Avian Influenza

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Influenza is an old disease but remains vital nowadays. Three types of influenza viruses, namely A, B, C, have been identified; among them influenza A virus has pandemic potential. The first outbreak of human illness due to avian influenza virus (H5N1) occurred in 1997 in Hong Kong with a mortality of 30%. The most recent outbreak of the avian influenza epidemic has been going on in Asian countries since 2003. As of March 2005, 44 incidental human infections and 32 deaths have been documented. Human influenza viruses differ with other avian influenza viruses on the choice of cellular receptors. Avian influenza viruses bind to cell-surface glycoproteins or glycolipids containing terminal sialyl-galactosyl residues linked by 2-3-linkage [Neu5Ac(α2-3)Gal], whereas human viruses, including the earliest available isolates from the 1957 and 1968 pandemics, bind to receptors that contain terminal 2-6-linked sialyl-galactosyl moieties [Neu5Ac(α2-6)Gal]. Recent evidence suggests that human bronchial ciliated epithelial cells contain Neu5Ac(α2-3)Gal and can be infected with avian influenza viruses. Nevertheless, avian influenza viruses can not infect non-ciliated bronchial epithelial cells. Hence, adaptation of the avian influenza virus to non-ciliated cells is a prerequisite for a pandemic virus to emerge. Biological behaviors of influenza viruses indicate that once a pandemic virus emerges, isolation is not likely to contain this epidemic. A specific vaccine against the pandemic strain will not be available until 6 to 12 months after the inception of the pandemic. Judicious use of antiviral agents and stringent disease control measures are imperative to decrease the impact of a future pandemic. *(Chang Gung Med J 2005;28:753-7)*

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Three types of influenza viruses, namely A, B, C, classified on the basis of their nucleoproteins, have been identified so far. Among them, the influenza A virus has pandemic potential. Two important surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), are embedded in the membrane. Hemagglutinin mediates receptor binding and membrane fusion, and neuraminidase facilitates cleavage of the viral progeny from infected cells, prevents viral aggregation, and aids movement of the virus through the mucosal respiratory epithelium.[1] All known 16 H and 9 N subtypes of the influenza A virus have been confirmed in apparently healthy free-ranging avian species, including waterfowl which are thought to be natural reservoirs of the influenza A virus.[2,3] Waterfowl carry viruses in their gastrointestinal tracts and do not develop the disease. Viruses spread worldwide following seasonal migration patterns of migratory birds. Outdoor production of ducks, chickens and pigs provides these animals the opportunity to contact with wild waterfowl and the viruses they carry. This is especially true of the ecological environment of South East Asia.

Occasionally, the influenza A virus causes dis-

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ease in avian species and leads to the so-called avian influenza. In Asia, the H5N1 avian influenza virus first emerged in southern China in 1996 and has gained prevalence steadily. Infection with this virus has continued to occur since then. It has affected several countries, including Cambodia, China, Indonesia, Japan, South Korea, Laos, Thailand, Vietnam, and Malaysia. The avian influenza virus has rarely been associated with human illness before 1997 when the first outbreak of H5N1 avian influenza virus in humans occurred in Hong Kong.[4] Eighteen cases were diagnosis and six of them died. Humans were infected with the disease after close contact with chickens or contaminated surfaces, without the involvement of an intermediate host.[5,6] Since 2004, there have been 69 documented human cases infected by H5N1 avian influenza viruses in Asia. The epidemic is still ongoing. Forty-six of the patients died, with a mortality rate of nearly 70%. Most of the human cases occurred in Vietnam and Thailand. Although the direct transmission of the virus from chickens to humans is of concern, the greatest worry is that human-to-human transmission may begin to occur. Serologic surveillance in Hong Kong after the first outbreak of avian influenza in humans in 1997 showed evidence of asymptomatic infections after contact in the human cases.[6] A case report from Thailand in 2004 clearly indicated the occurrence of one probable person-to-person transmission of human avian influenza through close contact, which led to death.[7] Hence, avian influenza might not only be a disease affecting only the poultry market chain, but it might also be a threat to human society with the possible occurrence of an avian influenza pandemic.

The first formal record of pandemic influenza occurred in 1918, leading to more than 50 million deaths.[8] Another three pandemics occurred in 1957, 1968 and 1977. The subtypes of the influenza A virus causing human disease in these pandemics were H1, H2, and H3. Actually, H1 and H3 have become endemic in human society since 1977 and remain globally significant causes of febrile respiratory illness. Every year, outbreaks of influenza are observed, with excessive hospitalization and deaths, especially in the elderly, in people with underlying chronic medical conditions, and in infants. Two models of mutations associated with influenza virus have been recognized, namely antigen shift and antigen drift. Antigen shifts result from the reassortment of the segmented genetic materials between different subtypes of viruses and can transform an influenza virus into a new subtype. Antigen drifts result from minor gene mutations and lead to a new strain instead of a new subtype. Because of these characteristics, influenza viruses are capable of causing repeated epidemics in human populations and even pandemics. Actually, studies of the pandemics in 1957 an 1968 revealed that an antigen shift resulted from reassortment of the influenza virus in pigs with disastrous outcomes.[9]

The occurrence of widespread H5N1 avian influenza virus in Asia has aroused a lot of concern because the virus may serve as a donor to a new H subtype and might result in a pandemic in humans due to the H5 influenza virus. Gene reassortment may occur in human and animal reservoirs other than the avian species, especially in pigs. This process is facilitated by agricultural practices in Asia which includes the close proximity between humans, ducks, poultry, and pigs. This ecological niche provides the H5N1 avian influenza virus good opportunities to develop mutations, which might aid in the adaptation to efficient human infection. Luckily, viruses isolated from human cases of avian influenza so far showed no major genetic mutations, suggesting that the viruses were still avian origin and the replication in humans remains restricted.

The influenza viruses that have adapted to humans differ from other avian influenza viruses on the type of cellular receptors. Avian influenza viruses bind to cell-surface glycopoeins or glycolipids containing terminal sialyl-galactosyl residues linked by 2-3-linkage [Neu5Ac(α2-3)Gal], whereas human viruses bind to receptors that contain terminal 2-6-linked sialyl-galactosyl moieties [Neu5Ac(α2-6)Gal]. It was thought that the lack of appropriate receptors limited the infection of avian influenza viruses in humans. However, a study using cultures of differentiated human airway epithelial cells suggested that human bronchial ciliated epithelial cells also contain Neu5Ac(α2-3)Gal and may be infected by avian influenza virus.[9] Non-ciliated epithelial cells lacked Neu5Ac(α2-3)Gal and were not infected by avian influenza viruses. Although avian influenza viruses can infect human airway epithelium, their replication may be limited by a non-optimal cellular tropism. Adaptation of avian influenza viruses to

non-ciliated cells is a prerequisite for a pandemic virus to emerge.

One of the major tasks for us is to contain a pandemic should it arise. Isolation and quarantine probably will not be enough to stop the spread of an influenza epidemic because patients infected with the influenza virus have been infectious for a few days prior to the onset of clinical symptoms. A strain-specific vaccine or anti-viral drugs against H5N1 avian influenza virus are therefore better choice. Amantadine and rimantadine are conventional drugs to treat infection due to the influenza A virus; however, drug resistance has been documented and hence, we can not rely on them to treat future infections caused by the H5N1 avian influenza virus. Zanamivir and oseltamivir are new anti-viral drugs that inhibit activity of the neuraminidase and keep viruses together with the infected cells. They are currently licensed for treatment and prevention of influenza. Luckily, the H5N1 avian influenza virus remains susceptible to both zanamivir and oseltamivir. Treatment of the patients alone may not prevent further spread of the viruses, however. If patients can be recognized early and treatment can be initiated incipiently, transmission may still be inefficient and local control of an outbreak could be achieved. Good clinical surveillance and drug delivery systems are also needed.

A/Vietnam/1194/2004 and A/Vietnam/1203/2004, which are the prototype vaccine strains recommended by the World Health Organization (WHO) for pandemic influenza vaccine production,[11] are genetically highly similar to the viruses isolated from confirmed or suggested human cases in southern Vietnam during the flu season in 2004-05. The virus was evolving at a slow pace. Studies of the characteristics of the prototype vaccine provided essential information to combat a pandemic. However, should a pandemic really begin, a strain-specific vaccine will not be available within months because of the time needed for manufacturing. Even if they are produced, there will not be enough supply for the whole world during the first year of the pandemic. It is difficult to predict when or whether the H5N1 avian influenza virus will start to spread among humans. How soon the pandemic will affect Taiwan should it arise is also elusive. Taiwan is located close to China and South East Asia, which is geographically the "hot area" of recent outbreaks of the H5N1 avian influenza. Traffic between Taiwan and the countries in the "hot area", of both humans and waterfowl, is heavy. Current solutions for Taiwan in anticipation of an influenza pandemic comprise of developing local capabilities to produce influenza vaccine and stockpiling enough anti-viral drugs. Hopefully, through a sound public health system, we can manage to reduce the damage caused by a pandemic of avian influenza in Taiwan.

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禽流感

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流行性感冒是個流行已久卻仍活躍於時下的疾病。三種流行性感冒病毒被辨識出來，分別命名爲 A、B、C 型；其中 A 型流行性感冒病毒有引發世界大流行的潛能。1997 年在香港，人類第一次因爲禽類 H5N1 流行性感冒病毒造成疾病的爆發，死亡率約三成。這樣的禽流感病毒在 2003 年後持續在東南亞流行，直到 2005 年 3 月，造成了 44 例人類感染，其中 32 例死亡。人類的流感病毒和禽流感病毒感染細胞所藉由的接受器不同。禽流感病毒使用細胞表面的 Neu5Ac(α2-3)Gal，而人類的流感病毒－包括最早期 1957 及 1968 年世界大流行所分離出的病毒，則利用 Neu5Ac(α2-6)Gal。最新的研究證實人類支氣管纖毛細胞有 Neu5Ac(α2-3)Gal 而能被禽流感病毒感染，然而禽流感病毒並不能感染人類支氣管非纖毛細胞。因此禽流感病毒要造成世界流行的前提必需能適應並感染非纖毛細胞。依照流行性病毒的生物特性，一旦世界流行的病毒株形成，光靠病患的隔離將無法控制疫情。針對流行病毒株的疫苗也要在疫情開始後的 6 到 12 個月才能製造出來。明確的用抗病毒藥物和嚴格的感控措施是非常重要的，將賴以減低世界流行造成的衝擊。(長庚醫誌 2005;28:753-7)

關鍵字：禽流感病毒，流行性感冒，世界大流行，Neu5Ac(α2-6)Gal，Neu5Ac(α2-3)Gal。

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