhagic vaginal discharge in females), distressing aches and pains, and increasing prostration.[22] Pneumonia was the most common complication, regardless of whether it was combined with secondary bacterial infection or not.[22,23] In severe cases, shortness of breath accompanied by mahogany spots around the mouth and violaceous heliotrope cyanosis developed. Within 24–48 hours, patients suffocated to death and had blood-stained fluid in the mouth. These signs were compatible with acute pulmonary edema, proved at autopsy.[23] Brem et al reported that many cases demonstrated hemorrhagic phenomenon and leukopenia in the initial stages, which indicated blood dyscrasia.[24] Of the fatal cases, 51.8% had initial leukocyte counts $\leq 5000/mm^3$, while 21.7% of the non-fatal cases did.[24] Leukopenia was highly associated with fatal outcome in the 1918 pandemic (chi-square test, $p < 0.001$). Due to limited laboratory examinations at that time, it was not certain if bleeding tendency was related to thrombocytopenia or abnormal clotting times. The 1918 virus strain had suppressive effects on bone marrow, and led to hosts becoming more vulnerable to certain bacteria such as *Streptococcus pneumoniae*, *S. hemolyticus* and *S. viridans*.[24] Postmortem lung examinations revealed extensive lung damage throughout the respiratory tree. Another striking finding was the enormous number of large mononuclear cells in the lungs in the earlier stages of the disease.[23]

The constellation of leukopenia, hemorrhagic diathesis and pulmonary edema in healthy young adults during the 1918 pandemic were unique features that contrasted with those observed in the 1957 and 1968 pandemics and during the interpandemic periods. There were specific extrapulmonary findings reported as well in the 1918 pandemic. Lecount described distinctive pathologic features among 200 influenza A cases.[25] Splenomegaly, superficial fatty change of the liver, swelling of the kidneys and brain tissue were frequently found. Sometimes, generalized jaundice and hyperplasia of lymphoid tissue were observed. Walker reported 100 autopsy cases at Camp Sherman.[23] The most common findings other than those in the respiratory system were pericarditis (65%), acute liver congestion (67%), acute kidney congestion (74%), acute spleen congestion (56%) and jaundice (25%); 48% of cases had acute myocarditis and 28% had acute hepatitis with grossly yellowish livers. Marked fatty degeneration of hepatocytes was seen microscopically.

To sum up, extensive organ involvement was an outstanding feature in the 1918 pandemic. Up till now, there has been no evidence of direct virus invasion of multiple organs.[18] As a result, multiple organ dysfunction might be the result of dysregulation of systemic inflammatory responses. These findings support the concept that some severe cases were associated with overactivation of inflammatory cytokines, leading to pulmonary edema, infection-associated hemophagocytic syndrome and multiple organ failure. Hemophagocytic syndrome, first described in 1979, is characterized by high fever, pancytopenia, hepatosplenomegaly, liver dysfunction, high ferritin and triglyceride levels, which could account for the leukopenia, bleeding tendency, splenomegaly, jaundice, hepatic fatty change and multiple organ failure seen in severe cases during the 1918 pandemic.[26,27] Increased proliferation and overactivation of macrophages throughout the reticuloendothelial system resulted in abnormal phagocytic activity and massive secretion of cytokines. Rapid viral replication in the respiratory system led to sustained immune system activation. The excess inflammatory response was the pathogenic pathway to the deadly complications.

## H5N1 Infection in Humans

Avian influenza virus H5N1 could cross the species barrier and infect humans as evidenced by the 1997 outbreak in Hong Kong. Analysis of human H5N1 infections in Hong Kong, Vietnam, Thailand and Cambodia revealed that fever and cough were the most common initial symptoms.[2–4,28,29] Almost all patients had clinically apparent pneumonia. Gastrointestinal symptoms including vomiting, diarrhea, abdominal pain, pleuritic pain, and bleeding from the nose and gums have also been observed early in the course of illness in some cases. One report described two patients who presented with an encephalopathic illness and diarrhea without apparent respiratory symptoms. The fatality rate among hospitalized patients has been high (33–100%, varying by country), although the overall rate is probably much lower.[29] Fifty to 80% of cases had lymphopenia and 33–80% had thrombocytopenia. Abnormal liver function was detected in 61–83% of cases. Acute respiratory distress syndrome (ARDS) complicated 76.5% (13/17) of cases in Thailand, and 44.4% (8/18) of cases in Hong Kong. Multiple organ failure with signs of renal dysfunction and sometimes cardiac compromise has been common. Most patients did not have preexisting disease, which was quite different from what happened during interpandemic periods when patients with underlying cardiovascular, pulmonary and renal diseases were more susceptible to severe influenza infection. Leukopenia, thrombocytopenia, ARDS and, particularly, lymphopenia were associated with poor outcome.[4,29] In severe human H5N1 infections in Hong Kong, reactive hemophagocytic syndrome was a remarkable pathologic feature in three fatal cases,[30,31] as were increased blood levels of interferon-$\gamma$, tumor necrosis factor-$\alpha$, interleukin-6, soluble interleukin-2 receptor, interferon-induced protein-10 and monokines induced by interferon-$\gamma$.[30,31] Hence, apparent dysregulation of cytokine responses

contribute to the pathogenesis of human H5N1 infections.

Immunomodulatory agents are thought to be beneficial in treating fulminant cases. However, data concerning treatment efficacy from Vietnam and Thailand in early 2004 showed that no significantly different mortality rates were noted between patients who had or had not received steroid therapy (50% *vs* 75%, $p = 0.334$). In a randomized trial in Vietnam, all four patients given dexamethasone died.[29] It is still premature to conclude on the usefulness of steroid treatment in H5N1 infections because there were many variations in dose, timing and duration of treatment.

NA inhibitors such as oseltamivir and zanamivir are effective against influenza A H5N1 virus, including the avian flu viruses that caused outbreaks between 1997 and 1999 and the currently circulating ones. They inhibit viral replication in cell cultures, reduce NA activity and protect infected mice from death.[32–35] The use of oseltamivir in Vietnam and Thailand has been sporadic and failed to impact significantly on patient survival (67% and 56%, $p = 1.000$). However, most of the treatments did not start until 2 days after disease onset. Experience of zanamivir is lacking. How effective NA inhibitors are against human H5N1 infection is not firmly established. Nevertheless, since NA inhibitors are currently the only options for treatment or prophylaxis in H5N1 human infections, they form an important part of a strategy for dealing with the possibly upcoming pandemic. In the 1968 and 1977 pandemics, adamantanes were found to have a protective efficacy of around 70%, only slightly lower than the efficacy reported during the interpandemic period. The protective efficacy of NA inhibitors during a pandemic would be expected to be at least as high as that of the adamantanes.[32] In view of the recent isolation of an oseltamivir-resistant H5N1 virus from a Vietnamese patient, zanamivir should be included as part of pandemic preparedness in addition to oseltamivir.

In the influenza A pandemics of 1957 and 1968, the clinical illnesses were more confined to the respiratory system, while in the 1918 pandemic and human H5N1 infections since 1997, multisystem dysfunction and immune dysregulation developed in infected individuals. This is an indication that highly pathogenic influenza A viruses, through direct adaptation to humans, would stimulate more severe and inappropriate immune responses than a reassortant virus.

There have been 12 definite or probable pandemics in the past 400 years,[36] of which 11 originated in China, Russia and Asia. No apparent seasonality was observed, but they occurred more frequently in spring and summer than in autumn and winter. Higher temperatures and humidity would seem to favor the spread of a pandemic.

## Conclusion

It has been almost 40 years since the last pandemic in 1968. All the conditions favoring an influenza pandemic are looming, including successful evolvement of a candidate strain (H5N1 influenza A virus), extensive seeding in Asia, and long-enough interpandemic time. If our current control measures implemented in Asia turn out to be inadequate, a pandemic in 2006 or 2007 is highly likely. Appropriate use of NA inhibitors and judicious modulation of inflammatory cascades caused by avian influenza A virus may be crucial to clinical management of human H5N1 infections. Since the risk of influenza A epidemics and pandemics will remain for the foreseeable future, newer and improved influenza vaccines should be developed. More studies on the epidemiology, evolution and pathogenesis of avian influenza A virus infection are warranted.

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